Case Report

Anti-N-methyl-D-aspartate receptor autoimmune encephalitis due to ovarian teratoma in a 17-year-old young woman: case report and review of the literature

Ennio Polilli[1,*], Anna D'Andreagiovanni[2], Pierluigi Tocco[3], Maurizio Rosati[4], Ylenia Della Rocca[1,5], Giancarlo Di Iorio[1], Maria Vittoria De Angelis[3], Giustino Parruti[6], Antonella Frattari[7]

[1]*Clinical Pathology Unit, Pescara General Hospital, Pescara, Italy*
[2]*Neuro-physiopathology Unit, Pescara General Hospital, Pescara, Italy*
[3]*Stroke Unit and Emergency Neurology, Pescara General Hospital, Pescara, Italy*
[4]*Obstetrics and Gynecology Unit, Pescara General Hospital, Pescara, Italy*
[5]*Department of Life Sciences, Health and Health Professions; Link Cmpus University, Roma, Italy*
[6]*Infectious Diseases Unit, Pescara General Hospital, Pescara, Italy*
[7]*Intensive Care Unit, Pescara General Hospital, Pescara, Italy*

Article Info

[*]***Corresponding Author:***
Ennio Polilli
Clinical Pathology Unit, Pescara General Hospital, Pescara, Italy
Via Fonte Romana, 8, 65124 Pescara PE
Phone: +39 0854252598
E-mail: en.polilli@gmail.com

Keywords

Anti-NMDA receptor encephalitis, Anti-NMDAR autoimmune disease, Ovarian teratoma, Autoimmune encephalitis, Anti-NMDAR antibodies

Abstract

Many cases of encephalitis are caused by an autoimmune response, and some are associated with underlying malignancies. Here we present the case of a 17-year-old female patient who was admitted to the pediatric ward with acute gastroenteritis, seizures, and behavioral changes. A brain computed tomography (CT) scan ruled out acute infarction, haemorrhage, mass lesions, and other intracranial injuries, while the initial EEG showed no epileptic discharges. In the absence of a definitive diagnosis, midazolam was administered to treat tonic–clonic seizures, while ceftriaxone and acyclovir were started for suspected infection. However, her condition deteriorated further and she was transferred to the ICU, where she was intubated. A Cell-Based Assay (CBA) revealed the presence of anti-NMDAR antibodies and a contrast-enhanced brain MRI showed leptomeningeal enhancement without limbic involvement. She was subsequently treated with intravenous immunoglobulins and high-dose corticosteroids. A subsequent transabdominal ultrasound scan revealed an oval, fluid-filled ovarian cyst. Based on these findings, her right ovary was removed, resulting in a gradual improvement in her condition. This case highlights that paraneoplastic autoimmune encephalitis may be misclassified due to persistent psychiatric symptoms with negative EEG and CSF findings. When clinical suspicion remains high despite negative initial instrumental and laboratory findings, it is essential to repeat these investigations. In such cases, neuroantibody testing may play a crucial role in establishing the diagnosis.

Background

Encephalitis occurs in approximately 0.07–12.6 cases per 100,000 people each year, with several cases attributed to an autoimmune response [1]. The most frequently reported cases among individuals testing positive for anti-surface antibodies are anti-leucine-rich glioma-inactivated 1 (anti-LGI1) and anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis [1]. Anti-NMDAR autoimmune disease is caused by high levels of antibodies against the NR1 subunit of the N-methyl-D-aspartate receptor glutamate-gated ion channels and occurs more frequently in children and adult women aged 15–40 years [2].

