

CASE REPORT



A case report: anti-NMDA receptor encephalitis

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ABSTRACT

N-methyl-D-aspartate receptor (NMDAR) antibody encephalitis is a potentially fatal autoimmune syndrome in which there is antibody production against the NMDAR causing profound dysregulation of neurotransmission. The syndrome is frequently associated with ovarian teratomas and women are disproportionately affected. Patients most often present with a constellation of neuropsychiatric signs and symptoms, including memory loss, hallucinations, and decreased level of consciousness. This condition is lethal if left untreated. Immunotherapy and surgical resection of the culprit malignancy often results in the rapid resolution of symptoms.

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1. Case

A 26-year-old female without significant past medical history presented to the Emergency Department complaining of persistent nausea and vomiting, as well as multiple pre-syncope episodes. Her family also noted that she had been suffering increasing memory loss over the previous few weeks, often not recognizing members of her own family. There was no reported history of substance use. In the emergency department, the patient's mental status rapidly worsened. She developed expressive aphasia with nonsensical speech, followed by decreased consciousness. She was admitted to the intensive care unit for close neurologic monitoring and further workup. Given concern for viral encephalitis, acyclovir was started empirically.

Vital signs were within normal limits. Neurological exam was significant for expressive aphasia, inability to follow commands, and orientation to self only. Babinski response was present bilaterally. There was intermittent ophthalmoplegia and hyperreflexia was found in both lower and upper extremities. Laboratory studies and urine toxicology were unrevealing of any profound metabolic or toxic disturbance.

Imaging including CT and MRI/MRA of the brain revealed no intracranial or neurovascular lesions ruling out vascular or mass lesions as causes of her encephalopathy. Lumbar puncture and CSF analysis revealed a lymphocytic pleocytosis, but no organisms on gram stain. EEG was significant for mild encephalopathy with no focal lateralizing or epileptiform discharges. HIV, herpes, and syphilis screens were also negative. Acyclovir was discontinued. At this juncture, the possibility of an autoimmune phenomenon was entertained as all objective data were unrevealing.

In order to assess for paraneoplastic syndrome, tumor markers, and CSF autoimmune antibody serologies were sent, and the patient underwent CT scan of the chest, abdomen, and pelvis. The latter revealed an 8 cm × 4 cm cystic lesion, suspected to be a teratoma, within the right ovary (Figure 1).

She was started on intravenous immunoglobulin (IVIG) for presumed anti-NMDA receptor encephalitis and experienced minimal improvement in neurologic status by day 2 of therapy. She then underwent successful laparoscopic resection of the ovarian mass. Pathology confirmed a poorly differentiated teratoma (Figure 2). The patient's mental status drastically improved by postoperative day 1, and completely normalized by postoperative day 2. She completed a 5-day course of IVIG and was discharged home. Although CSF and serum assays for a wide array of autoimmune antibodies, including anti-*N*-methyl-D-aspartate receptor (NMDAR), anti-amphiphysin, and anti-voltage-gated potassium channel-complex (VGKC), were negative, given the characteristic neuropsychiatric dysfunction and rapid resolution of symptoms in a young lady with an underlying teratoma, anti-NMDAR encephalitis was the final diagnosis.

2. Etiology

Anti-NMDAR encephalitis is a relatively rare diagnosis with just a few hundred cases reported in the literature but its true prevalence, especially in individuals with purely psychiatric manifestations, is yet to be determined as a large majority present to a psychiatrist first [1].

NMDARs play a central role in synaptic transmission helping to modulate human memory, cognition,

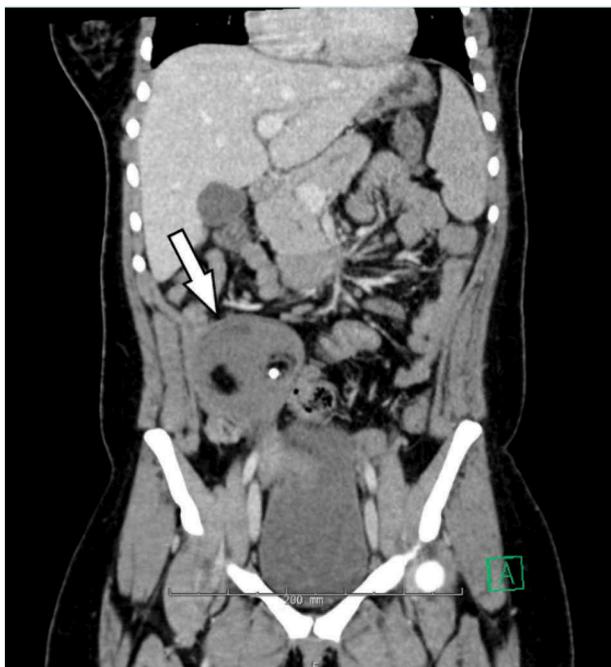


Figure 1. 8 cm × 4 cm right ovarian mass suggestive of teratoma with hyperdense tooth visible (white arrow).

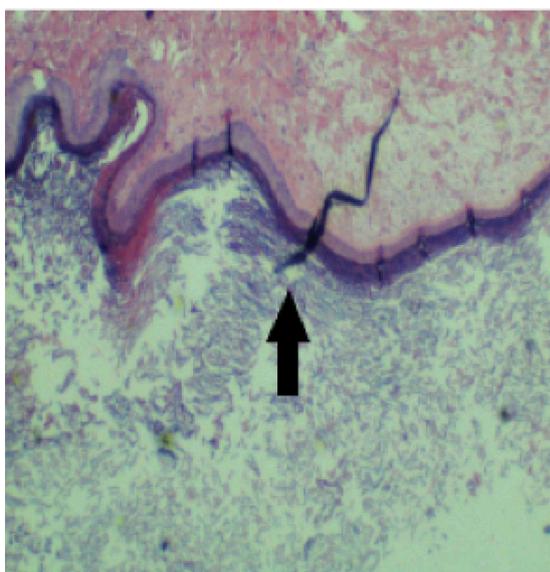


Figure 2. Histopathology of teratoma illustrating fine hair protrusions (black arrow).

and learning and have been implicated in neural plasticity [2]. Activity of the NMDAR is affected not only by several exogenous substances, including PCP, ketamine, and ethanol, but also endogenous brain-immune interactions that can have tremendous clinical consequence.

