Case Report

Anti-NMDAR autoimmune encephalitis: a diagnostic challenge in clinical laboratories

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Article Info

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Keywords

anti-NMDAR encephalitis, autoimmune encephalitis, autoimmunity, neuroimmunology, immunotherapy, ovarian teratoma

Abstract

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is an antibody-mediated neurological disease which is acute, severe and with a complicated differential diagnosis. In 38% of cases, it arises as a paraneoplastic neurological syndrome (PNS) associated with cancer. Ovarian teratomas are the most frequently associated tumors, especially in young women. However, teratomas are usually mature and benign and psychiatric and neurological symptoms improve after resection.

Clinical laboratories play a key role in the diagnosis and prognosis of these diseases, highlighting the importance of laboratory test results to prompt the search for the associated tumor. In addition, communication between laboratory medicine specialists and clinicians, as well as a multidisciplinary approach, are essential for early disease identification and treatment.

Introduction

Autoimmune encephalitis (AE) is a non-infectious inflammatory brain disease mediated by the immune system. The most prevalent is anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis, caused by the production of antibodies targeting an extracellular epitope of the neuronal subunit GluN1 of the NMDAR [1]. This disease was first described and characterized in 2007 [2]. According to the 2021 diagnostic criteria update for paraneoplastic neurological syndromes (PNS), it is classified as an intermediate-risk antibody with 38% of cases associated with cancer [3].

Diagnosis of anti-NMDAR encephalitis is usually delayed due to the rarity of the disease and the broadness of the differential diagnosis. This differential diagnosis should include primary psychiatric disorders (mainly acute psychotic episode and first outbreak of schizophrenia), infectious encephalitis (especially due to viral causes, like herpes simplex infection), psychotropic drug use (phencyclidine, ketamine, amphetamine and their derivatives), neuroleptic malignant syndrome and lethal catatonia [1].

NMDAR encephalitis is a clinically stereotyped diffuse encephalitis in which most patients develop symptoms progressively, following a particular sequence. In the first week, pseudoviral prodromes occur, followed by psychiatric symptoms (such as psychosis, agitation, hallucinations, mania, verbosity, mutism, insomnia, amnestic deficits, etc.). Later, other symptoms such as dyskinesia, dissociative reactions, hypoventilation, dysautonomia, catatonia or coma might appear. After the resolution of acute brain symptoms, sequelae such as executive dysfunction, impulsivity or cognitive deficits may remain [4].

The association of anti-NMDAR encephalitis with tumors depends on age and sex. Ovarian teratomas are the most frequent tumor type, predominantly affecting women aged 12 to 45 years and, in most cases, presenting as mature and benign tumors. Extraovarian teratomas, neuroblastomas and Hodgkin lymphomas have also been described. However, children of both sexes and young adult men rarely have tumors [1, 3, 5].

Clinical-Diagnostic Case

A 16-year-old female, with no drug allergies or personal history, came to the Emergency Department (ED) with dysarthria, hypokinesia, memory loss, insomnia, irritability, hyporexia, aggressiveness and incongruent behavior.

The following were urgently performed:

