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Psychotic onset, catatonic course and ovarian teratoma in a female patient diagnosed with Anti-N-Methyl-D-Aspartate receptor encephalitis: A multidisciplinary case report

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Abstract

Anti-N-Methyl-D-Aspartate Receptor (NMDAR) encephalitis is a rare but treatable form of autoimmune encephalitis in which psychiatric and neurological symptoms can coexist. Diagnostic delays may occur, especially in cases where psychiatric symptoms are prominent. It should be considered in patients with subcautious onset symptoms resistant to psychiatric treatment and neurological evaluation should be performed. In this study, a case of paraneoplastic anti-NMDAR encephalitis who presented with psychiatric symptoms and was treated with early diagnosis is presented. The female patient, whose complaints started with psychiatric symptoms, had no pathological findings in her brain Magnetic Resonance İmaging (MRI). Generalized slow wave activity was observed in Electroencephalography (EEG), and anti-NMDAR antibodies were positive in serum and Cerebrospinal Fluid (CSF). 1000 mg/day methylprednisolone was administered for 5 days, followed by 25 g/day İntravenous İmmunoglobulin (IVIG) for 5 days. Ovarian teratoma was detected with systemic imaging. After treatment, psychotic symptoms disappeared, amnesic symptoms decreased, and cognitive response time was significantly shortened. Anti-NMDAR encephalitis should be considered in cases presenting with resistant psychiatric symptoms and responding poorly to antipsychotic treatment; brain MRI, EEG, and CSF findings should be examined in differential diagnosis. Tumor screening illuminates the paraneoplastic aspect of the diagnosis, while early immunotherapy directly affects disease prognosis. A multidisciplinary approach is one of the cornerstones of effective treatment planning.

Keywords: Autoimmune encephalitis; Anti-N-Methyl-D-Aspartate receptor; Early diagnosis and treatment.

Introduction

Anti-N-Methyl-D-Aspartate (NMDA) receptor encephalitis is a progressive encephalitis syndrome first described in 2007, which usually presents initially with psychotic symptoms. It is thought to occur as a result of an autoimmune response of anti-NMDA receptor antibodies, particularly against the NR1 subunit, in the limbic system and cortical structures. The disease is more common in young women and has been found to be associated with ovarian teratoma in nearly 50% of cases [1,2].

The clinical course usually begins with flu-like symptoms in the prodromal period, followed by diverse symptoms such as psychotic manifestations, behavioral changes, convulsions,

dysphasia, dysautonomia, hypoventilation, and catatonia. The diagnosis is made by positivity of anti-NMDAR antibodies in serum and/or Cerebrospinal Fluid (CSF). Brain Magnetic Resonance İmaging (MRI) is usually normal; in Electroencephalography (EEG), slowing and sometimes generalized dysrhythmia may be observed [3].

In the diagnostic process of autoimmune encephalitis, a holistic approach based not only on antibody positivity but also on the combined evaluation of clinical findings, brain imaging, and CSF analyses is adopted. Even in cases where antibody tests may be negative, if the clinical picture raises high suspicion, the diagnosis should not be abandoned [4,5]. For this reason, especially early treatment initiated before antineuronal antibody results are obtained plays a decisive role on prognosis [5].

In this article, we present the detailed clinical course and treatment process of a 32-year-old female patient who initially presented with psychotic findings, developed catatonia, was later diagnosed with anti-NMDAR antibody positivity, was found to have an ovarian teratoma, and was treated with a multidisciplinary approach.

Case presentation

A 32-year-old married woman with three children presented to the emergency department with visual hallucinations of nonexistent objects, behavioral changes, and cataleptic symptoms persisting for the past 2 months. In her psychiatric examination, the evaluation could only be performed at a limited level due to the patient being in a rigid posture and having speech impairment. The patient appeared consistent with her age, and her self-care was normal. Her affect was observed as dysphoric, and she participated in the interview with limited cooperation. According to information obtained from her relatives, the patient had persecutory delusions about harm coming to her family and children, visual hallucinations that her children were killed and that she saw blood in her hands, as well as auditory hallucinations accompanied by exclamations of "My God."