Up to 90% of patients with anti-NMDAR encephalitis develop psychiatric or behavioral symptoms within two weeks of disease onset, leading clinicians to suspect primary psychiatric disorder [3,4,5]. These symptoms frequently co-occur with neurological signs such as impaired alertness, seizures, memory deficits, autonomic instability, speech dysfunction, decreased consciousness, and involuntary movements. Autonomic manifestations such as hypersalivation, hyperthermia, tachycardia/bradycardia, urinary incontinence, hypo/hypertension, and erectile dysfunction have also been reported [4]. Failure to screen for an underlying autoimmune neurological disease in these cases may result in misdiagnosis or delayed diagnosis [5]. Consequently, central hypoventilation and epileptic status requiring intensive care unit transfer may develop [2]. Finally, several reports have pointed out that anti-NMDAR autoimmune disease may be associated with an underlying cancer in a consistent number of cases, suggesting that it may involve paraneoplastic syndrome [6].

Herein, we describe a case of a 17-year-old woman who was admitted to our hospital with rapidly deteriorating neurological symptoms.

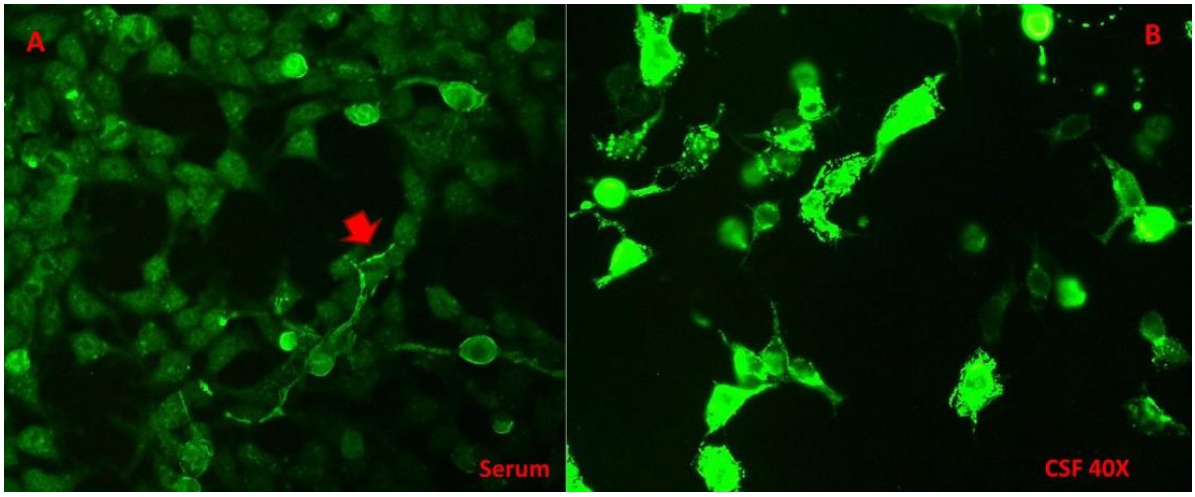
Case presentation

A 17-year-old Caucasian woman with a previous unremarkable medical history was hospitalized for acute gastroenteritis with seizures, psychosis, and personality changes in the paediatric ward of local hospital in March 2022. A brain computed tomography (CT) excluded acute brain infarction, haemorrhage, mass lesion, or other intracranial injuries. The patient showedself-limiting, stereotyped seizures associated with hyperventilation, tachycardia, and loss of consciousness. Haematochemical analyses revealed high White Blood Cell (WBC) counts (17.02 x10^3 µL), C-Reactive Protein (CRP) at 27 mg/L and unremarkable Procalcitonin (PCT) levels (<0.02 ng/mL). Cerebrospinal fluid (CSF) sampling was performed, using PCR for mycobacteria, herpes viruses and parvoviruses, yielding all negative results. CSF cultures were negative, too. In the same day, on suspicion of a conversion disorder, she was referred for consultation with a psychiatrist, who ordered an electroencephalogram (EEG) and a brain magnetic resonance imaging (MRI) scan. The EEG with intermittent light stimulation, hyperpnea, and placebo infusion documented the absence of epileptic discharges. In the absence of a clear clinical diagnosis, midazolam (0.034 mg/kg/h) was administered to treat tonic-clonic seizures, and ceftriaxone (4 g/day) and acyclovir (1,950 mg/day) for suspected infection.