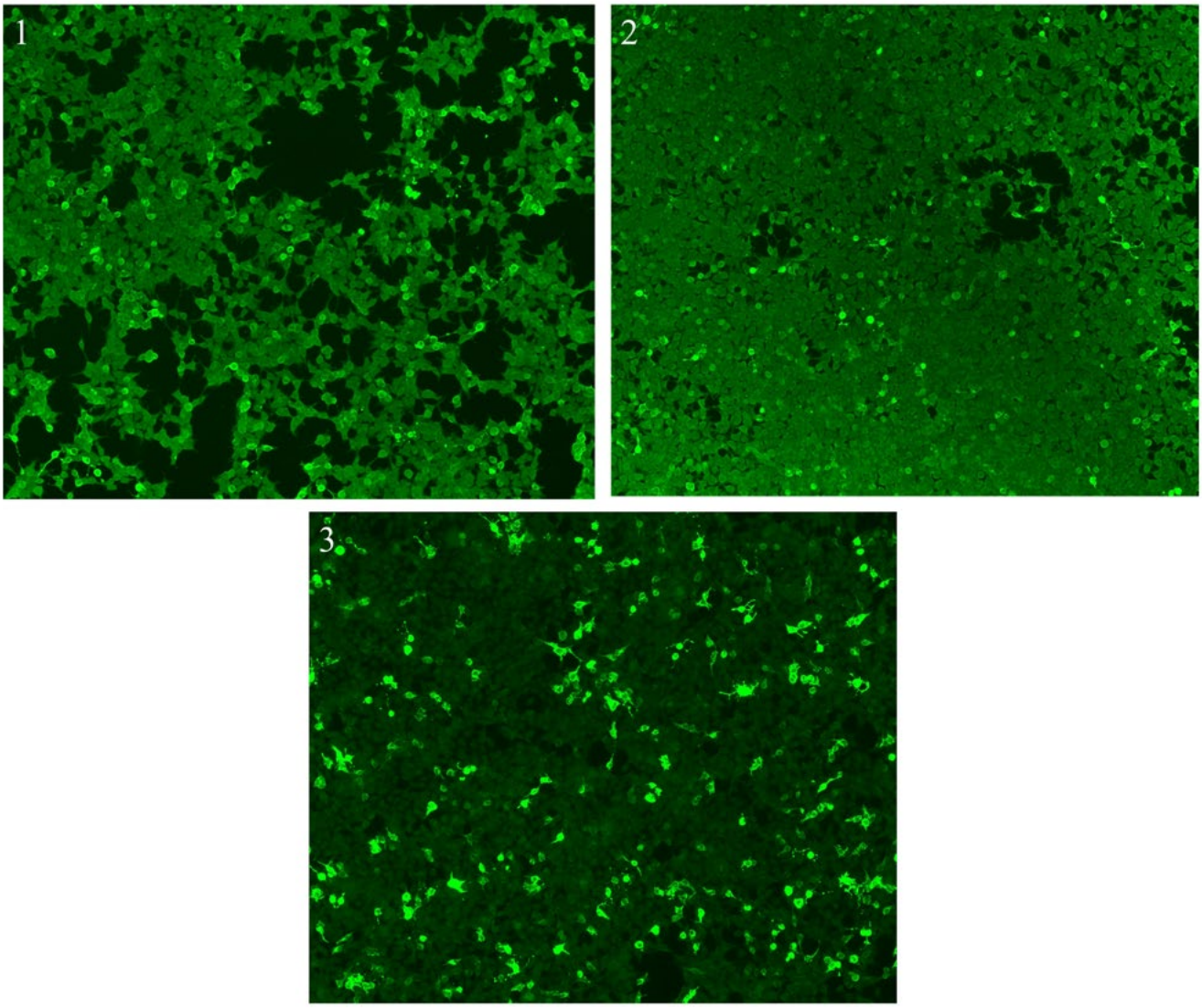
- Blood and urine tests, with drug determination: no pathological findings.
- Computed tomography (CT) scan of the brain and magnetic resonance imaging (MRI) of the skull with intravenous contrast: no evidence of alterations, tests within normal limits.
- Electroencephalogram (EEG): brain bioelectric activity within normal limits for the patient's age.

The patient was admitted to Psychiatric ward and, given the clinical worsening, treatment with corticosteroids (methylprednisolone 1 g/24 hours), immunoglobulins and neuroleptics (haloperidol and olanzapine) was started. Due to suspicion of AE, the patient was transferred to the Neurology ward. Cerebrospinal fluid (CSF) was obtained by lumbar puncture and analyzed in the clinical laboratory: clear and colorless appearance, glucose 56 mg/dL (40-70 mg/dL), proteins 29 mg/dL (15-40 mg/dL), lactate 1.4 mmol/L (1.1-2.8 mmol/L), 1 erythrocyte/µL, 11 leukocytes/µL (90% mononuclear and 10% polymorphonuclear), bacteriological (Gram stain, culture, PCRs of Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae, Listeria monocytogenes and Streptococcus agalactiae) and viral analyses (PCRs of enterovirus, cytomegalovirus, Epstein-Barr virus, herpes virus 6, herpes simplex virus 1, herpes simplex virus 2, varicella zoster virus, Escherichia coli K1) were both negative.

