Clinical Case Report

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Successful treatment of anti-NMDA receptor encephalitis with early teratoma removal and plasmapheresis

A case report

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Abstract

Rationale: This report describes a Successful treatment of anti-NMDA receptor encephalitis with early teratoma removal and plasmapheresis.

Patient Concerns: We present a 31-year-old Caucasian nulliparous patient who was admitted as an emergency with general illness status accompanied by holocranial cephalalgia and fever.

Diagnoses: The previous symptoms were followed by disorientation, persecutory delusion, incoherent language, and tonic-clonic seizure.

Interventions: The patient was admitted in the intensive care unit (ICU) with Glasgow score 7.

Outcomes: Most of complementary exams (brain CT, brain MRI, blood analysis, PCR for virus on CSF) were normal except CSF leucocytosis and hyperproteinorrhachia. An abdominopelvic ultrasound revealed a 5-cm solid-cystic tumor in the left adnexal region, suggestive of teratoma. At that stage, the possibility of autoimmune encephalitis was considered, and confirmed later.

Lessons: This disease can only be successfully treated with fast surgical intervention and an early implementation of immunosuppressive therapies. The optimal timing of initiation and duration of therapeutic plasma exchange necessary to achieve good outcomes in patients with NMDAR remains unknown. This case report intends to increase awareness about the importance of early surgical treatment and early implementation of this potentially life-saving therapy and of continuing the treatment until complete remission of symptoms.

Abbreviations: Anti-NMDAR = anti-*N*-methyl-D-aspartate receptor, CSF= cerebrospinal fluid, HSE = herpes simplex encephalitis, IVIg = intravenous immunoglobulins, TPE = therapeutic plasma exchange, PCR = polymerase chain reaction, CT = computed tomography, MRI = magnetic resonance imaging, EEG = electroencephalograms, mRS = modified Rankin scale, CNS = central nervous system.

Keywords: anti-NMDA receptor encephalitis, ovarian teratoma removal, plasmapheresis, survival, young woman

1. Introduction

Anti-*N*-methyl-D-aspartate-receptor (NMDAR) encephalitis is an autoimmune disorder with a wide spectrum of neuropsychiatric symptoms with a progressive clinical course and the possibility of effective management, which was first described in 2005 by Vitaliani et al.[1]

A positive serum or CSF sample screening for antibodies to the NMDAR subunit remains the gold standard in the diagnosis and must be performed in all patients with an acute onset of psychiatric symptoms with atypical features or unusual movements.

The triggers of the disorder include viral infections, tumors, and other unknown factors. Herpes simplex encephalitis (HSE) plays a vital role in triggering the synthesis of anti-NMDAR antibodies.[2] In young adult women, encephalitis is frequently accompanied with ovarian teratomas,[3,4] while in men and children the presence of a tumor is uncommon.[5]

Elimination of the ovarian tumor and early immunotherapy frequently improves the outcome with complete recovery or only a residual neurological deficit.[6–8]

There is still an important lack of data regarding the optimal treatment of the disease, predominantly since the type of immunotherapy that is most effective in controlling the symptoms of the disease remains a matter of debate. Numerous patients, particularly those with a severe form of the disease, do not respond to first-line immunotherapy [steroids or intravenous immunoglobulins (IVIg)] and may require therapeutic plasma exchange (TPE).

We report a case of an ovarian mature cystic teratoma in a young woman which was associated with clinical anti-NMDAR

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encephalitis and the successful therapeutic management applied by a multidisciplinary team.

2. Case report

The patient is a 31-year-old Caucasian nulliparous woman who was admitted as an emergency on March 23, 2017 with general malaise accompanied by holocranial cephalalgia and bilateral otalgia of 3 days of evolution. The only relevant element in her history is the presence of migraines without aura. The general emergencies unit diagnosed her with temporomandibular joint dysfunction and she returned on the same day with disorientation, persecutory delusion, and incoherent language. After an assessment by the Service of Psychiatry, she was diagnosed with anxiety syndrome secondary to a stressful family situation. On the next day, she was transferred by the emergency services with convulsive tonic-clonic seizure which was controlled with intranasal midazolam, and she was assessed by the Service of Neurology. She showed intermittently incoherent language and altered behavior. During anamnesis, she claims that "there are cameras recording us" or "they want to hurt us." During the observation period in the emergency department, she presented an episode of fever with a temperature of 38.3°C. The blood results were normal, and the CSF showed 75 leukocytes/mm^3 (mononuclear) and hyperproteinorrhachia at 88 mg/dL, with clear fluid. The computed tomography (CT) scan did not reveal significant alterations. The patient was initially diagnosed with lymphocytic encephalitis and prescribed an antibiotic treatment against Gram−, Gram+, herpesvirus, and tuberculosis (ceftriaxone, ampicillin, vancomycin, rifater and aciclovir), and antiseizure treatment with levetiracetam.

