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CASE REPORT

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Anti N-Methyl-D-Aspartate (NMDA) receptor encephalitis: from psychosis to cognitive impairment

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Abstract

In this study, while presenting a clinical case with early psychiatric manifestations, we emphasized the need to pay attention to neurological diagnoses such as Anti N-Methyl-D-Aspartate Receptor (NMDAR) encephalitis at the time of manifestation of these common symptoms.

KEYWORDS

anti N-Methyl-D-aspartate receptor encephalitis, cognitive impairment, neuroleptic malignant syndrome, psychosis

1 | INTRODUCTION

N-Methyl-D-Aspartate Receptor (NMDAR) is glutamate-gated ion channel that is associated with normal brain function.[1] N-Methyl-D-Aspartate Receptor play an important role in cognition and behavior. NMDAR blocking agents may cause manifestations such as psychosis.[2] In recent years, the role of anti-NMDAR antibodies in the development of psychiatric symptoms has been emphasized.[3] Anti-NMDAR autoimmune encephalitis is a relatively new neuropsychiatric disease that has been described in the last two decades.[4] Characteristics such as psychosis, seizures, abnormal movements, coma, and dysautonomia are manifestations of this disorder.[5] So that up to two thirds of these patients are first referred to psychiatric centers.[6] Cognitive deficits such as working memory deficits have also been suggested as long-lasting consequences of the disease.[7] In this study, while presenting a clinical case with early psychiatric manifestations, we point out the need to pay attention to rare neurological diagnoses in the presence of patients with common psychiatric manifestations.

2 | CASE HISTORY

The patient was a 14-year-old girl who suddenly became delusional and talked irrelevantly. She became pessimistic about those around her and considered them her enemies. She mentioned that her mother was her enemy and that she intended to destroy her. She also said that the neighbors intended to harm her. In a short time, she had a severe reduction in contact with others and a decrease in personal hygiene. A few days later, she was transported to the general hospital following physical aggression and breaking windows. In the hospital, she was sedated with medication due to the severity of her aggression. There, she received various specialized consultations. Various services, including neurology, infectious diseases, internal medicine, and emergency medicine, discharged the patient from their services and asked for psychiatric consultation. Due to the fact that the patient's psychiatric manifestations could not be justified by his clinical condition, the patient was referred to a reference hospital for further evaluation of neurological issues. During psychiatric and neurological diagnostic evaluation, while receiving some doses of the injectable haloperidol/biperiden during a week in the emergency room at the time of the initial assessment, she developed fever (her body temperature rose up 39°C) and became in a stupor state and disconnected from the environment in the referral hospital. She developed muscle rigidity during the assessment. At that time, in the laboratory tests, the CPK was equal to 4000 U/L. Also, in order to find the possible source of infection as a cause of fever, peripheral blood smear, urine analysis, blood and urine culture, and chest X-ray were performed that all the results were negative. According to the symptoms, she was diagnosed with neuroleptic malignant syndrome (NMS). Subsequently, the use of neuroleptic drugs was discontinued and she was treated with bromocriptine (2.5 mg twice a day for up to seven days) and other clinical supportive care measures for the treatment of NMS.

Also, in the initial diagnostic evaluations, in the first hospital, the cerebrospinal fluid analysis was reported to be normal. Later, herpes simplex virus (HSV) PCR in CSF was reported negative. In addition, brain MRI with contrast was reported to be normal. Also, in the referral hospital, tests related to vasculitis disorders, such as systemic lupus erythematosus (SLE), were normal as well. Other tests for chronic infections such as tuberculosis, brucellosis, and neurosyphilis (PPD, Wright, Coombs Wright, and VDRL tests) were reported to be normal. The patient did not have a history of recent travel, but all necessary measures were taken to investigate related tropical infections with the opinion and advice of an infectious disease specialist. In the diagnostic evaluations, mitochondrial disorders were evaluated in the laboratory tests (blood lactate and pyruvate and their ratio) which was reported as normal.

Also, the patient underwent neurological examination. There was no papilloedema. The pupil reflex was normal, and the eye movements seemed normal despite the patient's lack of proper cooperation. In the examination of the limbs, despite the lack of proper cooperation, based on the observation of the patient's movements, there was no paralysis and deep tendon reflexes (DTR) related to the limbs were 2+ and symmetric and plantar reflex was normal (down). At this stage, pain, temperature or deep touch sensory examinations were not possible due to the patient's condition. We also occasionally observed oromandibular dyskinesia and dystonic condition in the patient's left hand.

