A rare and challenging case of teratoma-associated Anti-NMDA receptor encephalitis

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ABSTRACT

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune disease that is often underdiagnosed due to the variability and complexity of its clinical presentation and is frequently misdiagnosed as viral encephalitis. It is sometimes characterized as a form of limbic encephalitis, which predominantly affects children and younger adults, with a female-to-male ratio of 4:1. The neurological disease is commonly associated with an underlying tumour. Its pathophysiology is attributed to the formation and binding of IgG1 and G3 antibodies to the NR1 subunit of the NMDA receptor in the central nervous system. We present the case of a 23-year-old woman with a one-year history of episodic mood lability and psychosis who sought medical attention at the emergency department due to the sudden onset of agitation, hallucinations, and altered mental status. Brain magnetic resonance imaging revealed findings suggesting possible encephalitis. A cerebrospinal fluid analysis was positive for NMDAR antibodies, and a transvaginal ultrasound later revealed a right ovarian mass, from which a biopsy confirmed a mature cystic teratoma. Despite surgical resection of the tumour and medical treatment, the patient experienced persistent cognitive impairment and gait dysfunction following three months of hospitalization in the neuroscience intensive care unit. In light of the complexity and aggressiveness of the clinical symptoms of NMDAR encephalitis, the disease has a relatively good prognosis, especially following surgical resection of the associated malignancy and medical treatment in most patients. On the other hand, a delay in diagnosis and treatment may result in long-term functional deficits and poorer clinical outcomes.

Keywords: Encephalitis, teratoma, hippocampal, anti-NMDAR, neurology

Introduction

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is a rare neurological disorder with an estimated incidence of only 1.5 cases per million persons.[1] However, despite the rarity, it is a treatable condition if identified and diagnosed early.[2] The pathophysiology is mediated by autoantibodies targeting the NMDA receptors in the central nervous system (CNS), causing synaptic disconnection.[2] It is the most common form of non-viral encephalitis and primarily affects children and young adults.[3]

Up to 45% of cases are associated with teratomas, which have been identified as a trigger of NMDAR encephalitis that can induce antibody production through molecular mimicry.[4] Symptoms are often confused with schizophrenia, substance-induced psychosis, and other psychiatric disorders.[2-4] The clinical presentation includes an initial viral-like prodrome followed by a range of symptoms from severe anxiety to psychosis, seizures, and autonomic dysfunction.[4,5]

This clinical picture is often complicated by cardiac arrhythmias, hyperthermia, respiratory distress, and altered mental status, necessitating intubation and admission to the neuroscience intensive care unit (NSICU).[6] Early surgical excision of the associated culprit tumour for patients with teratomas results in better clinical outcomes and fewer relapses.[7] A delay in diagnosis and treatment may lead to severe clinical outcomes and potentially death, with an estimated mortality rate ranging between 5 and 7%.[8] Physicians should maintain a high index of clinical suspicion in young female patients with symptoms resembling acute and aggressive psychiatric manifestations.

Here, we present the case of a 23-year-old female with a history of acute-on-chronic aggression and paranoia who was found to have teratoma-associated NMDAR encephalitis. This condition was complicated by neurocognitive and physical deficits after hospital recovery.

Case Report

A 23-year-old woman with a one-year history of episodic mood swings and psychosis presented to the emergency department (ED) with a sudden onset of aggression, auditory hallucinations, and confusion lasting for one hour. According to her friend, the patient was at the airport for a flight when she noticed an abrupt change in mental status and behaviour. Over the past year, she had been complaining of episodic fever and nausea before a sudden change in conduct. Since the onset of her symptoms, the patient has been under the care of a psychiatrist who diagnosed schizophrenia and was being treated with risperidone (2 mg/day).

Upon presentation to the ED, she was involuntarily placed in a psychiatric unit due to her aggression and delirium. The patient was febrile (100.6 °F) without focal neurological deficits or meningeal signs. A Montreal Cognitive Assessment score was 11 out of 30. All other vital parameters were within normal limits. Physical examination was deferred due to the patient's agitation and noncompliance. Laboratory test results revealed hypokalaemia (3.2 mEq/L), neutrophilia (78.6%), and a normal white cell count (10,500 WBCs/μL). All other values were within the reference range. During a random visit to the patient in the psychiatric hold unit, a non-responsive client was seen exhibiting lip-smacking and foaming by the mouth. A presumptive diagnosis of seizure was made, and the patient was administered lorazepam 4 mg intravenously. Upon witnessing the apparent seizure, a neurologist was consulted. The patient was subsequently intubated and admitted to the NSICU for further management.