On March 25, the patient was admitted in the intensive care unit (ICU) with Glasgow score 7 and signs of unrest, language without response to pain and apraxia of lid opening. She presented with neck and upper limb dystonia, oculomasticatory myorhythmia, and involuntary movements of the lower limbs. During admission, the condition of the patient worsened, with no language, and she presented with progressive rigidity of the back of the neck which spread to the entire body, including the mandible, with sialorrhea. Sedation was applied, followed by orotracheal intubation and mechanical ventilation. A more exhaustive study was performed with a complete analysis (complete blood count, biochemical analysis, coagulation, renal function, hepatic function, electrolyte levels, polymerase chain reaction [PCR], glucose, urine analysis, and urine sediment) which revealed normal values except for PCR, which was 12.2 on March 27 (levels were normal on admission). Brain CT and magnetic resonance imaging (MRI) were performed, without pathological findings (Fig. 1), and several lumbar punctures that showed CSF with leukocytes 187/mm^3 on March 27 and proteins 111.5 mg/dL. On March 28 results for antibodies against neuronal nuclear antigens (anti-Hu, -Yo, -Ri, -CV2, -PMA2, -amphiphysin, -recoverin, -SOX1, -titin, -Zic4, -GAD65, and -Tr) were negative. PCR was performed for enterovirus, herpesvirus, and *Mycobacterium tuberculosis*, which were negative in CSF. At that stage, the possibility of autoimmune encephalitis was considered, and a CSF sample was submitted to an external laboratory for the study of anti-NMDA glutamate receptor antibodies.

After showing immunoglobulin A levels within normal values, the patient was treated with immunoglobulins, 0.4 g/kg/day for 2 days, followed by 1 g/day methylprednisolone for 5 days. Given the lack of improvement after the second dose of immunoglobulins, rituximab was administered at 375 mg/m^2/week.

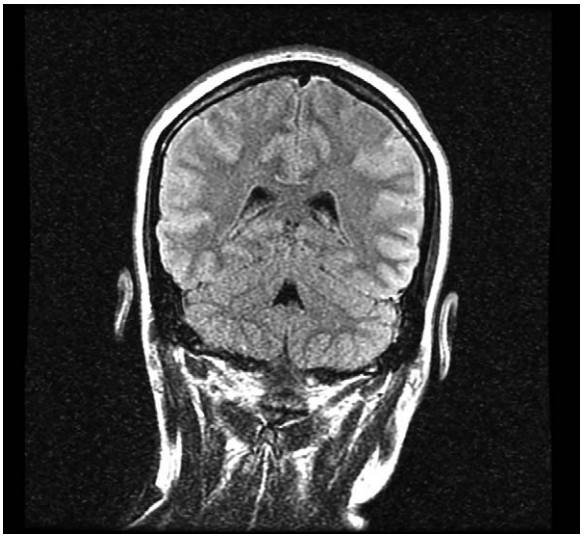

Figure 1. MRI—nonpathological findings. MRI = magnetic resonance imaging.

On March 31, 2017, an abdominopelvic ultrasound revealed a moderate amount of free fluid in the pelvis, and a 5-cm solid-cystic tumor in the left adnexal region, suggestive of teratoma (Fig. 2). Given the suspicion of autoimmune encephalitis secondary to teratoma, an emergency surgical excision was decided by the Service of Gynecology. A laparoscopic left salpingo-oophorectomy was performed and it showed an image compatible with teratoma (Fig. 3)—which was confirmed in the postoperative analysis by pathological anatomy: "Mature cystic teratoma." Multiple lavages of the abdominal cavity were performed to prevent—according to the literature—a chemical peritonitis caused by a potential spillage of the fluid of the sebaceous cyst.

Similarly, on April 4 our suspicions were confirmed with positive results in CSF for oligoclonal bands and anti-NMDA glutamate receptor antibodies, with titre 1:64 (negative in blood). Anti-AMPA 1 and 2 glutamate receptor, anti-LGI1, anti-GABAB1/B2 receptor and anti-VGKC antibodies were negative.

