Post-Abortum Anti-N-Methyl-D-Aspartate Encephalitis Mimicking Herpetic Encephalitis: A Case Report and Literature Review

Saied Zakaria¹, Ben Sassi Samia¹, Nabli Fatma¹, Sinda Ben Fadhel², Jeridi Cyrine¹, Blel Samir¹

¹Neurology Department, Mongi Ben Hmida National Institute of Neurology, Tunis, Tunisia
²Outpatient Department, Mongi Ben Hmida National Institute of Neurology, Tunis, Tunisia

Corresponding author: Saied Zakaria, Neurology Department, Mongi Ben Hmida National Institute of Neurology, University of Tunis El Manar. Av. JbelLakhdhar. 1007, la Rabta Bab Saâdoun, Tunis Tunisia, E-mail: zakariasaid@hotmail.com, Tel: +21698478478


Abstract

We describe the case of a 32-year-old-woman, who developed psychomotor agitation and memory disorders, followed by headache, insomnia and generalized seizures in the context of fever one week following a voluntary abortion. The clinical, biological and radiological findings initially showed an infectious etiology, especially herpetic encephalitis. However, worsening of the cognitive and neurological symptoms was observed under specific anti-infective therapy. The presence of Anti-N-Methyl-D-aspartate (NMDA) antibodies allowed the diagnosis of a dysimmune etiology of the disease. Endovaginal and transvaginal ultrasound examinations did not show ovarian teratoma. Later, the patient recovered with corticotherapy. In the light of our case, reported cases of NMDA encephalitis occurring during pregnancy or after abortion, and all autoimmune encephalitis (AE) were reviewed. Clinical diagnosis and a therapeutic approach for the disease were also proposed.

Anti-NMDA encephalitis is currently a well-recognized dysimmune encephalitis. However, its occurrence in a perigestational period, especially after abortion, is rare and may not be recognized. Neurologists, family physicians and obstetricians should be aware of this highly serious but reversible dysimmune entity. Specific pathomechanisms related to the physiological changes in pregnancy, the way to use immunomodulator treatments as well as obstetrical cares should be better determined in the future.

Keywords: Anti-NMDA Receptor Encephalitis; Autoimmune Disorders; Gestation; Teratoma; Immunomodulation
Introduction

NMDA receptors antibody encephalitis is an autoimmune disease in which antibodies are produced against synaptic glutamate receptors. It occurs in a context of paraneoplastic, autoimmune or previous infections, particularly with viral agents. The disease affects young people in the reproductive age group. Some studies have shown a female preponderance of this disease, with a female-to-male sex ratio of 4/1 [1]. Prognosis is generally favorable [2]. Ovarian teratoma is the most common associated neoplasm reported in the largest cohorts.

Also, it is known that pregnancy and postpartum periods may be influenced by significant immunomodulation for the mother [3]. The increasing levels of pregnancy hormones and proinflammatory cell-mediated immune responses induced by T cells and natural killer cells are thought to be involved in significant changes in immune homeostasis during perigestational period [3]. Pregnancy loss is also related to multifactorial causes. A part of recurrent spontaneous abortions were found to be associated with certain autoimmune antibodies and alteration in the expression of some HLA class may also induce abortion [4].

Occurrence of anti-NMDA receptors encephalitis in a peri-gestational period is rare and may be not recognized. Only few reported cases of anti-NMDA receptors encephalitis during pregnancy have been described.

Herein, we report a case of anti-NMDA receptor encephalitis, mimicking herpetic encephalitis, diagnosed one week after a voluntary abortion in the late first trimester of pregnancy.

Case Report

A 32-year-old woman presented with psychomotor agitation and memory disorders persisting for 3 weeks.

The symptoms appeared one week after a voluntary abortion performed in the late first trimester of a normally-progressing pregnancy. The patient rapidly developed an abnormal behavior with hetero-aggression and memory disorders, followed by headache and insomnia a week later. (Figure 1)

On examination, she was sub-febrile (38.5°C), confused and agitated. Her neck was stiff but Kerning’s and Brudzinski’s signs were negative. Her pulse rate was 108 beats/min, and slight hypotension was observed (85/60 mmHg). The reminder of the physical examination was unremarkable. Chest radiography showed no abnormalities.