Given the clinical presentation, a seizure protocol was implemented. A non-contrast computed tomography (CT) scan of the brain was unremarkable. Subsequent brain magnetic resonance imaging (MRI) showed

Table 1. CSF Findings

	Value	Normal range
Total protein	38.3 mg/dL	15-45 mg/dL
Glucose	55 mg/dL	40-70 mg/dL
Appearance	Colourless	Colourless
Opening pressure	17 cm H2O	0-20 cm H2O
WBCs	1/mm3	0-5/mm3
RBCs	Nil	Nil
Monocyte	9 %	0-30 %
Lymphocyte	99%	28-96%
IgG	3.4 mg/dL	0-6 mg/dL
VDRL	Negative	Negative
Cryptococcal antigen	Negative	Negative
Oligoclonal band	Negative	Negative
Oligoclonal band number	0	0-1
Albumin index	3.5	0-9
IgG index	0.59	<0.7
IgG/albumin ratio	0.19	<0.28
NMDA IgG antibody titre	1:50	<1:1
Meningitis/ encephalitis PCR panel	Negative	Negative

CSF, cerebrospinal fluid; WBCs, white blood cells; RBCs, red blood cells; IgG, immunoglobulin G; VDRL, venereal disease research laboratory; PCR, polymerase chain reaction

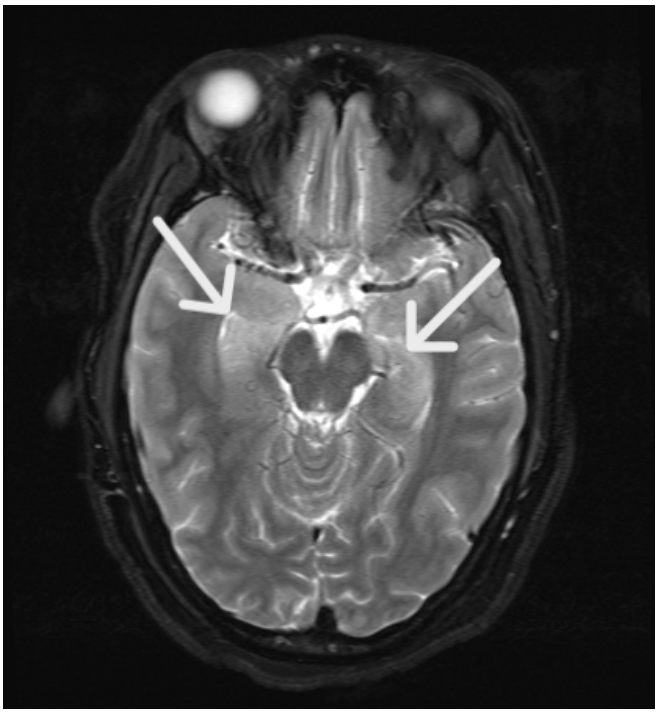

Figure 1. Axial brain MRI showing hyperintense T2-FLAIR signal within the bilateral hippocampi (white arrows), left greater than right.

bilateral hippocampal hyperintensities in attenuated fluid inversion recovery (T2-FLAIR) weighted sequence (Figure 1), and empiric intravenous (IV) acyclovir was started. Due to clinical suspicion of encephalitis, a transvaginal ultrasound was performed later and revealed a mass in the right ovary (Figure 2). Pathological results from a biopsy of the mass confirmed a mature cystic teratoma. An electroencephalogram (EEG) demonstrated extreme delta brush activity, and cerebrospinal fluid analysis (Table 1) from a lumbar puncture showed lymphocytic pleocytosis with normal glucose and protein levels. An autoimmune/paraneoplastic antibody panel revealed a positive anti-NR1 antibody consistent with a diagnosis of NMDAR encephalitis, prompting the cessation of acyclovir therapy.

