American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2021; 22: e933240
DOI: 10.12659/AJCR.933240

Received: 2021.05.21
Accepted: 2021.09.11
Available online: 2021.09.17
Published: 2021.10.19

Anti-N-methyl-D-aspartate Receptor Encephalitis as a Paraneoplastic Presentation of Mature Ovarian Teratoma

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF Zachary A. Koenig
ABCDEF Joel B. Yednock
ABCDEF James Lewis Akers

West Virginia University School of Medicine, Morgantown, WV, USA

Corresponding Author: Zachary A. Koenig, e-mail: Zakoenig@mix.wvu.edu
Financial support: None declared
Conflict of interest: None declared

Patient: Female, 26-year-old
Final Diagnosis: Anti NMDA receptor encephalitis • familial adenomatous polyposis
Symptoms: Autonomic instability • catatonia • ovarian cyst • psychosis
Medication: —
Clinical Procedure: Ovariectomy
Specialty: General and Internal Medicine

Objective: Unusual clinical course

Background: Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is a potentially fatal form of autoimmune encephalitis that involves autoantibodies directed against the NR1 subunit of the receptor. This leads to dysregulation of neurotransmission and resultant psychotic and neuroanatomical symptoms. Anti-NMDAR encephalitis classically presents in women who have ovarian teratomas, but it also has been associated with a preceding herpes infection, testicular germ cell tumor, small cell lung cancer, and neuroblastoma.

Case Report: The present case report illustrates the course of severe anti-NMDAR encephalitis in a patient who had poor prognostic factors, including a high anti-NMDAR titer in cerebrospinal fluid and extreme delta brush electroencephalography pattern. In addition, it underscores the importance of a multidisciplinary approach when treating these patients.

Conclusions: Despite being the most common form of autoimmune encephalitis, anti-NMDAR encephalitis remains underrecognized in clinical settings because of discrepancies in patient presentations and their resulting hospital courses. These variations make it difficult to devise an appropriate immunotherapy regimen and plan for intensive care management. It has been estimated that 25% of patients with anti-NMDAR encephalitis experience permanent neuropsychiatric debilitation or death even when they receive mainstay treatment. Relapse is estimated to occur in 15% to 24% of patients and is more common in individuals who do not have underlying tumors. Nonetheless, approximately 75% of patients with anti-NMDAR encephalitis recover or have only mild sequelae.

Keywords: Anti-N-methyl-D-aspartate Receptor Encephalitis • Paraneoplastic Syndromes, Nervous System • Teratoma

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/933240

1503 — 3 15

This work is licensed under Creative Common Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

Background

Autoimmune encephalitis is a rare form of brain parenchymal inflammation that is associated with antibodies directed against intracellular or surface neuronal proteins found within the gray matter. The incidence of autoimmune encephalitis has increased from 0.4 in 100 000 to 1.2 in 100 000 individuals between 1995 and 2015. In fact, one population-based study found that the prevalences of autoimmune encephalitis (13.7 in 100 000) and infectious encephalitis (11.6 in 100 000) were not statistically significantly different [1]. Despite this, much more attention is paid to the infectious etiologies of encephalitis. Autoimmune encephalitis remains a novel disease, and there is rising recognition of it, which stems from increased testing for autoantibodies. However, diagnosis, treatment options, and medication escalation or termination remain controversial topics among interdisciplinary specialists.

One of the most common causes of autoimmune encephalitis is anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis. Nonetheless, it is still quite rare, with an estimated prevalence of 1 in 1.5 million people per year [2]. The median age at diagnosis is 21 years and it affects women more frequently than men, as is the case with other autoimmune diseases. There have been reports describing anti-NMDAR encephalitis in infants as young as 2 months of age and patients as old as 85 years of age [3].

Although anti-NMDAR encephalitis originally was reported in a 2007 study, hundreds of case series have emerged over the past decade, facilitating precise documentation of its typical pathophysiologic course [4]. Rapid production of B-cell-derived immunoglobulins is believed to underly the pathophysiology of anti-NMDAR encephalitis. These antibodies cause crosslinking and internalization of inhibitory NMDA receptors on post-synaptic neurons. This, in turn, leads to central neuronal hyperactivity via post-synaptic glutamate neurotransmission [5]. NMDA receptor expression within the central nervous system (CNS) is most concentrated in the hippocampus, brainstem, and neocortex [6].