Due to respiratory acidosis and an oxygen saturation (sO_2) at 82.7%, she was transferred to our ICU, where she underwent sedation and mechanical ventilation. Laboratory analyses at entry showed WBC and CRP values of 16,500 cells/µL and 68 mg/L, respectively, with PCT 0.4 ng/mL. Based on epileptogenic frontal activity during her second EEG, carbamazepine (400 mg/24 hours) was added to midazolam.

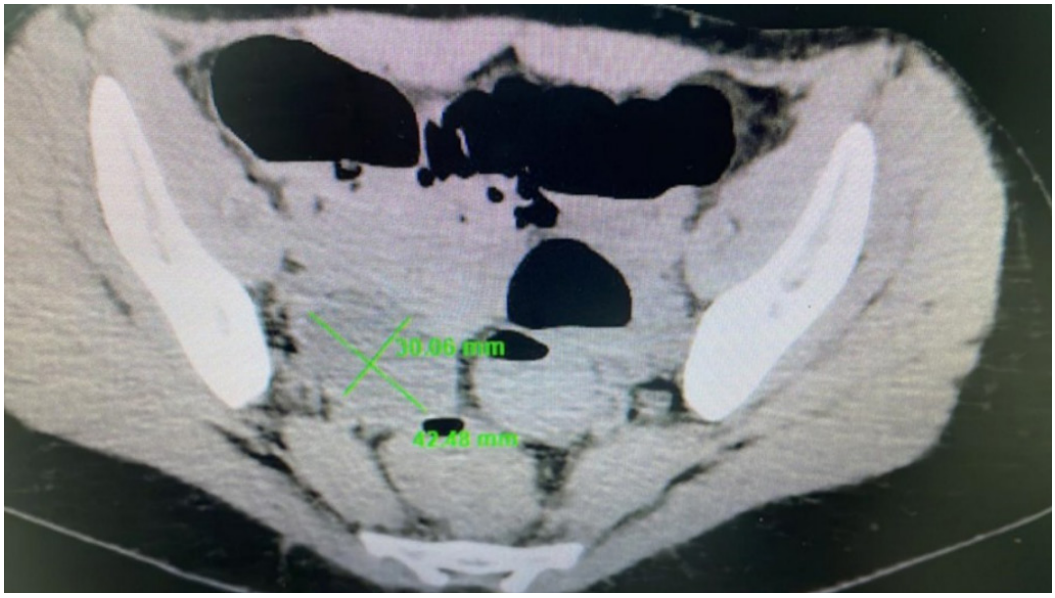
In the following day, a molecular search for herpes viruses, once more performed on peripheral blood samples, turned out negative. A second lumbar puncture, to investigate the possible presence of an autoimmune disease, revealed antibodies against neuronal surface antigens using indirect immunofluorescence assays on transfected cells (CBA, Cell-Based Assay, Euroimmun, Lubecca, Germany). Anti-NMDAR autoantibodies were analysed on the same day and were detected in both serum (Figure 1A) and CSF (Figure 1B), while anti-AMPA1/2, CASPR2, LGI1, GABArB1/2, and DPPX antibodies were all negative. Serum and CSF samples were analyzed at a 1:10 dilution and undiluted, respectively, as indicated in the manufacturer's instructions for use (IFU). The following day, the contrast-enhanced brain MRI showed no focal abnormalities on FLAIR sequences, with only leptomeningeal enhancement likely related to the previous lumbar puncture. No evidence of limbic involvement was observed.

Figure 1: Anti-NMDAR antibodies positive in serum (A) and CSF (B).