With the initial treatment of NMS, there was a relative improvement in the patient in terms of clinical condition. She recovered from fever and tachycardia, and her laboratory tests returned to normal and she was in stable condition in terms of vital signs.

Subsequently, after an initial recovery and while continuing hospitalization in the second hospital, she again experienced a 40-degree fever and underwent diagnostic evaluation for infectious problems. In routine workup, Complete Blood Count (CBC), Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), Blood Urea Nitrogen (BUN), creatinine (Cr), and routine electrolytes were normal. In addition to symptomatic treatment to control fever, she was treated with empirical antibiotics (imipenem 500mg /IV/two times daily plus vancomycine 750 mg/IV/two times daily). Related diagnostic evaluations including peripheral blood smear, urine analysis, blood and urine culture, chest X-ray, and lumbar puncture were negative. It was while there was no clinical response to antibiotic therapy. Due to nonresponse to any antibiotic treatment with sufficient duration and dosage, this treatment was discontinued by the consulted infectious disease specialist.

According to the patient's clinical manifestations, one of the initial probable diagnoses for the patient in the referral hospital was issues related to autoimmune encephalopathies, for which blood tests (panels—Hu. Yo, VC2. Ri, Ma2, Amphiphysin, NMDA receptor, Caspr2, and AMPA receptor) were requested for the patient. During the control of the patient's clinical condition, the answers of the requested panels related to the patient were prepared, which reported positive results in terms of anti-NMDAR antibodies in blood. Based on this and due to the lack of any clinical response of the patient to antibiotic treatments and other care measures and medication side effects caused by antipsychotics without a specific improvement in the patient's psychiatric condition, the initial diagnosis of autoimmune encephalitis was made for the patient. According to anti-NMDAR Ab positive, the patient was treated with corticosteroids. Treatment was started with a daily intravenous of 1000 mg methylprednisolone for 5 days and then continued with oral prednisolone 50 mg/day and gradually reduced and discontinued over a

period of one month. However, in the meantime, the patient's behavioral symptoms and agitation were controlled using sodium valproate at a daily dose of 500 mg and a low dose of olanzapine at a dose of one quarter to half a 5 mg tablet daily. Also, regular clinical examinations and related laboratory tests were performed regularly to potential risk assessment of NMS recurrence. Tumor workup was negative for teratoma and other tumors.

Following the preparation of the anti-NMDAR Ab test result and the onset of corticosteroids, the clinical response was clear and rapid. The patient's fever went down, and she recovered from delirious states. However, she still did not establish effective verbal communication. Gradually, the patient regained the ability to eat normally and was able to grasp the spoon while eating and began to write in broken lines. Also, she began talking to family and acquaintances, but generally did not communicate well with the medical and nursing team.

At the time of discharge (after twenty-two days of hospitalization and one week after starting corticosteroid treatment), the psychotic symptoms had marked improvement and orientation was complete, but short-term memory (immediate and delayed recall), sustained attention, verbal fluency, and executive function were abnormal, using bedside mental state screening tests including mini-mental state examination test (MMSE), trail-making tests A and B and clock drawing test. Reading was normal but writing was partially disturbed. One month after discharge, she underwent a follow-up visit by a psychiatrist and a neurologist. The patient's condition was under control in terms of psychiatric issues. She had a good relationship with those around him and was not worried about being harmed by them. Her sleep and appetite were also good. Applying MMSE, verbal fluency, and trail-making tests, she still had some degrees of impairment in attention, verbal fluency, and executive function, with normal orientation and improvements in memory.

The patient was followed up two months after the first visit and then every 3 months. Nine months after her discharge, she was allowed to return to school. There, she had a good educational status. In addition, in terms of functional status, reading and writing performance, and verbal communication, she was in normal condition. However, she sometimes complained of fatigue and still had some degree of impaired concentration. Following her situation at school, her behavior compared to her peers was reported to be appropriate.