Regarding premorbid personality traits, the patient was reported to be meticulous in character. During the interview, repetitive movements and imitation of others' actions (echopraxia) were observed. History was also obtained that she imitated others' voices at home. During the examination, involuntary facial movements resembling grimacing around the mouth were also observed. The patient was hospitalized in the psychiatry ward and underwent 5 sessions of Electroconvulsive Therapy (ECT). In medical treatment, lorazepam 7.5 mg/day and olanzapine 20 mg/day were administered. Since the symptoms persisted after treatment, brain imaging, EEG, and lumbar puncture were performed to investigate organicity. Due to suspicion of autoimmune encephalitis, an antineuronal antibody panel was studied, and anti-NMDAR positivity was found in serum. About 2 weeks after admission, the patient was transferred to the Neurology ward.

On neurological examination, she was conscious, oriented, and cooperative. Her reaction time was prolonged. Cranial nerves were intact, and there was no neck stiffness. Pupils were isochoric, and light reflexes were bilaterally present. No motor deficit was found. Deep tendon reflexes were normoactive, and no pathological reflexes were present. Anti-NMDAR antibody positivity was detected in a sample obtained from CSF. Contrast-enhanced brain MRI showed no pathological signal intensity (Figure 1). Diffusion MRI was normal (Figure 2). In EEG, high-amplitude, bilateral synchronous, generalized sharp and slow wave activity was observed in the frontal regions of both hemispheres. Hyperventilation and intermittent photic stimulation did not elicit any activity. These findings were consistent with the presence of generalized paroxysmal dysrhythmia during wakefulness (Figure 3).

The patient was treated with 1000 mg/day methylprednisolone for 5 days, followed by 25 g/day IVIG for 5 days. During clinical follow-up, amnesic symptoms decreased, schizophreniform findings disappeared, and her cognitive state improved, with more precise and shorter responses to questions and a significantly reduced reaction time.

For malignancy screening, contrast-enhanced CT of the neck, thorax, abdomen, and pelvis and gynecological evaluation with Transvaginal Ultrasonography (TVUSG) were performed. A nodular lesion measuring 66×60 mm, containing adipose tissue and calcified densities, was detected in the right adnexal region (Figures 4 & 5). The appearance was evaluated as compatible with ovarian teratoma.

Other systemic screenings were negative. The patient was discharged and taken into outpatient follow-up after clinical improvement and stabilization of her general condition.

After discharge, following gynecological examination and imaging, laparoscopic cystectomy was planned with the preliminary diagnosis of teratoma.

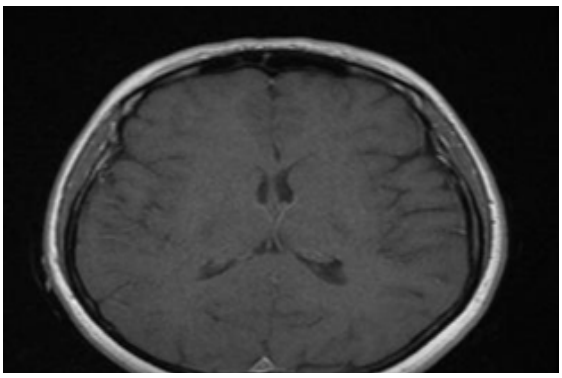

Figure 1: Contrast-enhanced brain MRI showing no pathological signal intensity.

Discussion

Autoimmune encephalitides constitute a broad group of diseases mediated by autoantibodies against central nervous system antigens, in which psychiatric and neurological symptoms can be observed together or sequentially. The most common form in this group is anti-N-Methyl-D-Aspartate Receptor (anti-NMDAR) encephalitis. Anti-NMDAR encephalitis is usually seen in young women and manifests with symptoms such as psychotic features, agitation, hallucinations, epileptic seizures, dyskinesias, speech disorders, autonomic instability, and hypoventilation [6,7].