Based on these findings, the patient started high-dose methylprednisolone (1g/die) and intravenous immunoglobulin (IVIG) at 0.4 g/kg for five days, followed by IVIG alone at 0.4 g/kg daily for a further five days. On the same day, atransabdominal ultrasound showed an oval, fluid-filled cystic, 44x28 mm, right ovary mass, confirmed by a contrast abdominal/pelvic CT scan (Figure 2).

Figure 2: Fluido-cystic ovaric mass observed by abdomen/pelvic CT-scan (44x28mm).



Due to epileptic abnormalities on EEG, levetiracetam 500 mg twice daily was added. In the following days, clinical and instrumental signs of frontal seizures disappeared, sedation was tapered and the patient was extubated. On the ninth day after admission, the patient underwent laparoscopic excision of the right ovary, in parallel with biopsy of the left ovary. Right ovary histology confirmed the presence of a differentiated ovarian teratoma, with mature glial cells. Postoperative clinical conditions were stable, and the patient was discharged to the Gynaecology ward. Control NMDAR antibody assays performed on both serum and CSF after one year both showed negative results.

Discussion and conclusions

After first line investigations performed to rule out encephalitis, our patient was referred to a psychiatrist, which may have increased the risk of delayed diagnosis. There are three main reasons why our patient may have been at a greater risk for a delayed diagnosis. First, her first EEG turned out negative, in line with previous reports indicating the frequency of normal EEGs at presentation as approximately 4%. Typical EEGs show non-specific, slow, and disorganized activity, as well as electrographic seizures [7]. Second, the results of the physical examination, cell count, and chemical analysis of the first CSF sample were negative.

NMDAR disease is generally associated with inflammatory changes in the CSF, such as pleocytosis, elevated CSF protein levels, and positive OCBs (Oligoclonal bands) [8]. Third, MRI showed isolated leptomeningeal enhancement rather

thanhippocampal lesions, the most specific abnormalities associated with autoimmune encephalitis [9]. In these cases, MRI may show T2/FLAIR hyperintensities in the medial temporal lobes and occasionally in other cortical or subcortical regions. However, the scan's sensitivity and specificity are low to moderate, reliably identifying only 30–50% of patients with this condition. Many patients will have normal results, particularly in the early stages. Therefore, diagnosis should be based primarily on clinical features and confirmed by imaging and laboratory investigations of both CSF and serum [7].

Finally, in our case, a definitive diagnosis was made only after a cell-based assay, which identified the presence of anti-NMDAR antibodies in both serum and CSF.

CSF may provide more accurate information on immunopathological processes in the central nervous system and enhances the accuracy of diagnoses [10–12]. For instance, approximately 14% of patients tested positive for anti-NMDAR antibodies in CSF may have negative results in the serum [12]. Additionally, serum tests can be influenced by immune activity elsewhere in the body or by cross-reactivity, which may lead to false positives and affect treatment decisions. Furthermore, a small proportion of healthy people may test positive for NMDAR antibodies in their serum [13].

Antibody testing plays an important role in autoimmune encephalitis, as it links the clinical symptoms to their underlying cause. Detecting neuronal autoantibodies in serum and cerebrospinal fluid leads to a specific diagnosis and a prompt administration of appropriate immunotherapy. Furthermore, antibody testing may confirm the autoimmune disease etiology and support more precise classification, as specific autoantibodies are associated with distinct prognoses, therapeutic approaches, and long-term management strategies. For instance, the risk of relapse is higher in anti-LGI1 encephalitis than in anti-NMDAR encephalitis, often requiring long-term immunosuppressive therapy, whereas NMDAR encephalitis typically requires more intensive immunotherapy during the acute phase. In contrast, more intense immunotherapy is required for NMDAR encephalitis in the acute phase [14, 15, 16, 17]. Additionally, specific antibodies, such as anti-Hu or anti-Yo, may target screening for underlying tumors, aiding the identification of paraneoplastic syndromes and enabling timely cancer treatment [18]. However, a negative result does not rule out the diagnosis, and test sensitivity can vary depending on the specific antibody and type of sample. Therefore, research of antibodies should complement, rather than replace, clinical judgment, neuroimaging, electroencephalography, and cerebrospinal fluid analysis [12].