Much of the difficulty in making the diagnosis of anti-NMDA receptor encephalitis is still due to the broad spectrum of clinical presentations. Following prodromal flu-like symptoms, anti-NMDA receptor encephalitis involves a psychiatric phase that consists of psychosis, hallucinations, or paranoia. Language disintegration such as echolalia, decreased verbal output, and mutism is common as well. As the disease progresses, there are alterations in sensorium, epileptic seizures, frank dysautonomia, oro-facial dyskinesias, and dissociative responses to stimuli [3,4,7].

Case Report

A previously healthy 26-year-old woman presented to a local rural medical center because she was unable to talk and was having suicidal ideation. Her medical history included a tubal ligation and familial adenomatous polyposis. Notably, she had no history of psychiatric illness. On examination in the Emergency Department, she had atypical psychosis, catatonic behavior, and decreased oral intake. She was admitted to the psychiatric unit and treated with Zyprexa and Ativan, without improvement.

The patient's family later told the medical center staff that several weeks before, she had developed a rash on her forehead and neck, which she thought was caused by a tick bite during a camping trip. The patient's Lyme disease titers were positive, and given her symptoms, workup was done for aseptic meningitis, nervous system Lyme disease, and psychogenic catatonia. Cerebrospinal fluid (CSF) analysis showed lymphocytic pleocytosis (130 leukocytes/µL), elevated protein (77 mg/dL), and normal glucose (58 mg/dL). However, the opening pressure was not noted. Initial brain computed tomography (CT) without contrast showed no acute intracranial processes.

The patient was treated empirically with acyclovir and ceftriaxone but did not improve and was transferred to a tertiary care facility for continued therapy. Her encephalopathy worsened and she became unable to talk to physicians other than simply repeating the word "yes." She had marked hypotension, with pressures as low as 87/50 mmHg. She also was unable to ambulate without assistance. She presented with active unpurposeful movements in both upper extremities but diffuse weakness in both lower extremities.

Eventually, the patient had to be intubated and mechanically ventilated due to worsening psychosis. Her family stated that she was experiencing monetary issues and a custody battle, which led to a mental breakdown. Initial electroencephalography (EEG) and magnetic resonance imaging (MRI) were unremarkable. A repeat CSF analysis showed an opening pressure of 22.5 mm H_2O, elevated protein (48 mg/dL), and decreased glucose (48 mg/dL) and was positive for oligoclonal bands. No microorganisms were present in the CSF.

As a result, paraneoplastic or autoimmune encephalitis was added to the patient's differential diagnoses. Initial laboratory testing revealed a low level of vitamin A (22.8 µg/dL), for which solumedrol was initiated. She was treated empirically with 5 days of i.v. immunoglobulin and prednisone (60 mg/d) as well as a proton pump inhibitor and trimethoprim/sulfamethoxazole for prophylaxis. Additional workup included a whole-body CT with i.v. contrast, which revealed a left

This work is licensed under Creative Common Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

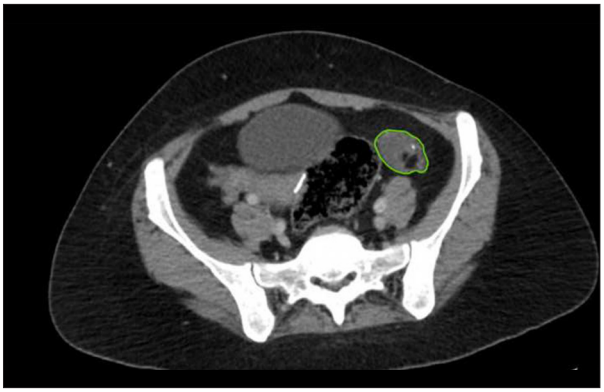

Figure 1. A dermoid cyst measuring approximately 3.2×2.5 cm is seen in the left ovary (marked in green).