The patient underwent surgical removal of the right ovarian mass via salpingo-oophorectomy and subsequently started medical treatment with IV methylprednisolone, IV immunoglobulin, rituximab infusions, and five sessions of plasmapheresis. Her NSICU course was then complicated by worsening neurological status, including ten episodes of clinical seizures requiring lacosamide 200 mg twice daily and levetiracetam 2 grams every 12 hours. The

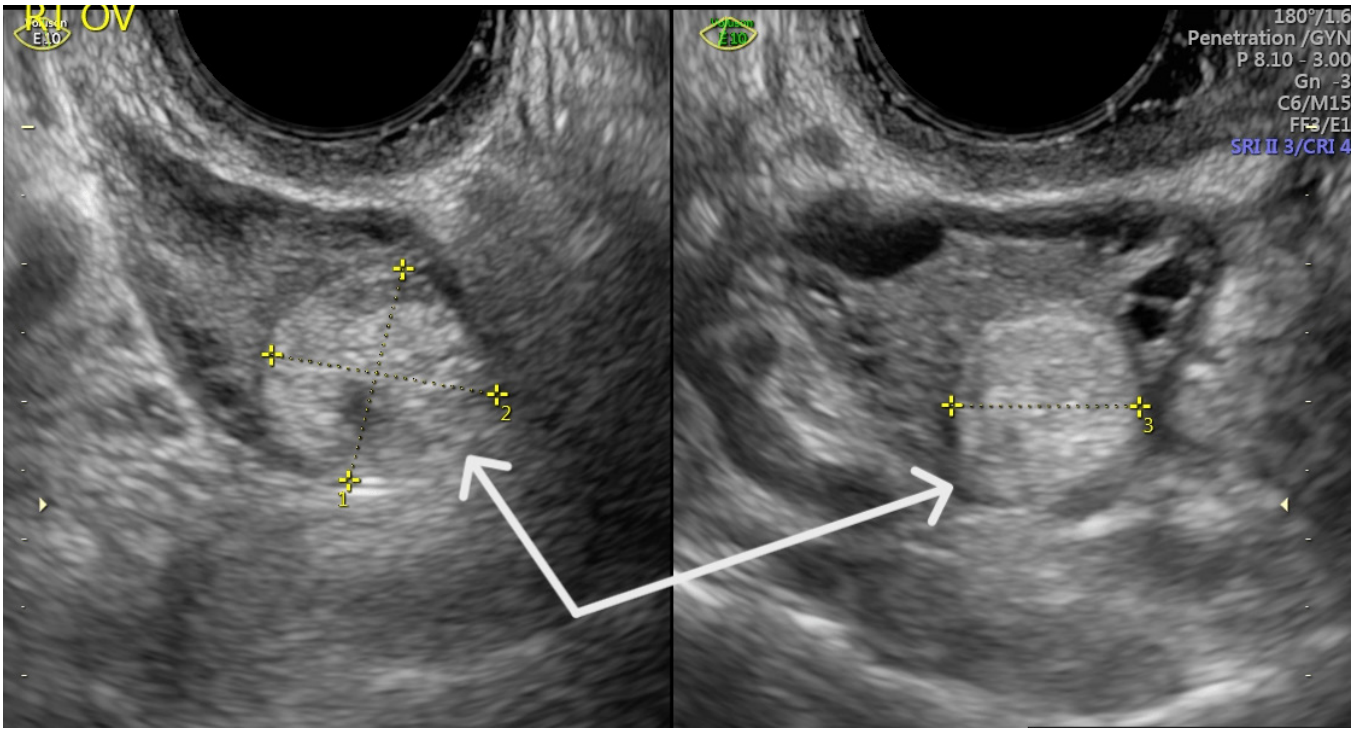

Figure 2. Transvaginal ultrasound showing a right ovarian echogenic complex mass (white arrows) that measures 1.7 x 1.6 x 1.3 cm.

patient exhibited paroxysmal sympathetic hyperactivity that required scheduled lorazepam, quetiapine, and baclofen. She also developed respiratory failure needing ventilator support through a tracheostomy and orofacial dyskinesia, which was confirmed to be non-epileptic during paralytic EEG trials. The accumulation of events in the NSICU necessitated an extended stay. After three months, the patient showed clinical improvement, and a neurology consultation was requested for continued inpatient care. Three days after the consultation for the management of mild alterations in mental status, the patient was discharged with a multidisciplinary approach to care, which required regular two-week follow-ups at the neurology clinic and physical therapy.