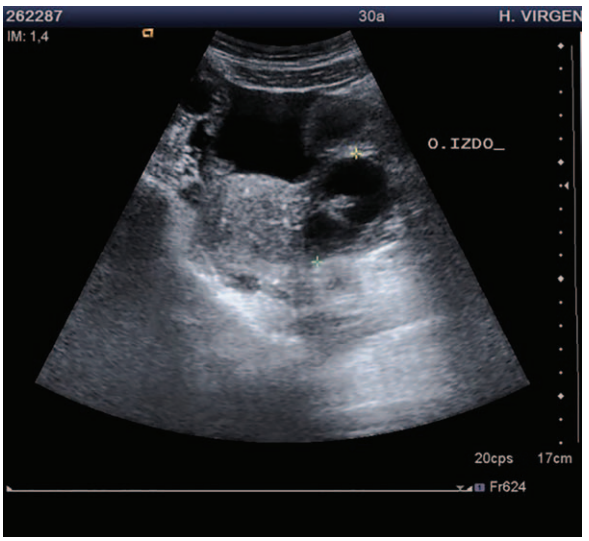

Figure 2. US—image compatible with 5 cm left ovarian teratoma. US = Ultrasound.

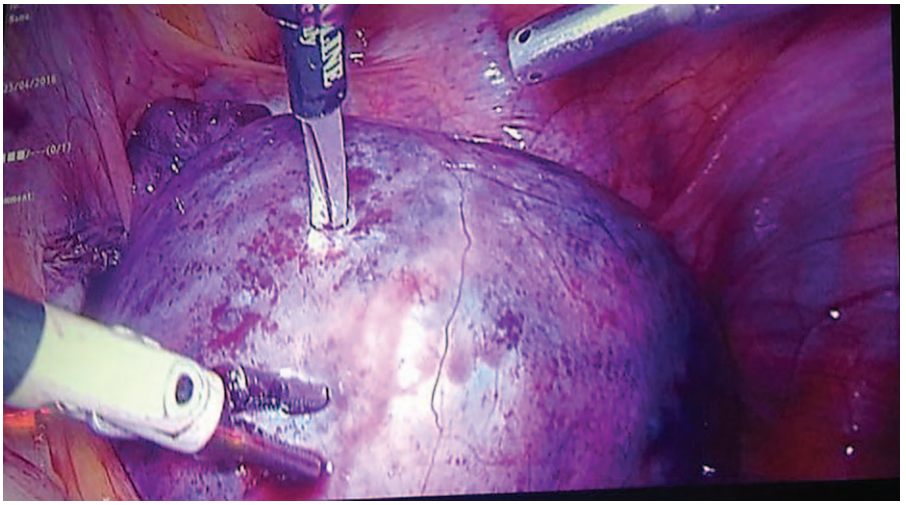

Figure 3. Laparoscopic surgery—image compatible with ovarian teratoma.

In the immediate postoperative period, the patient showed a slight improvement of her general symptoms. Afterward, she presented with fever of infectious origin, a maintained colonization of enterococci in blood and of multi-resistant *Pseudomonas aeruginosa* in bronchial aspirate. Consequently, the treatment with monoclonal antibodies was interrupted and plasmapheresis cycles were initiated (3 cycles with 5 sessions per cycle in total), with alternate-day high doses of steroids. A slight improvement in the myoclonus was observed after each session. The jejunal biopsy was negative for Whipple's disease on April 10. Repeated electroencephalograms (EEG) were performed, and they revealed generalized slowing with unspecific characteristics and without evidence of paroxysmal activity. Since May 11, a slight improvement was observed, with a decrease in myoclonic activity, which made it possible to reduce the sedation doses.

On June 27, after several days without fever and without any evidence of infection, treatment with rituximab was initiated again. In total, 4 doses were administered without relapse of infection.

On July 12, during one of the periods in which sedation was withdrawn and with almost no antiseizure treatment, the EEG (Fig. 4) showed clear epileptic activity and the antiseizure treatment was increased.