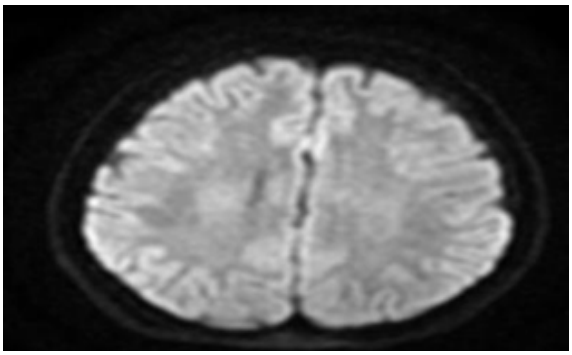

Figure 2: Diffusion-weighted MRI demonstrating no abnormal restriction of diffusion, consistent with the absence of acute parenchymal lesions.

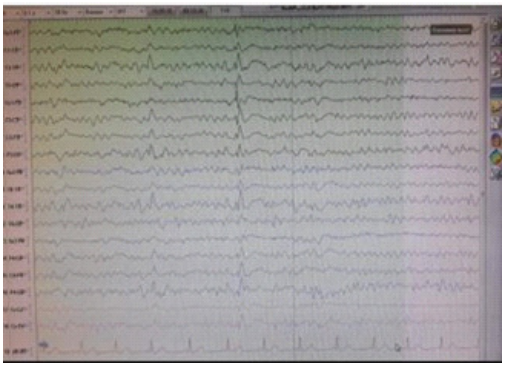

Figure 3: Electroencephalogram (EEG) revealing high-amplitude, bilateral, synchronous generalized sharp and slow-wave activity predominantly in the frontal regions during wakefulness, consistent with generalized paroxysmal dysrhythmia.

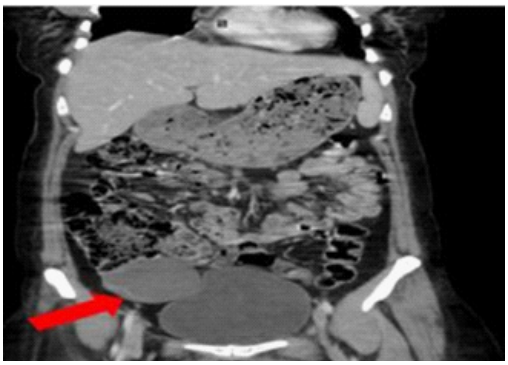

Figure 4: Contrast-enhanced pelvic CT scan demonstrating a well-circumscribed nodular lesion (66×60 mm) in the right adnexal region, containing areas of adipose tissue and calcified densities (red arrow), suggestive of ovarian teratoma.

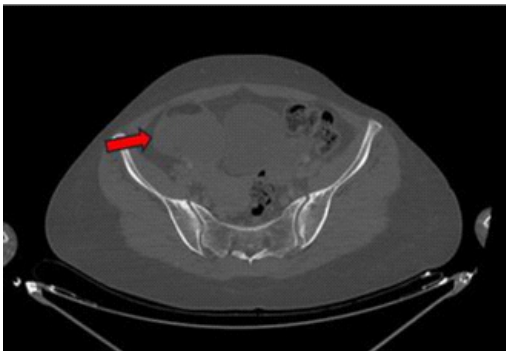

Figure 5: Transvaginal Ultrasonography (TVUSG) image of the right adnexal mass with heterogeneous echotexture and calcified components, compatible with mature cystic teratoma.

Studies have reported that anti-NMDAR encephalitis is the most common subtype among autoimmune encephalitides. Other types of encephalitis against LGI1, CASPR2, AMPAR, and GABA-A receptors are observed less frequently [6]. In a 2023 study by Braczkowski et al. [6], the clinical and paraneoplastic spectrums of encephalitides were compared according to different autoantibody types; in this analysis, the high incidence of anti-NMDAR encephalitis at a young age and the broadness of its clinical spectrum were emphasized. In the study of Gable et al. [7] based on the California Encephalitis Project data, it was also reported that anti-NMDAR encephalitis was more frequently identified in individuals under the age of 30 compared to viral causes such as HSV-1 and enterovirus.

