Case Reports in Women's Health 42 (2024) e00612

Contents lists available at ScienceDirect

Case Reports in Women's Health

journal homepage: www.elsevier.com/locate/crwh

# Anti-NMDA encephalitis secondary to an ovarian teratoma presenting as altered mental status in a 32-year-old woman: A case report

Grace Jarmoc [a,*], Candace Smith [a], Emma Finnerty [a], Nyia L. Noel [a,b], Ariel Marks [a,c]

[a] Chobanian and Avedisian School of Medicine, Boston University, 72 E. Concord Street, Boston, MA 02118, USA
[b] Boston Medical Center, Department of Obstetrics and Gynecology, 725 Albany St, Boston, MA 02118, USA
[c] Boston Medical Center, Department of Neurology, 725 Albany St, Boston, MA 02118, USA

ARTICLE INFO

*Keywords:*
Ovarian teratoma
Encephalitis
NMDA receptor encephalitis
Case report

ABSTRACT

NMDA-R encephalitis is an autoimmune encephalitis that is known to be associated with ovarian teratomas. Eighty to 100 % of patients initially present with neuropsychiatric symptoms. Early recognition and intervention are critical to management and prognosis. This case demonstrates non-specific presenting symptoms of NMDA-R encephalitis.

A 32-year-old woman presented to the emergency room with headache, nausea, vomiting, and photophobia. She was discharged with probable aseptic meningitis. Eight days later, she represented with delusional thought content, perseverative speech, and bizarre behavior. Cerebrospinal fluid studies showed elevated protein and mild pleocytosis. A computed tomography scan with contrast showed a 35-mm complex cystic lesion in the right adnexa, which was resected. Confirmatory pathology showed a mature cystic teratoma. Paraneoplastic panel later resulted positive for NMDA-R encephalitis. The patient was treated with methylprednisolone, IVIG, plasmapheresis, and rituximab. The clinical course was complicated by a hypersensitivity reaction to rituximab, non-convulsive status epilepticus requiring intubation, dysphagia requiring a PEG placement, a rectal ulcer causing acute blood loss anemia requiring multiple blood transfusions, bilateral hearing loss, and a left lung pneumothorax. The patient's mood, cognition, and motor function were favorably improving 19 months after diagnosis.

This case illustrates presenting signs of NMDA-R encephalitis in a young woman as headache and altered mental status followed by psychosis and epilepsy. Treatment should involve a multidisciplinary team and be individualized and escalated in patients with worsening clinical status refractory to first-line therapy. Further research is warranted to understand the optimal treatment strategy for this disease.

## 1. Introduction

Anti-*N*-methyl-D-aspartate (NMDA) encephalitis is a rare autoimmune encephalitis, whereby the body creates antibodies that attack the NMDA receptors in the brain. NMDA receptor dysfunction is known to be associated with deficits in memory, psychosis and excitotoxic brain injury [1]. This condition is more common in people assigned female sex at birth. Eighty to 100 % of patients initially present with neuropsychiatric symptoms and progression to orofacial dyskinesia, seizures, and encephalopathy [2–5]. Given its unusual presentation, it can be misdiagnosed. First-line therapy includes intravenous methylprednisolone, plus intravenous immunoglobulin, plasmapheresis, teratoma removal, or a combination of methods. Severe cases require escalation to second-line therapy within two weeks using rituximab or cyclophosphamide [2,6].

NMDA receptor encephalitis has been reported in females, males, and children [7]. While it is most often associated with an ovarian teratoma, a type of germ cell tumor, it has been reported in the absence of tumors [7]. Ovarian teratomas are the most common type of ovarian neoplasm. They can consist of ectodermal tissue, including epithelium and neural tissue, mesodermal tissue, inducing muscle, fat, bone, and cartilage, and endodermal tissue, including thyroid tissue and gastrointestinal epithelium [8,9].