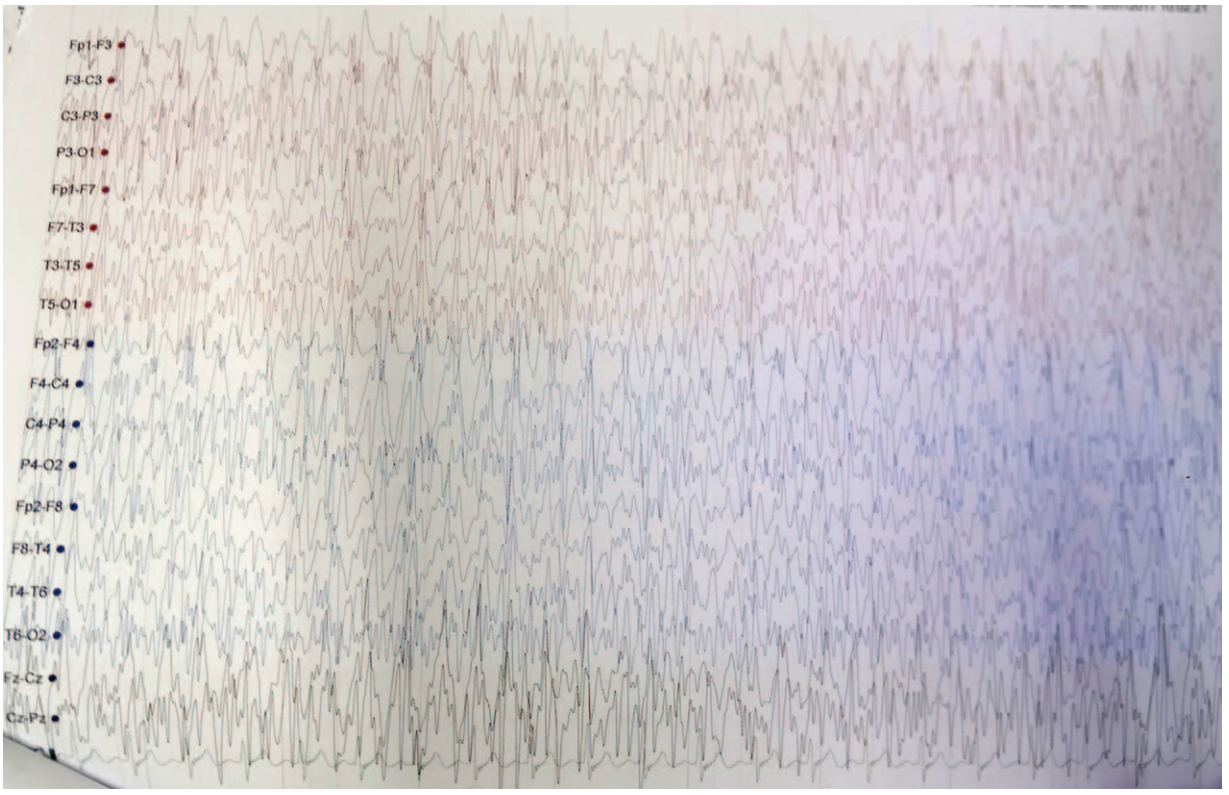

Figure 4. Epileptic activity in EEG. EEG = electroencephalograms.

Table 1

Follow-up of cerebrospinal fluid (CSF) and blood parameters.

	25/03	27/03	07/04	02/06	30/08	Normal range
Anti-NMDAr antibodies*			1:64	1:64	1:16	<1:10
Leukocytes (leucocytes/mm^3)	75	187	35	3	1	<4
Proteins, mg/dL	88	98	31	112	66	1.00–40.00
Glucose, mg/dL	73	63	72	54	63	40-80
Macroscopic appearance	Clear	Clear		Clear	Clear	
Oligoclonal bands (CSF)			Positive	Positive (weak)		
Ig G serum blood test, mg/dL		873	4560	2430		751–1560
Serum oligoclonal bands				Negative		

Anti- NMDAr = anti-*N*-methyl-D-aspartate receptor, CSF = cerebrospinal fluid, Ig G = immunoglobulin G.
* Significant levels of anti-NMDA antibodies are considered from title 1:2.

Given the profuse sialorrhea of the patient, which even interfered with her fluid balance, botulinum toxin was applied on July 22. Sialorrhea disappeared without signs of mouth dryness until discharge. On September 7, the tracheotomy cannula was removed.

The CSF and blood parameters during this period are presented in Table 1.

After 5 months in the ICU and several weeks in the Service of Neurology, the patient was discharged on September 29, 2017 with Glasgow score 15 and modified Rankin Scale (mRS) 3. She was capable of maintaining a conversation with some fluency and presented with slight dysarthria and ambulation with assistance. The anti-NMDA antibodies started to decrease 5 months after surgery. The patient is currently under antiepileptic and rehabilitation treatment, and she is monitored by the Service of Neurology.

Due to there is no concern that a patient's anonymity cannot be maintained in written text or with use of photographs we consider that the ethical approval was waived or not necessary. However, the patient has provided informed consent for publication of the case.