Several authors have reported that delayed initiation of immunotherapy is an important negative prognostic factor, highlighting the importance of timely and accurate diagnosis [19]. Titulaer et al. (2013) reported that early immunotherapy and avoiding ICU transfer are both independent predictors of favorable outcome [14]. Although large randomized controlled trials enrolling patients with NMDAR encephalitis are lacking, retrospective studies suggest that early diagnosis and treatment are associated with a good prognosis, fewer relapses, and milder signs and symptoms [5]. However, a consistent percentage ofpatients may require long-term care in the ICU, with increased risk of severe nosocomial pneumonia and/or other nosocomial complications [20]. Our patient was transferred to ICU due to hypoventilation, and developed a Serratia marcescens respiratory infection following intubation, promptly controlled with targeted antibiotic treatment. Thus, our case suggests that investigations for autoimmune encephalitis should be started as soon as possible, even at the Emergency Department, in patients presenting with psychiatric behaviors associated with neurological signs of encephalitis [15], as overall mortality rates for patients with NMDAR autoimmune brain disease are approximately 10%, rising to 15% for anti-NMDAR, anti-LGI1, or anti-GABABR encephalitis [16]. Patients with NMDAR encephalitis and ovarian teratomas frequently have more severe neurological signs at presentation. In such cases, early surgical treatment is mandatory for full recovery without recurrences [21]. An observational study reported that immunotherapy and tumor removal, when applicable, resulted in significant neurological improvement in 81% of patients with a median follow-up of 24 months [9]. To investigate the possible presence of an underlying teratoma, our patient underwent a CT scan, revealing an oval fluid-cystic ovarian mass in the right ovary. Timely identification of a teratoma and its subsequent resection are associated with a significantly better prognosis, including faster neurological recovery and a reduced risk of long-term complications. Most cases of mature ovarian teratoma in young patients are asymptomatic and are typically diagnosed only when abdominal pain occurs due to complications such as torsion or rupture, which may constitute surgical emergencies [22]. In some cases, the tumor is identified following a diagnosis of autoimmune encephalitis [22]. Anti-NMDAR encephalitis is the most common form of autoimmune encephalitis associated with ovarian teratomas, although this is not invariably the case [21]. The prevalence of an underlying ovarian neoplasm in these patients ranges from 26.9% to 38% [21]. Although there are currently no guidelines recommending imaging screening for teratomas in young females, imaging is essential when patients present with abdominal pain, increased abdominal girth, or neurological symptoms [22, 23]. In clinical practice, a combination of imaging techniques is typically employed to screen for an underlying tumor. Pelvic ultrasound is often the preferred option, as it is widely available, safe, and relatively inexpensive. However, it can miss smaller or more complex lesions. Therefore, in these cases, CT or MRI is the choice for a more accurate diagnosis. Additionally, if CT or MRI are also negative, but clinical suspicion remains high, PET can help identify lesions with higher metabolic activity that might otherwise be overlooked [23]. Relapse occurs in approximately 10–25% of patients with anti-NMDAR encephalitis, especially in those who do not start immunotherapy or whose underlying remains unidentified [24]. Relapses can occur months or even years after the first episode, so long-term follow-up is needed [24]. This includes regular neurological investigations, monitoring for any psychiatric or cognitive changes, and periodic tumor screening. Diagnosing relapse early allows for timely re-treatment and is linked to better outcomes [14, 24].

In line with previous reports, immunotherapy and early excision of the tumor led to rapid control of neurological signs; one month after discharge, our patient was indeed completely asymptomatic [21]. In conclusion, anti-NMDAR encephalitis is an autoimmune process that can mimic primary psychiatric illness at presentation [5]. Correct and timely identification of patients with anti-NMDAR autoimmune encephalitis remains challenging, and clinical suspicion must be put forth despite negative first-line instrumental or laboratory findings at presentation.