## 2. Case Presentation

A 32-year-old woman with unremarkable past medical history presented to the emergency room with ten days of headache, nausea,

* Corresponding author at: 72 E. Concord St, Boston, MA 02118, USA.
*E-mail address:* Grace.Jarmoc@bmc.org (G. Jarmoc).

https://doi.org/10.1016/j.crwh.2024.e00612
Received 25 March 2024; Received in revised form 9 April 2024; Accepted 1 May 2024
Available online 3 May 2024

vomiting, and photophobia. A lumbar puncture was performed, with cerebrospinal fluid (CSF) studies significant for total nucleated cells 128/UL with a lymphocyte predominance. A magnetic resonance imaging (MRI) brain scan was without parenchymal or meningeal enhancement. She had a negative infectious work-up and was discharged with probable aseptic meningitis.

Eight days later, she represented with delusional thought content and agitation. She was febrile to 102.3 and tachycardic. Her physical exam was significant for disorganized thought process and perseverative speech. Her CBC and CMP were unremarkable. A toxicology screen for amphetamines, barbiturates, cocaine, opiates, and benzodiazepines was negative. She was admitted for further work-up.

### 2.1. Diagnostic assessment

A lumbar puncture was repeated on second presentation, with CSF studies showing elevated protein (90 MG/DL) and mild pleocytosis (protein, CSF, 90MG/DL, glucose, CSF, 45 MG/DL, total nucleated cells 50/UL, lymphocytes 88%). Her repeat meningitis/encephalitis panel was negative. A repeat MRI scan was unchanged from prior. The patient demonstrated worsening mental status and psychiatry was consulted due to a concern for catatonia. Additionally, she started long-term electroencephalogram (EEG) monitoring, which showed generalized rhythmic delta activity, which is nonspecific but is consistent with severe cerebral dysfunction. A computed tomography scan of the chest, abdomen and pelvis showed a 35-mm complex cystic lesion in the right adnexa, concerning for a dermoid cyst. A transvaginal ultrasound scan was done to further characterize the mass. The ultrasound demonstrated a complex cystic mass within the right ovary that measured 3.7 × 2.9 × 2.5 cm and contained an 8-mm internal calcification with an adjacent fatty component. An autoimmune encephalitis panel resulted after 10 days, confirming NMDA receptor encephalitis.

### 2.2. Therapeutic intervention

Two days after representation to the emergency department, the patient was started on intravenous methylprednisolone 1 g daily for 5 days and 2 g/kg IVIG over 2 days for empiric treatment of autoimmune encephalitis. The ovarian mass that was discovered was subsequently resected by obstetrics and gynecology. The surgical pathology resulted, showing a mature cystic teratoma containing mature neural tissue. The patient's mental status worsened, and she started second-line therapy, which included intravenous rituximab 1 g, two weeks, apart for CD20 suppression. She required ICU-level monitoring for hypersensitivity desensitization to rituximab and for up-titration of anti-seizure medications with concern for development of non-convulsive status epilepticus. During her hospitalization, her clinical status began to slowly improve.

### 2.3. Follow-up and outcomes

The patient was discharged home after a 68-day hospital stay to a rehabilitation facility. The hospital course was complicated by hypersensitivity reaction to rituximab, non-convulsive status epilepticus requiring intubation, dysphagia requiring a percutaneous endoscopic gastrostomy tube (PEG) placement, a rectal ulcer causing acute blood loss anemia requiring multiple blood transfusions, bilateral hearing loss, and left lung pneumothorax.

She received a third, fourth dose and fifth dose of intravenous rituximab 1 g at 6 months, 12 months, and 18 months after symptom onset. Her treatment plan involved completing 5 cycles of intravenous rituximab. Her hearing returned, and she had a normal evaluation from audiology on discharge. At the time of writing, she continued on antiepileptic drugs for epilepsy and her last definitive seizure was over one year ago. She was progressing with speech and language pathology, and physical therapy. She met her occupation therapy goals 15 months out from diagnosis and no longer required occupation therapy support. Her mood, cognition, and motor function were favorably improving 19 months out from diagnosis. She underwent neuropsychological testing and did not show any evidence of neuropsychological impairment other than limited psychomotor speed. The patient could perform instrumental activities of daily living independently. She continued follow-up with neurology and neuropsychiatry.