At the two-week follow-up, she reported self-observed residual deficits, including difficulty concentrating on everyday tasks, poor memory, increased fatigue, generalized weakness, and difficulty with ambulation. A Mini-Mental State Examination (MMSE)[9] was subsequently performed, yielding a result of 21/30, indicative of mild cognitive impairment (MCI). The patient continued to follow up at our clinic and at the two-year interval since her diagnosis, the patient continued to experience cognitive impairment (MMSE = 23/30), along with fatigability, gait dysfunction, and poor memory. These persistent symptoms have resulted in a decreased quality of life, difficulties in academic and occupational achievements, and social withdrawal.

Discussion

NMDAR encephalitis, although rare, is the most common form of autoimmune encephalitis.[5,7-9] It is characterized by a cluster of neurological symptoms with a positive antibody in the CSF that can lead to debilitating long-term consequences if not diagnosed and treated early.[7-10] Although commonly associated with ovarian teratomas, NMDAR encephalitis has also been reported in patients without paraneoplastic association.[11] Differential diagnosis for the disease includes schizophrenia, viral encephalitis, serotonin syndrome, systemic lupus erythematosus cerebritis, toxic ingestion, hashitoxicosis, and other forms of limbic encephalitis.[12] Despite the possibility of the many diagnostic overlaps, the autoimmune encephalitis, with reasonable clinical suspicion, is easily diagnosed and differentiated from the others by detecting NMDAR autoantibodies in the serum or CSF.[10-12]

The autoimmune encephalitis can result in long-term sequelae, including neurocognitive deficits that may lead to psychosocial dysfunction.[10] Early diagnosis and prompt management are crucial in preventing the development of these inadequacies and may improve clinical outcomes, especially in patients with associated teratoma.[13]

In a recent case study, which reported the clinical outcomes of seizures, cognitive impairment, and relapses as measured by the Modified Rankin Scale (mRS) in three patients with a delay in the diagnosis of NMDAR encephalitis, it was found that the patient diagnosed 13 months after the initial symptoms showed no relapses, seizure activity, or cognitive impairment after hospitalization (mRS = 0).[14,15] The patient with the longest delay in diagnosis, eight years after the initial symptoms, exhibited focal seizures and MCI post-hospitalization (mRS = 1). In contrast, the patient with the shortest delay in diagnosis showed a better clinical prognosis. Another study conducted in Western China demonstrated favourable long-term functional outcomes and fewer relapses in patients who received timely immunotherapy and prompt diagnosis.[16]

In our case, the patient was misdiagnosed with schizophrenia, which ultimately delayed the correct diagnosis for a year. After a complex hospital course lasting 12.5 weeks, with frequent neurology clinic visits and physical therapy, the patient reported increased fatigue as well as difficulties with walking, memory, and concentration that have persisted for two years. Her father also reported the patient's inability to perform well in school and at work. The accumulation of these deficits has led to social withdrawal and a low quality of life.

In cases of teratoma-associated anti-NMDAR encephalitis, treatment, especially after surgical removal of the tumour, usually leads to a favourable prognosis.[7,13] Therefore, early recognition is crucial for the best long-term outcomes and the recovery of these patients after hospitalization. We recommend that low-income countries such as South Sudan consider investing in more diagnostic tools, including CT scans and MRIs, to avoid traveling abroad for this and more common diagnoses to be made. These investments can shorten the time needed to treat such complex and other diseases and improve the overall prognosis of patients with early diagnosis.

Conclusion

NMDAR encephalitis remains underdiagnosed despite the growing body of literature. This phenomenon occurs due to low clinician suspicion and the complexity of the disease presentation. As a consequence of delayed diagnosis and management, patients may experience undesirable

functional deficits and poorer clinical outcomes compared to those who receive prompt treatment. Therefore, we recommend screening all younger patients, especially females, for anti-NMDAR encephalitis if they present with neuropsychiatric symptoms.

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Authors' Contributions: KE wrote the article, analysed, and interpreted the patient data. DL collected the imaging and proofread the paper. Both authors read and approved the final manuscript.

Images: All from the hospital system

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