The structure of the NMDAR is composed primarily of ubiquitous NR1 and NR2 subunits [2]. The antibodies in anti-NMDAR encephalitis are directed against an epitope found on the NR1 subunit primarily in the frontotemporal and hippocampal regions likely owing to the high density of these receptors in these regions [3,4]. This geographic pattern helps

explain common psychiatric signs and symptoms seen in this disease, including decreased cognition and personality changes.

Frequently, anti-NMDAR antibody formation has been associated with the presence of certain malignancies, but the initiating event triggering antibody production has yet to be identified. In the literature, ovarian teratomas accounted for 94% of all neoplasms responsible for the formation of anti-NMDAR encephalitis, with clinical improvement after tumor removal [5].

3. Diagnosis

The psychiatric manifestation of anti-NMDAR encephalitis syndrome is preceded by a nonspecific prodromal stage that can include headaches, low-grade fevers, diarrhea, or upper respiratory infection symptoms [4,6]. This is followed by prominent psychiatric changes like anxiety, paranoia, mania, hyper-religiosity, delusions, and hallucinations that initiate within 2 weeks. Short-term memory loss evaluation is hindered by accompanying language deficits from echolalia to mutism [5,6].

Neuromotor dysfunction with ataxia and choreiform movements and autonomic instability may also occur as the disease progresses. Complex seizures present relatively early but overlap between epileptiform movements and orofacial dyskinesias may present a clinical dilemma in proper identification. Furthermore, overlap of the syndromic symptoms with that of schizophrenia often leads to misdiagnosis and inappropriate treatments [5].

Brain MRI has been reportedly negative in up to 50–70% of patients [4,6]. When irregularities are seen, it is often subtle T2 or FLAIR sequence hyperintensities in the hippocampal, frontobasal, insular, or basal ganglia regions [6]. EEG may show abnormal slowing, but is nonspecific in 90% of patients and there is no role for brain biopsy in diagnosis [7].

Current diagnosis is based upon finding anti-NMDAR antibodies in the CSF or serum. CSF studies show lymphocytic pleocytosis and normal to mild elevation of protein. Oligoclonal bands may be present in 60% of patients [6]. Although there is controversy between testing for serum or CSF antibody titers, CSF titers generally appear to correlate with disease activity [4,5]. The CSF antibody has been found to be more sensitive but there are still some explanations for why one might find a falsely negative result. This may include smaller quantities of antibodies produced, antigen denaturation during tissue-based immunofixation and variability between human and mouse epitopes used in analysis. In our patient, serum titers were negative as were CSF antibody titers, which is atypical, but given her characteristic neuropsychiatric dysfunction with rapid symptom resolution after ovarian teratoma removal,

a presumptive diagnosis of anti-NMDAR encephalitis fit the bill.

4. Treatment

Immunomodulation and neoplasm removal targeting both symptomatic and causal factors are mainstays of treatment [4]. Immunotherapy such as with steroids, plasmapheresis and IVIG helps reduce antibody titers. Tumor removal in those with identifiable lesions leads to rapid clinical improvement. Second-line therapy consists of Rituximab or cyclophosphamide [4,5]. Benzodiazepines and antipsychotics round out the pharmacotherapies employed in the treatment of seizures, psychosis and behavioral dysfunction.

Recovery from illness following treatment is generally good with up to 75% of patients achieving full recovery or left with minimal residual deficits [4]. Severe disability may result in the remaining 25% with mortality rates of 4–7%. Reported relapse rates range between 12% and 24%, more often in those without teratoma [4]. The largest cohort study to date of 577 patients reported 53% recovery based on the modified Rankin Scale, and 97% of those who improved had good outcome at 24 months [8].

Prognosis is guarded and disease can often be lethal with irreversible damage to cortical regions such as the hippocampus in those who experience delay in identification and treatment. Independent predictors of good clinical outcome include time to identification and treatment, admission not requiring ICU care, and lesser initial symptomatology [4].

5. Conclusion

Anti-NMDAR encephalitis is an increasingly recognized, potentially lethal syndrome of psychiatric and neuromotor dysfunction in patients, often younger in age, who have an underlying neoplasm. Diagnosis is challenging and misdiagnosis is frequent given overlap of symptoms with multiple other infectious, neuroanatomic and psychiatric disease processes, and nonspecific or unremarkable findings on lumbar puncture, EEG, and neuroimaging. Early identification, immunotherapy, and malignancy work-up are the mainstays of management. Delays in these steps are dangerous as approximately 1 in 4 patients end up with debilitating neuropsychiatric dysfunction or death, even with appropriate treatment.

Clinicians, at the very least, should entertain this diagnosis in patients with acute neuropsychiatric deterioration, CSF with lymphocytic pleiocytosis, and otherwise unrevealing cranial imaging and metabolic testing.

Author's contribution

P. Bhat completed the background research, drafted and edited the manuscript. C. Sittabalam edited and completed the manuscript.

Disclosure statement

No potential conflict of interest was reported by the authors.

Informed consent

Informed consent was obtained from the patient for educational use of the below mentioned data and no personal patient information has been disclosed.

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