## 3. Discussion

Patients with NMDA receptor encephalitis associated with an ovarian teratoma often have more severe neurological symptoms at presentation [10]. Recovery occurred more frequently in patients with an ovarian teratoma that was removed versus patients who never had a teratoma [11].

In addition to teratoma removal, predictors for good outcomes after diagnosis with NMDA receptor encephalitis include early diagnosis, lower severity of initial symptoms, no ICU stay, and early escalation to second-line therapy [12–14]. The most robust study on NMDA receptor encephalitis by Titulaer et al. showed patient outcomes improved up to 18 months after symptom onset, with a 12% risk of relapse within 24 months [12]. Recovery is variable, ranging from full recovery in some patients to others with mild or marked sequelae from the disease. The majority of patients showed an improvement in functional status, with an improvement in neurological status seen in 81% of patients by 24 months [12]. A study by Dale et al. found earlier diagnosis and administration of rituximab, a second-line therapy given in more severe cases, are associated with better outcomes [13]. Additionally, recent case series demonstrated improved mental status after ovarian teratoma removal in 4 of 6 patients with confirmed NMDA receptor encephalitis [14].

It is important to consider the fertility goals of the patient prior to surgery to remove the teratoma. When possible, fertility-sparing surgery should be considered if it is in line with a patient's future reproductive goals. Patients have been able to become pregnant after teratoma removal and recovery [11]. Those who did not become pregnant did not experience changes in their menstrual cycles post-teratoma removal [11].

This case was subject to strengths and limitations. A strength of this case was early initiation of therapy for suspected autoimmune encephalitis, early multidisciplinary approach, and early diagnosis and removal of an ovarian teratoma. A limitation of this case report is that the patient had been followed only for 19 months after her diagnosis, and so her longer-term outcome is unknown.

This case demonstrates the non-specific presenting signs of NMDA receptor encephalitis as headache, nausea, and photophobia with progression to altered mental status, psychosis, and epilepsy. Treatment should be individualized and escalated in patients with worsening clinical status refractory to first-line therapy. This case highlights the need for a multidisciplinary approach for patients with this condition. While uncommon, NMDA receptor encephalitis should remain high on the differential of patients whose clinical progression is atypical. Further research is warranted to understand the optimal treatment strategy and long-term prognosis of this disease.

### Contributors

Grace Jarmoc contributed to conception of this case report, literature review, drafting and revision of this article, and clinical care.

Candace Smith contributed to literature review, drafting and revision of this article, and clinical care.

Emma Finnerty contributed to literature review, drafting, and revision of this article.

Nyia L. Noel contributed to clinical care and revision of this article.

Ariel Marks contributed to clinical care and revision of this article.

All authors approved the final manuscript.

*Funding*

This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

*Patient consent*

The patient was determined to have capacity to consent to this report and written consent was obtained.

*Provenance and peer review*

This article was not commissioned and was peer reviewed.

*Conflict of interest statement*

The authors declare that they have no conflict of interest regarding the publication of this case report.