Magnetic resonance imaging (MRI) of the brain showed a sub-cortical white matter lesion in the right internal temporal lobe, appearing hyper intense on T2-weighted and T2-Flair sequences. Gadolinium-enhanced T1-weighted image revealed gyriform right temporal meningeal enhancement with no enhancement of the sub-cortical white matter lesion. Diffusion-weighted MR images showed no diffusion restriction (Figure 2A-D). These radiological findings were suggestive of a herpetic infection as etiology. Routine serum analyses, including blood biochemistry and hemogram test were normal. Serum and urine toxicology screening was negative (for opiates, benzodiazepines, antidepressors and ethanol). Lumbar puncture revealed a xanthochromic fluid containing 20 white cells /mm3 and a moderate elevation of cerebrospinal fluid (CSF) proteins. Low glycorrhachia was present (Ratio glycorrhachia/Glucose in blood=0.4). No red blood cells were identified in CSF. Sputum smear examination was negative for acid-fast bacterium. Serologies for HIV, hepatitis B and C, as well as, syphilis were negative. Blood Cultures were negative. PCR analysis of the cerebrospinal fluid was negative for herpes simplex virus, cytomegalovirus and varicella zoster virus. Results of CSF bacterial cultures (Mycobacterium tuberculosis, Listeria monocytogenes) were negative. Presence of cryptococcal antigen in CSF was negative. The clinical course as well as the radiobiological findings oriented our initial diagnosis to a probable infectious encephalopathy. The patient was treated with Aciclovir at the moment of admission (10mg/kg three times per day) (Figure 1).
The clinical course was unfavourable with fluctuations in consciousness and psychomotor agitation. Until day 14 of anti-infectious treatments, the patient was sub-febrile. She developed three generalized tonic-clonic seizures. (Figure 1).

Our diagnosis was then reoriented to a possible dysimmune etiology. Autoimmune screening, including rheumatoid factor, antinuclear and anti-double-stranded DNA antibodies was negative. The Serum tested positive for antibodies against NMDA receptor. Thus, diagnosis of anti-NMDA receptor encephalitis was made. Methyl prednisolone 1 gr per day (× 5 days) was intravenously administered three weeks following the symptoms onset with a relay of oral Prednisone (0.5 mg/kg per day) (Figure 1).

A rapid recovery of both cognitive dysfunction and agitation was observed after the first days of corticotherapy. Endovaginal and transvaginal ultrasound examinations and computed tomography imaging to detect ovarian teratoma did not show abnormalities.

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**Figure 1:** Time line of clinical history in our patient and anti-NMDA encephalitis administered therapy

**Abbreviations:**
- CSF: cerebrospinal fluid
- CT: computed tomography imaging
- ED: Emergency department
- LP: Lumbar punction
- MP: Methylprednisolone
- MRI: Magnetic resonance imaging
- US: Ultrasounds
(A) T2 Flair weighted image demonstrating increase in T2 intensity in the right internal temporal region. (Arrow).
(B and C) T1-weighted MRI image after gadolinium intravenous injection demonstrating right meningeal enhancement within the region of T2/FLAIR hyperintensity. (Arrow).
(D) Diffusion-weighted image, There was no diffusion restriction on diffusion-weighted images.

**Figure 2:** Temporal MRI abnormalities during acute phase of the disease (2 weeks after onset)
After being discharged (at one month of treatment with corticosteroids), the patient was calm and well-oriented. Residual deficits of working memories, anomia and phonemic paraphasia were, however, observed. A speech therapy was prescribed with corticosteroid gradual tapering.

A follow-up cerebral MRI performed 6 months after treatment detected subsequent necrosis of cerebral parenchyma in the temporal region (Figure 3 A-C).

Figure 3: Control cerebral MRI performed 8 months after treatment

Axial plane (A) and coronal (B) T2/Flair weighted sequence showing a focal area of parenchyma loss in the right temporal region (Arrow). Dilatation of the homolateral temporal born of the lateral ventricle is also demonstrated (asterixis). Axial plane T2 weighted image (C) showing diffuse hyperintensity in both temporal cortices, and subcortical white matter (arrow).