In patients with anti-NMDAR encephalitis, cranial MRI usually provides limited diagnostic findings. In the series of Zhang et al. [8] with 53 cases, imaging was reported to be completely normal in 53% of patients. The most commonly detected finding in patients with imaging abnormalities was hippocampal involvement. The authors classified these findings into four different MRI patterns and emphasized that especially hippocampus-related lesions (Type 2 and Type 4) were significantly associated with poor clinical outcomes. Hippocampal lesions were found to be a strong predictor of poor prognosis. In our case, no pathology was found on MRI. This finding demonstrates that normal imaging does not exclude the disease and underlines the importance of complementary methods such as clinical evaluation and CSF antibody analysis.

In anti-NMDAR encephalitis, Electroencephalography (EEG) provides valuable information for diagnosis and prognosis. In the systematic review by Gillinder et al. [9] including 446 patients, EEG was found to be abnormal in 83.6% of cases. The most common finding was generalized encephalopathic slowing (60.3%). Pronounced slowing in the delta frequency range was identified in 18%, and the Extreme Delta Brush (EDB) pattern, considered specific for anti-NMDAR encephalitis, was described in 6.7%. EDB pattern and delta slowing were associated with poor prognosis and need for intensive care. In addition, epileptiform activity was detected in only 15% of patients, although the rate of clinical seizures was higher, indicating a low rate of EEG detection. In our case, during recording, high-amplitude, bilateral synchronous, generalized sharp and slow wave activity was observed in the frontal regions of both hemispheres. Hyperventilation and intermittent photic stimulation did not elicit any activity. These findings indicated the presence of generalized paroxysmal dysrhythmia during wakefulness, consistent with EEG abnormalities frequently reported in anti-NMDAR encephalitis cases. EEG is particularly supportive of diagnosis and contributes to differential diagnosis in cases presenting with atypical symptoms.

CSF analyses in anti-NMDAR encephalitis often show inflammatory changes such as lymphocytic pleocytosis, increased protein level, and oligoclonal band positivity. In the multicenter study of Dürr et al. [10], cell increase was found in 79% and intrathecal immunoglobulin synthesis in 44% of CSF samples. However, this inflammatory profile may not be observed in every patient. In our case, apart from 1700 erythrocytes, no cellular response was detected in CSF examination, protein level was measured as 53 mg/dL, and albumin as 0.4 g/L. The absence of pleocytosis in CSF may indicate a more atypical or late stage of the disease, as well as supporting that CSF may be normal or show limited changes in some anti-NMDAR encephalitis cases. Therefore, CSF analysis is not always sufficient alone for diag-

nosis; it should be interpreted together with antibody presence and clinical findings.

Anti-NMDAR encephalitis is a form of autoimmune encephalitis especially seen in young women and frequently associated with ovarian teratoma. In the comprehensive 2024 review by Alzghoul et al. [11], approximately 38% of anti-NMDAR encephalitis cases were reported to be associated with malignancies, the majority being ovarian teratomas. However, rare tumors such as small cell lung carcinoma, renal cell carcinoma, colorectal adenocarcinoma, and thyroid malignancies have also been reported in the literature. Therefore, the current approach is that malignancy screening should be performed in every patient diagnosed with anti-NMDAR encephalitis. Furthermore, even if no tumor is detected in the initial screening, periodic reassessment is recommended during follow-up due to the possibility of malignancy developing. In our case, ovarian teratoma was detected in the screenings performed, and this finding supported the diagnosis of paraneoplastic anti-NMDAR encephalitis. The presence of neural antigens in teratoma tissue suggests that these tumors may trigger autoantibody production, leading to the onset of the disease.