## References

[1] J.W. Newcomer, N.B. Farber, J.W. Olney, NMDA receptor function, memory, and brain aging, Dialogues Clin. Neurosci. 2 (3) (2000) 219–232.
[2] C.E. Uy, S. Binks, S.R. Irani, Autoimmune encephalitis: clinical spectrum and management, Pract. Neurol. 21 (5) (2021) 412–423, https://doi.org/10.1136/practneurol-2020-002567.
[3] M.A. Ellul, G. Wood, H.V.D. Tooren, A. Easton, A. Babu, B.D. Michael, Update on the diagnosis and management of autoimmune encephalitis, Clin. Med. (Lond.) 20 (4) (2020) 389–392, https://doi.org/10.7861/clinmed.2020-0241.
[4] C. Bost, O. Pascual, J. Honnorat, Autoimmune encephalitis in psychiatric institutions: current perspectives, Neuropsychiatr. Dis. Treat. (12) (2016 Oct 27) 2775–2787, https://doi.org/10.2147/NDT.S82380. PMID: 27822050; PMCID: PMC5089825.
[5] P. Maat, E. de Graaff, N.M. van Beveren, et al., Psychiatric phenomena as initial manifestation of encephalitis by anti-NMDAR antibodies, Acta Neuropsychiatr. 25 (3) (2013) 128–136.
[6] A.P. Mann, E. Grebenciucova, R.V. Lukas, Anti-N-methyl-D-aspartate-receptor encephalitis: diagnosis, optimal management, and challenges, Ther. Clin. Risk Manag. 10 (2014) 517–525, https://doi.org/10.2147/TCRM.S61967.
[7] A. Venkatesan, K. Adatia, Anti-NMDA-receptor encephalitis: from bench to clinic, ACS Chem. Neurosci. 8 (12) (2017) 2586–2595, https://doi.org/10.1021/acschemneuro.7b00319.
[8] E.K. Outwater, E.S. Siegelman, J.L. Hunt, Ovarian teratomas: tumor types and imaging characteristics, RadioGraphics 21 (2) (2001) 475–490, https://doi.org/10.1148/radiographics.21.2.g01mr09475.
[9] L. Saba, S. Guerriero, R. Sulcis, B. Virgilio, G. Melis, G. Mallarini, Mature and immature ovarian teratomas: CT, US and MR imaging characteristics, Eur. J. Radiol. 72 (3) (2009) 454–463, https://doi.org/10.1016/j.ejrad.2008.07.044.
[10] Y. Dai, J. Zhang, H. Ren, X. Zhou, J. Chen, L. Cui, J. Lang, H. Guan, D. Sun, Surgical outcomes in patients with anti-N-methyl D-aspartate receptor encephalitis with ovarian teratoma, Am. J. Obstet. Gynecol. 221 (5) (2019) 485.e1–485.e10, https://doi.org/10.1016/j.ajog.2019.05.026.
[11] N.R. Florance, R.L. Davis, C. Lam, C. Szperka, L. Zhou, S. Ahmad, C.J. Campen, H. Moss, N. Peter, A.J. Gleichman, C.A. Glaser, D.R. Lynch, M.R. Rosenfeld, J. Dalmau, Anti–N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents, Ann. Neurol. 66 (1) (2009) 11–18, https://doi.org/10.1002/ana.21756.
[12] M.J. Titulaer, L. McCracken, I. Gabilondo, T. Armangué, C. Glaser, T. Iizuka, L. S. Honig, S.M. Benseler, I. Kawachi, E. Martinez-Hernandez, E. Aguilar, N. Gresa-Arribas, N. Ryan-Florance, A. Torrents, A. Saiz, M.R. Rosenfeld, R. Balice-Gordon, F. Graus, J. Dalmau, Treatment and prognostic factors for long-term outcome in patients with anti-N-methyl-D-aspartate (NMDA) receptor encephalitis: a cohort study, Lancet Neurol. 12 (2) (2013) 157–165, https://doi.org/10.1016/S1474-4422(12)70310-1.
[13] R.C. Dale, F. Brilot, L.V. Duffy, M. Twilt, A.T. Waldman, S. Narula, E. Muscal, K. Deiva, E. Andersen, M.R. Eyre, D. Eleftheriou, P.A. Brogan, R. Kneen, G. Alper, B. Anlar, E. Wassmer, K. Heineman, C. Hemingway, C.J. Riney, M. Lim, Utility and safety of rituximab in pediatric autoimmune and inflammatory CNS disease, Neurology 83 (2) (2014) 142–150, https://doi.org/10.1212/WNL.0000000000000570.
[14] M. Yu, S. Li, J. Cheng, L. Zhou, Z. Jiang, W. Di, Ovarian teratoma-associated anti-NMDAR encephalitis: a single-institute series of six patients from China, Arch. Gynecol. Obstet. 303 (5) (2021) 1283–1294, https://doi.org/10.1007/s00404-020-05861-3.