A complete blood and urine analysis was performed, hematology and biochemistry results were within the reference values. Serology for the human immunodeficiency virus and syphilis were negative. In addition, autoimmunity tests in serum and CSF were performed, results were obtained after 10 days and clinically relevant analytical results were:

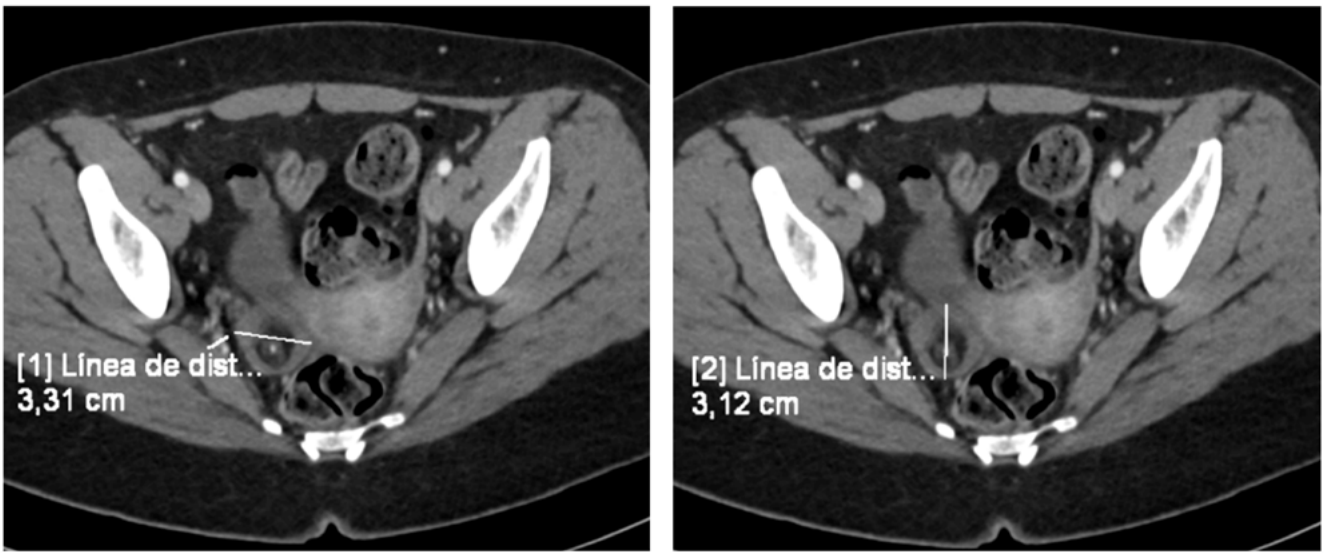
- Encephalitis study in serum (1:10 dilution) and CSF (1:1 dilution) "Neurology Mosaics EUROPattern" (EUROIMMUN®) by indirect immunofluorescence in transfected cells: negative for AMPAR1/R2, CASPR2, DPPX, GABAR and LGI1 and positive for NMDAR (Figure 1).
- PNS study in serum (1:101 dilution) "EUROLINE Paraneoplastic neurological syndromes 12 Ag (IgG)" (EUROIMMUN®) by immunoblot: negative for amphiphysin, CV2, PNMA2 (Ma2/Ta), Ri, Yo, Hu, recoverin, SOX1, titin, Zic4, GAD65 and Tr (DNER).

Figure 1: Results of indirect immunofluorescence commercial test based on a cell-based assay (CBA) using human embryonic kidney (HEK) cells transfected with a cDNA encoding NMDAR in: (1) serum, (2) cerebrospinal fluid (CSF) and (3) anti-NMDAR positive control. All images taken in an EUROPattern Microscope (EUROIMMUN®) at 10x magnification.