3 | DISCUSSION

Acute encephalitis is a rapidly progressive encephalopathy that usually manifests itself in less than 6 weeks and develops into inflammation.[8] There are various infectious and noninfectious causes for this condition. Noninfectious causes have become very important, especially in recent years. [9] In fact, due to the treatable nature of the immune encephalitis, much attention has been paid to this group in recent years.[10]

Lejuste et al noted the existence of several nonspecific psychiatric presentations in patients with a definitive diagnosis of Anti-NMDAR encephalitis. They stated that this diagnosis should be suspected if there are psychiatric manifestations, especially among women with some concomitant neurological symptoms.[11] This point has been emphasized in other case studies. Mohammad et al presented a clinical case, pointing out the vulnerability of this group of patients to classical neuroleptic medications and described these patients as susceptible to NMS due to the use of these drugs.[12] As can be seen, in our patient, a young woman with early psychiatric manifestations with some neurological symptoms such as impaired verbal communication and memory impairment needed to use antipsychotic medications, which led to the symptoms of NMS. A point that draws the need for more attention in similar situations to the possible diagnosis of Anti-NMDAR encephalitis.

NMDARs play important roles in excitatory neurotransmission and synaptic plasticity.[13] Tong et al, pointing to the various evidences obtained in recent years, introduced NMDARs as effective factors in the pathophysiology of neurological and psychiatric disorders.[14] They also reported a positive association between serum antibody levels and performance of verbal learning, working memory, and processing speed.

Based on the experiences gained so far, the treatment management of Anti-NMDAR encephalitis requires multidisciplinary measures that an important part of which is immunomodulation therapy. On the other hand, controlling behavior disturbance, psychosis and catatonia requires short-term and long-term psychiatric measures.[15] Xu et al, in their report on the treatment management of 220 patients with Anti-NMDAR encephalitis between 2011 and 2017, used first-line immunotherapy including glucocorticoids, IV immunoglobulin, or plasmapheresis alone or combined in 99.5% of cases and used second-line immunotherapy included rituximab, cyclophosphamide alone, or combined in 7.3% of cases. Long-term immunotherapy (for more than a year) was also used in 53.2% of patients.[16]

According to some reports, including the report of Liu et al, which assessed the outcome of seizures in patients with Anti-NMDAR encephalitis, seizure freedom usually occurs between 6 months and two years after the onset of symptoms and long-term use of antiepileptic drugs is usually not required.[17] Also, due to the common co-occurrence of ovarian teratoma, especially in women of reproductive age, with Anti-NMDAR encephalitis, attention to the aspects of surgical treatment is also part of the treatment management of this disease.[18]

Regarding the neuropsychological consequences of Anti-NMDAR encephalitis, Bruijn et al, following Dutch

children and adolescents with this disorder, reported that more than half of them returned to their previous school level. They reported ongoing problems such as fatigue and some cognitive deficits, including decreased concentration among a group of them.[19] Cainelli et al, referring to the limitations of information on the neuropsychological consequences of Anti-NMDAR encephalitis in children, reported long-term deficits in attention and executive function in about half of the children with Anti-NMDAR encephalitis under study.[20] Warren et al also cited cognitive symptoms as prominent symptoms during the patients' recovery.[21]

In our patient, 9 months after the illness, despite her return to the previous level of education, she still had occasional fatigue and some cognitive deficits (like some deficits in attention and executive function.). However, behavioral problems and other cognitive deficits showed marked improvement.

4 | CONCLUSIONS

Anti-NMDAR encephalitis has received serious attention from various aspects of diagnosis and treatment in recent years. The presence of overlap among psychiatric and neurological manifestations on the one hand and the response to immune regulatory therapies in the treatment of this disorder, emphasizes the need to pay attention to this disease and consider its possibility in cases of clinical suspicion. It seems necessary to pay attention to the long-term neuropsychological consequences of this disease, such as cognitive impairment and executive dysfunction, especially during the manifestation in childhood and adolescence. Further research in this area seems to be necessary.

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CONFLICT OF INTEREST

No conflicts of interest were declared.

AUTHOR CONTRIBUTIONS

Zahra Vahabi and Farnaz Etesam: involved in literature check, reviewed the manuscript, and edited the draft. **Atefeh Zandifar: involved in** literature check and wrote the initial draft of the manuscript. **Rahim Badrfam:** wrote the initial draft of the manuscript, reshaped it into this manuscript, final submission. **Fatemeh Alizadeh: involved in** literature check and reviewed the manuscript. All the authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the points made in this study are available at the request from the corresponding author.

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