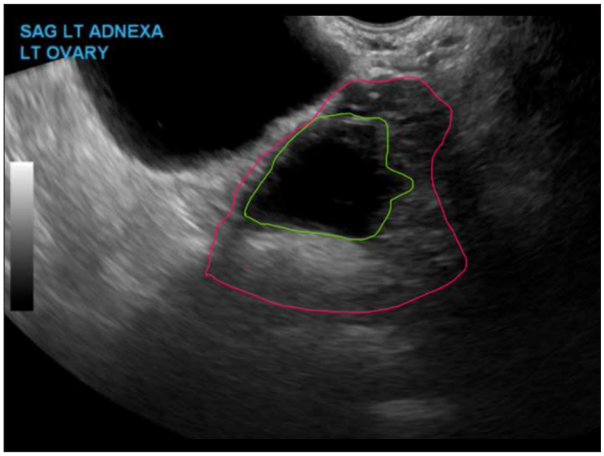

Figure 2. Computed tomography (CT) was concerning for a left ovarian dermoid cyst and sagittal ultrasonography of the left ovary corroborated those findings. The left ovary (marked in red) measured 4.4×4.3×2.6 cm. A cystic lesion (marked in green) measuring 2.6×3.4×3.5 cm was found within the ovary, corresponding to the dermoid cyst seen on the previous CT.

dermoid cyst measuring approximately 3.2×2.5 cm (**Figure 1**), a finding further corroborated by sagittal ultrasound of the left ovary (**Figure 2**).

The presence of the cyst prompted workup of the patient for anti-NMDAR encephalitis. In the ensuing days, she underwent left oophorectomy. Although there were no complications associated with the surgery, the patient's mental status did not improve after removal of the lesion. Pathology revealed a mature cystic teratoma. A repeat EEG showed no evidence of seizures but presence of abundant clusters of rhythmic delta slow waves (**Figure 3**). Several days later, a CSF paraneoplastic panel came back positive for NMDA-R antibodies at titers of 1: 32 (reference range, 1: 2).

The patient then was started on rituximab monotherapy (375 mg/m^2 once per week for a total of 4 weeks). She had progressive improvement with the rituximab therapy and was discharged after a 34-day hospital stay but did not come to any follow-up appointments.

Discussion

Immune-mediated encephalitis is subdivided into paraneoplastic and autoimmune subtypes. Paraneoplastic encephalitis invariably is related to an underlying tumor. Autoimmune encephalitis invariably involves autoantibodies, and thus can occur in the presence or absence of an underlying tumor [2]. We presented the case of a young woman with anti-NMDAR encephalitis that constituted both autoimmune and paraneoplastic subtypes because she was later found to have an underlying mature left ovarian teratoma.

The etiology and pathophysiology of teratoma-associated anti-NMDAR encephalitis remain largely unknown. To date, the strongest hypothesis is that there is ectopic expression of the NR1 receptor within the teratoma, which leads to B-cell generation of autoantibodies. These autoantibodies subsequently cross the blood-brain barrier via an unknown mechanism, but infection is believed to enhance the leakiness [8].

Within the CNS, the autoantibodies instigate a variety of physiological changes, depending on the systems affected. The effects on the dopaminergic, noradrenergic, and cholinergic systems are responsible for the autonomic instability seen in anti-NMDAR encephalitis. Inactivation of GABAergic neurons leads to the prototypical fronto-striatal syndrome and semi-rhythmic movements seen in anti-NMDAR encephalitis. Furthermore, there is a direct effect on the pontine-medullary respiratory network, leading to breathing dysfunction and hypoventilation [7-9].

Much of the workup of anti-NMDAR encephalitis is complicated by inability to communicate with the patient to obtain a thorough history. Physical examination frequently demonstrates autonomic instability, psychosis, dyskinesias, and language dysfunction [10]. The clinical situation is further complicated by the large overlap of these symptoms with those from other infectious, neurological, and psychiatric conditions.