List of abbreviations

NMDAR: N-methyl-D-aspartate receptors
ICU: Intensive Care Unit
CSF: Cerebrospinal fluid
EEG: Electroencephalogram
MRI: Magnetic Resonance Imaging
CT: Computed Tomography
WBC: White Blood Cells
CRP: C-Reactive Protein
PCT: Procalcitonin
FLAIR: Fluid Attenuated Inversion Recovery
AMPA1/2:
Alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid
CASPR2: Contactin-associated protein-like 2
LGI1: Leucine-rich glioma inactivated 1
GABArB1/2: Subunit B1 and B2 of gamma-aminobuturic acid receptor
DPPX: Dipeptidyl-peptidase-like protein 6
ED: Emergency Department

Declarations

Ethics approval and consent to participate

All procedures performed in this study were in accordance with the ethical standards of the Health Administrative Board of the Pescara General Hospital and with the amended Helsinki Declaration. Our patient's parents provided written informed consent to use and publish anonymised clinical data for institutional research purposes upon admission to the ED.

Consent for publication

Written informed consent was obtained from patient's parents for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Availability of data and materials

Data are available from the author upon reasonable request and with permission of Health Direction of Pescara General Hospital.

Competing interests

The authors declare that they have no competing interests.

Funding

No funding was required for this article.

Acknowledgements

The authors are indebted with all the staff of the Gynaecology and Intensive Care Units that took care of the patient during her stay in the Pescara General Hospital

References

1. Granerod J, Tam CC, Crowcroft NS, Davies NW, Borchert M, Thomas SL. Challenge of the unknown. A systematic review of acute encephalitis in non-outbreak situations. Neurology. 2010;75(10):924-932. https://doi.org/10.1212/WNL.0b013e3181f11d65.
2. Zhang Y, Liu G, Jiang M, Chen W, He Y, Su Y. Clinical Characteristics and Prognosis of Severe Anti-N-methyl-D-aspartate Receptor Encephalitis Patients. Neurocrit Care. 2018;29(2):264–272. https://doi.org/10.1007/s12028-018-0536-6
3. Kayser MS, Titulaer MJ, Gresa-Arribas N, Dalmau J. Frequency and characteristics of isolated psychiatric episodes in anti–N-methyl-d-aspartate receptor encephalitis. JAMA Neurol. 2013;70(9):1133–1139. https://doi.org/10.1001/jamaneurol.2013.3216
4. Nguyen L, Wang C. Anti-NMDA Receptor Autoimmune Encephalitis: Diagnosis and Management Strategies. Int J Gen Med. 2023;16:7–21. https://doi.org/10.2147/IJGM.S397429
5. Valente T, Gonçalves G, Duarte V, Jesus G. Anti-N-Methyl-D-Aspartate Receptor Encephalitis, A Diagnosis Not To Miss. Eur J Case Rep Intern Med. 2023;10(8):003974. https://doi.org/10.12890/2023_003974. eCollection 2023.
6. Akanuma H, Iizuka T, Abe D, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with small cell lung cancer and cytotoxic T-cell-mediated pathology: Case report. Front Immunol. 2022;13:952868. https://doi.org/10.3389/fimmu.2022.952868
7. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol. 2011:63-74. https://doi.org/10.1016/S1474-4422(10)70253-2.
8. Blinder T, Lewerenz J. Cerebrospinal Fluid Findings in Patients With Autoimmune Encephalitis-A Systematic Analysis. Front Neurol. 2019;10:804. https://doi.org/10.3389/fneur.2019.00804.
9. Beatty CW, Creutzfeldt CJ, Davis AP, Hoffer Z, Khot SP. The diagnostic conundrum and treatment dilemma of a patient with a rapidly progressive encephalopathy. Neurohospitalist. 2014;4(1):34-41. https://doi.org/10.1177/1941874413496792.
10. Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol. 2016;15(4):391–404.https://doi.org/10.1016/S1474-4422(15)00401-9
11. Ho ACC, Mohammad SS, Pillai SC, et al. High sensitivity and specificity in proposed clinical diagnostic criteria for anti-N-methyl-D-aspartate receptor encephalitis. Dev Med Child Neurol. 2017;59(12):1256–1260. https://doi.org/10.1111/dmcn.13579
12. Lee SK, Lee ST. The Laboratory Diagnosis of Autoimmune Encephalitis. J Epilepsy Res. 2016;6(2):45–52. https://doi.org/10.14581/jer.16010