A timeline of the events is present in Figure 5.

3. Discussion

Encephalitis is an acute or chronic inflammatory disease of the central nervous system (CNS) where the presence of the neuronal surface antibodies can be demonstrated.[6] The present clinical

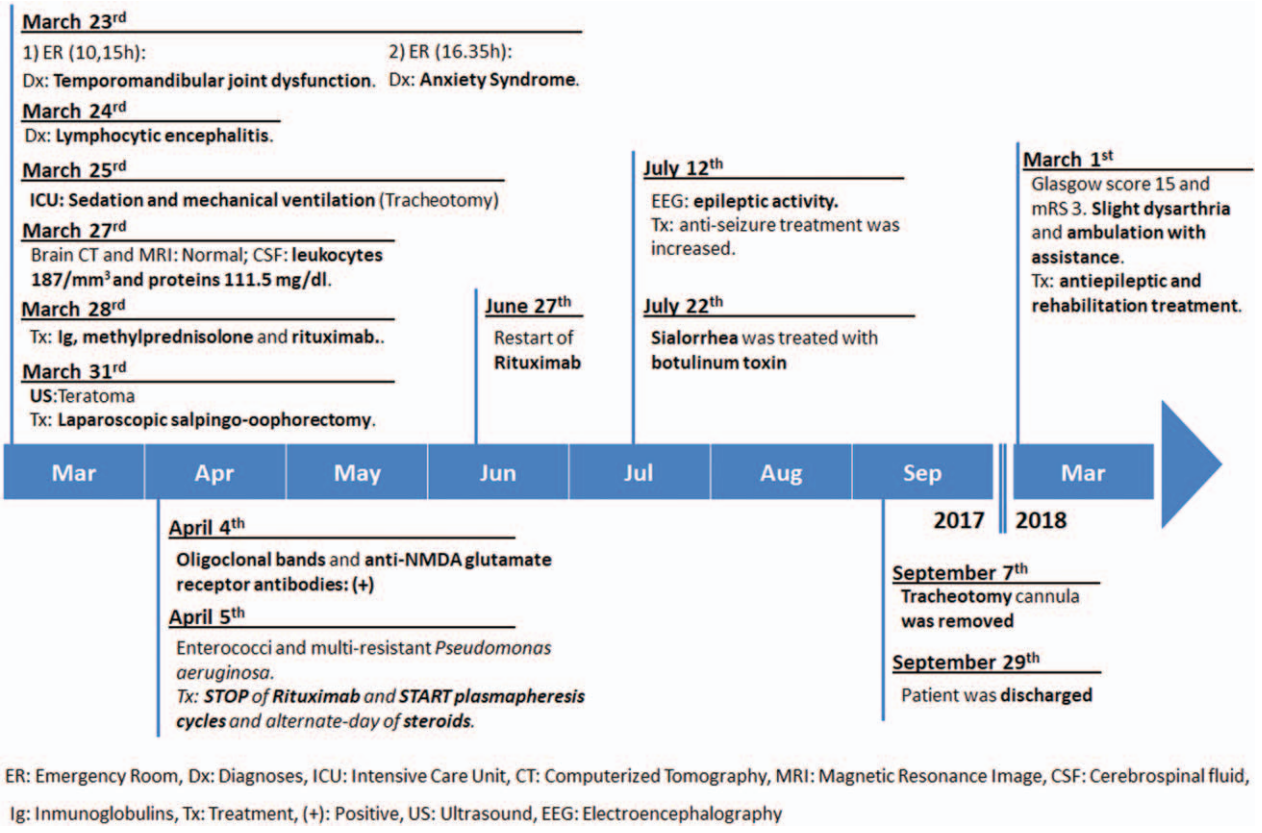

Figure 5. Timeline of events.

case described a progression of anti-NMDAR encephalitis. This relatively unusual disorder has a typical chronological presentation: sudden onset with prodromal, fever-like symptoms, followed by a psychiatric disorder, decreased level of consciousness with focal and clonic seizures, dyskinesias, and autonomic instability.[7] In our clinical case, all of the cited symptoms were observed, so the clinical course of the anti-NMDAR encephalitis was typical. Furthermore, the patient was a young woman, which is also a common feature of this type of autoimmunological encephalitis. The female patient population represents around 80% of reported cases.[8] Additionally, the coexistence of an ovarian tumor, a teratoma in this case, is also typical for anti-NMDAR encephalitis.