Axial plane (A) and coronal (B) T2/Flair weighted sequence showing a focal area of parenchyma loss in the right temporal region (Arrow). Dilatation of the homolateral temporal born of the lateral ventricle is also demonstrated (asterixis). Axial plane T2 weighted image (C) showing diffuse hyperintensity in both temporal cortices, and subcortical white matter (arrow).
After three years of follow-up, a gradual improvement of the clinical status was observed, especially with regard to memory disturbance and psychiatric symptoms. The patient did not present signs of relapses.

**Discussion**

NMDA receptors are ligand-gated ion channels mediating excitatory neurotransmission in the brain. The normal function of these receptors involves simultaneous binding of glycine and glutamates inducing their own activation, thus resulting in cation influx unto the cell [1].

In NMDA encephalitis, Ig G antibodies target the NR 1 subunit of the NMDA complex [5], resulting in a decrease in the number of functional NMDA mediated synaptic.

Almost all patients affected by this disease progress through predictable, discrete, and well-described phases: the prodromal phase with symptoms resembling upper respiratory infection. It is followed by behavior changes and psychiatric disorders lasting one to three weeks. In the end, the neurological phase that can last from weeks to months) may be potentially life-threatening [1] (Figure 4). Positivity of NMDA anti-bodies, both on serum and in CSF, remains the key examination to confirm the diagnosis.

Differential diagnosis with herpetic encephalitis was debated in earlier reported cases [6–9] both in patients with normal MRI [7,8] and those with MRI abnormalities [6,9].

Although over half of MRI imaging in NMDA encephalitis show no abnormalities, T2/ Flair hyperintensity of the medial temporal lobe is among the most reported abnormalities, followed by the frontal lobes and the hippocampus as sites of hyperintensity [10]. However, radiological findings can be non-specific and a large variability between patients was observed [11]. The presence of clinical signs of infection, such as fever in the case of our patient, or biological signs, like leukocytosis or elevated C-reactive protein serum levels, can mislead the clinician’s diagnosis to an infectious origin of encephalopathy.

In herpetic encephalitis, also, the medial temporal lobe is the most commonly involved area since the herpes virus is typically reactivated from the trigeminal ganglion that is close to this lobe [9].

Our patient presented symptoms one week following a voluntary abortion after three months of a normally-progressing pregnancy. An ovarian teratoma was identified and removed in only 4 patients. A caesarean section was performed in 4 patients because of the severity of the neurological manifestations. In the case reported by Chan LW et al. [12] involving a 23-year-old primigravida woman presenting a clinical picture similar to our case, pregnancy ended with a miscarriage within 2 days of hospitalization (Table 1).
Suggestive symptoms of AE: Acute or subacute onset (<3 months) of the following symptoms: memory disturbance, altered level of consciousness, coma, lethargy, movement disorders, unexplained seizures, unexplained psychiatric symptoms or personality change, sleep disturbance or abnormal sleep movements, autonomic disturbances (hypertension, tachycardia, hypoventilation)

- careful anamnesis and clinical examination
- Serum and CSF analysis
- Cerebral MRI, prolonged EEG

1: CNS infections, Prions disease, Metabolic or Mitochondrial encephalopathy, Drug toxicity, CNS neoplasms, cerebro-vascular disorders, rheumatologic disorders

Evidence of reasonable alternative diagnosis

Yes
- Specific treatment

No

Suspicion of AE

No

Consider diagnosis of sero-negative AE forms

Yes

Perform neuronal antibodies tests both on serum and CSF

Positive
- Consultation with AE experts
- AE specific therapy

Negative
- Repeat screening every 3 to 6 months up till 4 years
- Repeat screening every 3 to 6 months up till 4 years