13. Steiner J, Teegen B, Schiltz K, Bernstein HG, Stoecker W, Bogerts B. Prevalence of N-methyl-D-aspartate receptor autoantibodies in the peripheral blood: healthy control samples revisited. JAMA Psychiatry. 2014;71(7):838-839. https://doi.org/ doi:10.1001/jamapsychiatry.2014.469
14. Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-N-Methyl-D-Aspartate (NMDA) receptor encephalitis: acohort study. Lancet Neurol. 2013;12(2):157–165. https://doi.org/10.1016/S1474-4422(12)70310-1
15. Macher S, Zimprich F, De Simoni D, Höftberger R, Rommer PS. Management of Autoimmune Encephalitis: An Observational Monocentric Study of 38 Patients. Front Immunol. 2018;9:2708. https://doi.org/10.3389/fimmu.2018.02708
16. Zhong R, Chen Q, Zhang X, Zhang H, Lin W. Risk Factors for Mortality in Anti-NMDAR, Anti-LGI1, and Anti-GABABR Encephalitis. Front Immunol. 2022;13:845365. https://doi.org/10.3389/fimmu.2022.845365
17. Varley JA, Strippel C, Handel A, Irani SR. Autoimmune encephalitis: recent clinical and biological advances. J Neurol. 202;270(8):4118-4131. https://doi.org/10.1007/s00415-023-11685-3.
18. Linnoila JJ. Paraneoplastic antibodies targeting intracellular antigens. Handb Clin Neurol. 2024;200:335-346. https://doi.org/10.1016/B978-0-12-823912-4.00021-9
19. Broadley J, Seneviratne U, Beech P, et al. Prognosticating autoimmune encephalitis: A systematic review. J Autoimmun. 2019;96:24–34. https://doi.org/10.1016/j.jaut.2018.10.014
20. Niederman MS. Pneumonia: Considerations for the Critically Ill Patient. Crit Care Med. 2008;867–883. https://doi.org/10.1016/B978-032304841-5.50045-5
21. Dai Y, Zhang J, Ren H, et al. Surgical outcomes in patients with anti-N-methyl D-aspartate recep tor encephalitis with ovarian teratoma. Am J Obstet Gynecol. 2019;221(5):485.e1-485.e10. https://doi.org/10.1016/j.ajog.2019.05.026
22. O'Neill KE, Cooper AR. The approach to ovarian dermoids in adolescents and young women. J Pediatr Adolesc Gynecol. 2011;24(3):176-180. https://doi.org/10.1016/j.jpag.2010.11.006.
23. Zhang W. Ovarian teratoma in anti-NMDAR encephalitis: a life saved by imaging. Intensive Care Med. 2025. https://doi.org/10.1007/s00134-025-08180-w.
24. Ciano-Petersen NL, Villagrán-García M, Muñiz-Castrillo S, Farina A, Vogrig A, Goncalves D, Nicole F, Rogemond V, Picard G, Aubart M, Psimaras D, Oliver B, Serrano-Castro PJ, Joubert B, Honnorat J. Relapses in Anti-NMDAR Encephalitis: Clinical Characterization and Predictive Features. Neurol Neuroimmunol Neuroinflamm. 2025;12(4):e200421. https://doi.org/10.1212/NXI.0000000000200421.