When anti-NMDAR is suspected the diagnostic tests contain detection of NMDAR autoantibodies in CSF and/or in the serum as the fundamental part of diagnosis, predominantly because other laboratory tests and imaging studies are not relevant.[9] According to some authors, CSF antibody testing is highly sensitive and specific for anti-NMDAR encephalitis and false positive and negative results may occur when testing only serum.[10]

There is currently some discussion as to whether serum or CSF must be tested for in the presence of anti-NMDAR antibodies. In the present case, high levels of anti-NMDAR antibodies were detected in the CSF, but not in the plasma. The association between the prodromal flu-like symptoms and the antibodies against NMDAR is also a material of debate. Some authors emphasize the connection between a viral infection and injury of the blood–brain barrier, which facilitates transmission of NMDAR autoantibodies to the CNS.[11]

An EEG may be important in distinguishing between primary psychiatric disorder and encephalitis, since a vast majority of patients with anti-NMDAR encephalitis exhibit nonspecific slowing at a certain stage during the illness.

Treatment for anti-NMDAR encephalitis remains challenging, due to the fact that no complete guidelines have been published to date.

The wide majority of authors agree that treatment must target both the cause and the clinical consequences of the encephalitis. Anti-NMDAR encephalitis treatment is more effective in patients who have a primary tumor removed and there are cases in which ovarian teratomas were discovered years after the initial onset of symptoms, mainly in patients with a slow recovery.[12] Some authors believe in early oophorectomy even in cases when the presence of an ovarian tumor cannot be established in imaging studies. In a case described by Peery et al[12] postoperative biopsy discovered an occult teratoma, and the tumorectomy resulted in an improvement of the symptoms. In most cases, immunotherapy is the first-line treatment and includes corticosteroids, IVIg and TPE, unaccompanied or in combination.[13] The second-line treatment includes rituximab and cyclophosphamide, and is used in patients who show a late diagnosis or did not have a primary malignancy.[14]

In the present case, the patient was firstly treated with corticosteroids (methylprednisolone), IVIg and rituximab. Nevertheless, she started with repeated infections, so rituximab had to be stopped. This first-line immunosuppressive treatment failed to produce any improvement of the patient's clinical condition. She only improved following the TPE, although clinical improvement of anti-NMDAR encephalitis is not always achieved with TPE.[15,16] According to the guidelines published by the American Society for Apheresis, the use of TPE must be considered as a third-line treatment in paraneoplastic neurological syndromes (grade 2C).[17] Regarding the role of plasmapheresis, we still have several debates and conflicting data in the literature. According to Dalmau et al[5] the use of plasmapheresis should not be routinely. On the other hand, there are recent data supporting the use of plasmapheresis to improve the patient clinical status.[18,19] DeSena et al[20] compare the use of plasmapheresis alone versus before intravenous corticoids in the treatment of anti-NMDAR receptor encephalitis, with better results in the last case.

This case report has some strengths and some limitations. Regarding the limitations, it is not based on systematic studies so, it may not be generalizable. However, this case report may help the medical identification of this rare disease and therefore is an important educational article.

4. Conclusion

NMDAR encephalitis mainly affects young women with ovarian teratomas and is a potentially lethal but reversible disorder with a good clinical outcome if diagnosed and treated promptly. The gold standard for diagnosing anti-NMDAR encephalitis is the detection of IgG antibodies against the GluN1 subunit of NMDA receptors in either the CSF or plasma; however, other diagnostic measures, including EEG or MRI may also assist clinicians in obtaining the diagnosis. The early detection of tumor, its surgical removal, and early immunotherapy make it possible to shorten the progression of disease, improve the survival rates, and limit the negative long-term consequences for the patients. So far TPE must similarly be considered in the clinician's armamentarium, mainly in cases where initial treatment has failed. In the current case, a long-term follow-up examination revealed a good clinical outcome, without any major neurological or psychiatric complications following the anti-NMDAR encephalitis. A multidisciplinary team, including gynecologist, psychiatrists, neurologists and intensivists, must be involved in the process of recognition and management of the disease. Available data remain unclear and therefore there is an urgent need for good quality clinical trials.

Author contributions

Conceptualization: Monica Gomes Ferreira
Formal analysis: Monica Gomes Ferreira.
Project administration: Monica Gomes Ferreira.
Writing – original draft: Monica Gomes Ferreira, Victoria Lapresa Alcalde.
Writing – review & editing: Monica Gomes Ferreira, Maria Helena García Sánchez, Lourdes Hernández Hernández, María José Doyague Sánchez.

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