In our patient diagnosed with anti-NMDAR encephalitis, treatment was initiated as early as possible, as recommended in the literature; combined immunotherapy with intravenous high-dose methylprednisolone and then IVIG was applied as first-line treatment. In the large series of Titulaer et al. [2] including 577 cases, significant clinical improvement was observed within the first four weeks in 53% of patients who received first-line treatment, and 97% of these patients achieved complete or near-complete recovery at the end of 24 months. The study also emphasized that early initiation of treatment and absence of need for intensive care were strongly associated with good prognosis. In our case, similarly, treatment was initiated rapidly, and within the first weeks, schizophreniform findings disappeared, amnesic symptoms decreased, and cognitive response speed significantly increased. Since clinical improvement began early and remained stable, there was no need for second-line immunotherapies. In the Taiwan-based study by Kong et al. [12], in patients who did not respond to first-line treatment, rituximab and/or cyclophosphamide were used as second-line, and good functional outcomes were obtained in 71.4% of this group. In line with these findings, second-line therapies stand out as effective options that should be considered early when necessary. In our patient, maintenance therapy was not initiated according to the current clinical condition; however, considering the 12% two-year relapse risk reported in the literature, a close clinical follow-up process was planned. This is consistent with the current literature emphasizing that treatment strategies should be shaped according to the individual characteristics of each patient.

Although anti-NMDAR encephalitis usually progresses with severe clinical symptoms, with early diagnosis and appropriate treatment, a largely good prognosis can be achieved. In the review published by Wang and Xiao [13] in 2020, it was emphasized that early initiation of immunotherapy had a decisive effect on prognosis and that most patients who responded to treatment in time achieved functional recovery in the long term. Although EEG findings, especially patterns such as Extreme Delta Brush (EDB), are seen in severe cases and may indicate poor prognosis, the prognostic value of EDB is controversial in some studies. In the same study, factors such as autonomic dysfunction, consciousness disorders, and need for intensive care were reported to be associated with poor prognosis. On the other hand, movement disorders and epileptic seizures may regress after immunotherapy and are not directly related to long-term prognosis. In addition, if persistent cognitive and psychiatric symptoms continue despite treatment, the rehabilitation process of patients may be prolonged, and therefore, the implementation of aggressive treatment and multidisciplinary follow-up strategies in the early period is of great importance.

All these data reveal the necessity of a multidisciplinary and individualized approach in the diagnosis, treatment, and follow-up processes of anti-NMDAR encephalitis. Careful evaluation of clinical, radiological, and laboratory findings emphasized in the literature; initiation of treatment at the earliest possible period; and monitoring patients according to clinical response and updating the treatment plan if necessary are of great importance in reducing both mortality and long-term sequelae. In our case, diagnosis was made in the light of clinical, EEG, and CSF findings; with immunotherapy started rapidly, early clinical improvement was achieved, and a stable course was obtained without the need for intensive care. In line with the current literature, the absence of need for second-line and maintenance therapy in our patient supports the favorable prognosis; however, considering the risk of relapse, the necessity of long-term follow-up continues. This approach shows that autoimmune encephalitides are shaped not only by immune therapy but also by early awareness and dynamic clinical management.

Conclusion

Anti-NMDAR encephalitis is a neuroimmune disease that emerges with sudden psychiatric symptoms, cognitive changes, and motor symptoms in young adults, in which diagnosis and treatment are a race against time. Since its clinical course often mimics psychotic disorders, this possibility should be considered especially in cases resistant to treatment, and early neurological evaluation should be planned. EEG, CSF analysis, and antineuronal antibody tests are guiding in the diagnostic process, while ruling out underlying malignancies is also an integral part of the treatment process. The treatment approach should proceed stepwise; with early high-dose corticosteroid and IVIG therapy, significant clinical improvement can be achieved in most patients. If necessary, treatment can be reinforced with second-line agents such as rituximab or cyclophosphamide. In conclusion, an early diagnosis and appropriate immune treatment process conducted with multidisciplinary collaboration play a critical role both in accelerating short-term clinical recovery and in preventing long-term sequelae.

Declarations

Ethics statement: The case report was conducted in accordance with the principles of the Declaration of Helsinki.

Consent: Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Conflict of interest: The authors declare that there are no conflicts of interest related to this case report.

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