Figure 4: Flowchart of clinical-diagnostic approach to suspected AE. AE=Autoimmune encephalitis; CNS = central nervous system; CSF=cerebrospinal fluid; CT=computed tomography; EEG = Electroencephalography; MRI = magnetic resonance imaging; PET = positron emission tomography; US=ultrasound.
<table>
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<tr>
<th>Authors [réf]</th>
<th>Age</th>
<th>Gestation Age (weeks)</th>
<th>Clinical presentation</th>
<th>Teratoma screening</th>
<th>Outcomes</th>
<th>Immunomodulators therapies used</th>
</tr>
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<tbody>
<tr>
<td>L.W. Chan et al. [12]</td>
<td>23</td>
<td>First Trimester</td>
<td>Fever, acute confusion, behavior abnormalities, hallucinations</td>
<td>Right ovarian tumour</td>
<td>Miscarriage, Discharge on day 87</td>
<td>Metylprednisolone, Plasmapheresis, anti-CD20 therapy</td>
</tr>
<tr>
<td>Kumar MA et al. [18]</td>
<td>20</td>
<td>8</td>
<td>Behavior abnormalities, abnormal movements, decreased level of conscious</td>
<td>Bilateral mature teratoma</td>
<td>Abortion, Discharge on day 87 with minimal deficits</td>
<td>Mechanical ventilation, Intravenous immunoglobulin, left salpingo-oophorectomy</td>
</tr>
<tr>
<td>Jiyoung Kim et al. [17]</td>
<td>28</td>
<td>7</td>
<td>abnormal behavior, epileptic seizure, and hypoventilation then coma</td>
<td>No teratoma identified</td>
<td>Miscarriage, Discharge 22 weeks after hospitalisation</td>
<td>Mechanical ventilation, antiepileptic therapy, methylprednisolone (then relay by low dose of oral corticosteroids, intravenous immunoglobulin)</td>
</tr>
<tr>
<td>Javaad Ahmad et al. [13]</td>
<td>26</td>
<td>Abortion 3 months before appearance of neurological symptoms</td>
<td>Abnormal behavior, seizures, opisthotonic posturing, fever</td>
<td>right ovarian cyst (non-malignant transformation)</td>
<td>Bilateral oophorectomy, antiepileptic therapy, intravenous immunoglobulins, anti-CD 20 therapy</td>
<td></td>
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**Table 1:** Main clinical presentations in reported cases of anti-NMDA Receptor encephalitis preceded or followed by abortion

On the other hand, occurrence of anti-NMDA encephalitis after abortion was described earlier in a young woman who developed clinical signs three months after abortion. Her condition required bilateral oophorectomy in addition to immunosuppressive therapy for stabilization [13] (Table 1). In their Italian cohort of pediatric cases, Nosadini et al. [14] demonstrated that the risk of relapse is reduced by the use of combined immune therapies at first disease event. However, the use of long-term immunosuppression should be reserved only in case of disease relapse. The Clinical and paraclinical factors affecting the risk of relapse at the early stage of the disease still need to be identified [2].

A Gradual clinical improvement was observed during pregnancy in the majority of reported cases, with little or no sequelae [15]. Nevertheless, the right time to terminate pregnancy and the best obstetrical care (way of delivery) have not been well-established [5].

If identified, Immunomodulators and resection of ovarian teratoma leads to a favorable evolution of NMDA encephalitis, already described in pregnant women [5,16]. Our patient had a similar clinical course, involving a recovery period of three months under initial corticotherapy without the need to use another immunomodulator. Social behaviors and psychiatric disturbances were the last to improve as previously reported [6].

Our case report highlights the importance of considering anti-NMDA encephalitis and more broadly auto-immune (AE) encephalitis both in pregnant women or after abortion [13]. The occurrence of this entity during pregnancy and specially after...
abortion was rarely reported in the literature [12,13,17,18]. Jouber et al. [19] reported the characteristics of anti-NMDA encephalitis in pregnant women or in those becoming pregnant during recovery [11 patients]. When occurring during pregnancy, the majority of encephalitis appeared during the first and second trimester of pregnancy. A wide neurological symptoms including memory disturbances, movements disorders, seizures or unexplained psychiatric symptoms should awareness family physicians, emergency specialists and obstetrical cares of the possibility of anti-NMDA encephalitis (Figure 4) especially if appeared acutely or sub acutely.

NMDA encephalitis is the most common type of (AE). The latter may occur at any age and its diagnosis is still challenging for clinicians. This can be explained by the heterogeneity of the clinical phenotypes, the wide differential diagnosis and the lack of specific biomarkers other than the antibodies (Table 2) [20]. At the disease onset, immunological disturbances by targeting neuronal antigens lead to hyper excitability [21]. Two main categories can be distinguished: AE with antibodies targeting synaptic antigens receptors or ion channels, and AE with antibodies against intracellular antigens. In the former, antibodies are considered pathogenic and response to therapy is often effective. However, in the latter, T-cell-mediated cytotoxicity is more likely to be involved since antigens are inaccessible [21,22] and response to therapy in such cases is generally poor [22]. Typical symptoms of AE are subacute (< 3 months) or acute onset of short-term memory disturbance, altered level of consciousness, lethargy, personality change, psychiatric symptoms and seizures (that may be subclinical(Figure 4) [20,23]. Some clinical features are suggestive of more specific groups (Table 2). This is important since clinical presumption at the early stage can favor rapid initiation of therapy. Moreover, clinical presentation of AE may extend beyond central nervous symptoms [Table 2] [24,25].