Confirming the diagnosis of anti-NMDAR encephalitis often is a monotonous process. MRI findings often are absent in patients with the condition. EEG often shows slowing or epileptiform activity, which aids in excluding primary psychiatric disorders [11]. Although our patient showed EEG changes, this has low specificity in terms of making a diagnosis. For a definitive diagnosis, lumbar puncture is required because CSF antibodies against the NR1 subunit are invariably present when

This work is licensed under Creative Common Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

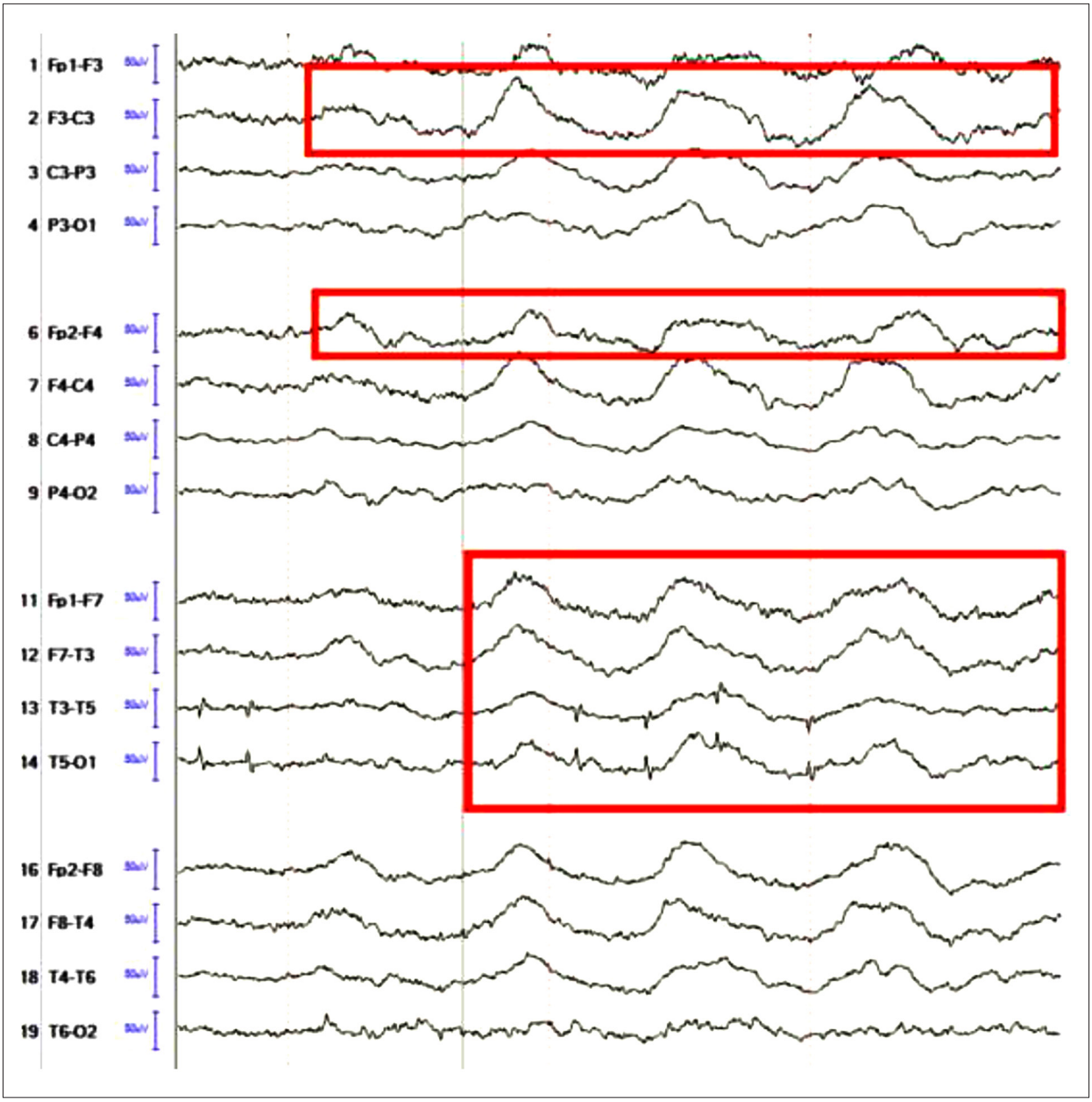

Figure 3. Tracings showing abundant runs of slowing rhythmic delta activity with superimposed beta activity. These clusters of rhythmic delta activity last up to 12 s, at 1.5 to 2 Hz.

symptoms occur. Further corroborating the diagnosis are oligoclonal bands, lymphocytic pleocytosis, and normal to mildly increased protein content, all of which were present in our patient. Testing serum alone is not recommended because it carries a high rate of both false-positive and false-negative results [12].