Due to the presence of anti-NMDAR antibodies, a chest CT scan and an abdominal-pelvic CT scan with intravenous contrast were performed. At the thoracic level, no pleuro-parenchymal alterations were observed, nor mediastinal, hilar or axillary lymphadenopathy. At the abdominal level, the right ovary was observed to be slightly enlarged, 3.3 x 3.1 cm in diameter, with a nodular image of heterogeneous density, an area of fatty density, another solid area and punctate calcification, compatible with ovarian teratoma (Figure 2). No further clinically significant findings were observed. Ovarian teratoma was confirmed by gynecological ultrasound: hypoechoic imaged inside of a 28 x 28 mm hyperechoic imaged inside of the 30 x 35 mm right ovary, suggestive of teratoma.

Figure 1: Ovarian teratoma measuring 3.3 x 3.1 cm on abdomino-pelvic computed tomography (CT) scan.



Clinical response to treatment was partial, although the symptomatic evolution was favorable, so the patient was discharged and surgery was scheduled. A laparoscopic cystectomy of the right ovary was performed and the anatomopathological results indicated a mature and benign teratoma.

After surgery, the psychopathology has improved and the patient presents anterograde amnesia of the episode. She is currently being monitored by Psychiatry and Neurology.

Discussion

AE is often confused with viral encephalitis, primary psychiatric processes, drug intake, and neuroleptic malignant syndrome [1]. Because of the frequent psychiatric symptoms at onset, correct diagnosis may be delayed. However, a majority of patients with anti-NMDAR encephalitis show abnormal findings on MRI or EEG, which can help guide diagnosis [6, 7].

Serum and CSF autoimmunity tests, like detection of anti-NMDAR antibodies, facilitates early diagnosis, allowing it to be a potentially treatable disease [7]. Demonstrating presence of IgG antibodies targeting the GluN1 subunit of the NMDA receptor in the CSF is more sensitive and specific than serum testing. However, to avoid false-negative or false-positive results, it is still recommended to test NMDAR antibodies in both CSF and serum [8, 9].

Antibody-positive patients should be examined for the presence of an underlying tumor, mainly an ovarian teratoma or a testicular germ-cell tumor [6]. These tumor cells often express NMDAR, triggering an immune response in which antibody production occurs both intrathecally, by cells that cross the blood-brain barrier, and systemically. These antibodies target neurons, causing inflammation and neurological damage [10]. Treatment is based on tumor resection and immunotherapy. Typically, first line immunotherapy includes high-dose intravenous corticosteroids, together with either high-dose intravenous immunoglobulins or plasma exchange, with responsive patients improving within 4 weeks. However, half of patients require second-line immunotherapy, consisting of rituximab and/or cyclophosphamide. Additionally, atypical or second-generation antipsychotic drugs, antiepileptics, dopamine vesicle depletion agents, adrenergic blockers and anesthetics/sedatives should also be considered for symptomatic treatment [4, 8]. Better understanding of the immunology and neurobiology of anti-NMDAR encephalitis is important to developing novel biomarkers and therapies [10].

In conclusion, clinical laboratories play a key role in both the diagnosis and prognosis of AEs, highlighting, in this case, the importance of laboratory test results to prompt the search for the associated tumor. Communication between laboratory medicine specialists and clinicians is essential for proper diagnosis, monitoring and treatment of patients. In addition, a multidisciplinary approach is important for the early identification and treatment of the disease, since diagnosis of anti-NMDAR encephalitis is very difficult to make at the point of first medical contact in the ED [11, 12].

Take home messages/ learning points

1. AE is a group of non-infectious inflammatory brain diseases mediated by the immune system and the most prevalent being the one targeting the NMDAR.
2. Association of anti-NMDAR encephalitis with tumors depends on age and sex, with ovarian teratoma being the most frequent tumor and, in most cases, mature and benign.

3. Diagnosis requires specialized testing for detection of NMDAR antibodies in patient CSF and it is recommended to also test serum.
4. Treatment is based on tumor resection and immunotherapy.
5. Clinical laboratories play a key role in the diagnosis and prognosis of this disease due to the importance of laboratory test results in clinical decision-making.

Disclosures

This study is in compliance with the ethical principles for medical research involving human subjects, in accordance with the Declaration of Helsinki.

Conflicts of interests

None declared.

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