Teratoma-associated anti-NMDAR encephalitis initially should be treated with high-dose methylprednisolone, i.v. immunoglobulins, plasma exchange, and tumor resection. However, this treatment is estimated to benefit only 53% of patients after 4 weeks of follow-up [13-15]. Step-up treatment involves rituximab or cyclophosphamide [15]. One study demonstrated a marked decrease in relapse rate with the addition of second-line immunotherapy in comparison to only first-line immunotherapy [15]. If a patient has a good response to any treatments, further management involves supportive care and annual tumor surveillance. Our patient did not demonstrate a therapeutic response to first-line treatment but showed marked improvement after 28 days with a second-line treatment.

This work is licensed under Creative Common Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

Conclusions

Prompt diagnosis, removal of the paraneoplastic tumor, and concomitant immunotherapy resulted in a good prognosis for the patient in the present case. A delay in recognizing anti-NMDAR encephalitis has the potential to cause great harm. It should be considered in any young individual who develops new-onset changes in behavior, psychosis, dyskinesias, and variable signs of autonomic instability.

Acknowledgements

The authors thank Dr. Eric Seachrist and Dr. Ann Murray for assisting with analysis of the EEG.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

References:

1. Dubey D, Pittock SJ, Kelly CR, et al. Autoimmune encephalitis epidemiology and a comparison to infectious encephalitis. Ann Neurol. 2018;83:166-77
2. Dalmau J, Armangué T, Planagumà J, et al. An update on anti-NMDA receptor encephalitis for neurologists and psychiatrists: mechanisms and models. Lancet Neurol. 2019;18:1045-57
3. Liu C, Zhu J, Zheng X-Y, et al. Anti-N-methyl-D-aspartate receptor encephalitis: a severe, potentially reversible autoimmune encephalitis. Mediators Inflamm. 2017;2017;6361479
4. Dalmau J, Tüzün E, Wu H, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol. 2007;61:25-36
5. Ding H, Jian Z, Stary CM, et al. Molecular pathogenesis of anti-NMDAR encephalitis. BioMed Res Int. 2015;2015:643409
6. Zhang T, Duan Y, Ye J, et al. Brain MRI characteristics of patients with anti-N-methyl-D-aspartate receptor encephalitis and their associations with 2-year clinical outcome. Am J Neuroradiol. 2018;39(5):824-29
7. Qu X-P, Vidaurre J, Peng X-L, et al. Seizure characteristics, outcome, and risk of epilepsy in pediatric anti-N-methyl-D-aspartate receptor encephalitis. Pediatr Neurol. 2020;105:35-40
8. Dalmau J, Lancaster E, Martinez-Hernandez E, et al. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol. 2011;10:63-74
9. Wright S, Hacohen Y, Jacobson L, et al. N-methyl-D-aspartate receptor antibody-mediated neurological disease: Results of a UK-based surveillance study in children. Arch Dis Child. 2015;100:521-26
10. Maramattom BV, Jacob A. N-methyl D-aspartate receptor encephalitis: A new addition to the spectrum of autoimmune encephalitis. Ann Indian Acad Neurol. 2011, 14: 153-7. 10.4103/0972-2327.85872
11. Schmitt SE, Pargeon K, Frechette ES, et al. Extreme delta brush: A unique EEG pattern in adults with anti-NMDA receptor encephalitis. Neurology. 2012;79:1094-100
12. Gresa-Arribas N, Titulaer MJ, Torrents A, et al. Antibody titres at diagnosis and during follow-up of anti-NMDA receptor encephalitis: A retrospective study. Lancet Neurol. 2014;13:167-77
13. Seki M, Suzuki S, Iizuka T, et al. Neurological response to early removal of ovarian teratoma in anti-NMDAR encephalitis. J Neurol Neurosurg Psychiatry. 2008;79:324-26
14. Suppiej A, Nosadini M, Zuliani L, et al. Plasma exchange in pediatric anti-NMDAR encephalitis: A systematic review. Brain Dev. 2016;38:613-22
15. Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: An observational cohort study. Lancet Neurol. 2013;12:157-65

This work is licensed under Creative Common Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]