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Main clinical characteristics</th>
<th>Associated tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMDA (13,17)</td>
<td>Young women, Psychiatric onset, oro-facial dyskinesia, dystonia, seizures, central hypoventilation, other dysautonomia signs</td>
<td>Ovarian teratoma (95%) extraovarian teratoma (2%).</td>
</tr>
<tr>
<td>LG1 (17, 30)</td>
<td>Faciobrachial dystonic seizures, near memory disorder, dysphonia, hyponatermia</td>
<td>Thymoma, Neuroendocrine tumors (11%).</td>
</tr>
<tr>
<td>CASPR 2 (13)</td>
<td>Cerebellar ataxia, signs of limbic encephalitis, peripheral nerve hyperexcitability (neuromyotonia)</td>
<td>Thymoma</td>
</tr>
<tr>
<td>GABA A (13,17,31)</td>
<td>Refractory seizures / status epilepticus, signs of encephalitis</td>
<td>Thymoma (25%), small-cell lung cancer.</td>
</tr>
<tr>
<td>GABA B (13,17)</td>
<td>Cerebellar ataxia, opsoclonus-myoclonus, memory loss, prominent seizures</td>
<td>Small-cell lung cancer (58%).</td>
</tr>
<tr>
<td>DDPX (13,24, 32)</td>
<td>Prodromal weight loss, diarrhea and other GI symptoms, PERM, startle, psychoses, irritability, mutism, insomnia,</td>
<td>Lymphoma (&lt;10%)</td>
</tr>
<tr>
<td>mGlur5 (13,31)</td>
<td>Young adult, Memory loss, myoclonus, cerebellar ataxia, other signs of encephalitis</td>
<td>Hodgkin’s lymphoma, small-cell lung cancer.</td>
</tr>
<tr>
<td>DR2 (13)</td>
<td>Children or adolescent, psychiatric signs, dystonia, chorea (basal ganglia lesions)</td>
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**AMPAR**: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; **CASPR2**: contactin-associated protein-2; **DDPX**: dipeptidyl-peptidase-like protein-6; **D2R**: dopamine-2 receptor; **GABA A**: γ-aminobutyric acid-A receptor; **GABA B**: γ-aminobutyric acid-B receptor; **LG1**: leucine-rich, glioma-inactivated protein-1; **mGlur5**: metabotropic glutamate receptor 5; **NMDAR**: N-methyl-D-aspartate receptor; **PERM**: progressive encephalomyelitis with rigidity and myoclonus

**Table 2**: Main clinical characteristics of auto-immune encephalitis (with specific neuronal antibodies) and associated tumors
In the majority of AE, brain MRI is abnormal (50-70%) [20]. T2-weighted and T2-Flair sequences show hyper intense abnormalities. Types and localization of MRI abnormalities vary depending on the associated antibody [20,25]. Brain MRI is also an important tool to exclude potential differential diagnosis of AE. Electroencephalography is recommended in the initial work-up [20]. Extreme delta brush is a characteristic pattern of NMDA encephalitis, with a poor prognosis value [26]. In AE, CSF analysis typically shows mild pleocytosis. Presence of oligoclonal bands is uncommon [23]. Proteinorachia can be normal or slightly elevated and glucorachia is normal [20].

Detection of a specific IgG antibodies allows a definitive diagnosis of AE [23]. Testing antibodies in both serum and CSF is recommended [20]. The gold standard techniques, actually used with high levels of sensitivity and specificity are cell-based assays and immunochemistry on murin brain tissues [20,27]. However, titers of antibodies poorly correlate with the clinical course [23]. In at least 7% of cases, antibodies screening is negative [20], Thus, diagnosis should not exclusively be made based on the results of these biomarkers (Figure 4). This situation is referred to as autoantibody-negative (probable AE), while definite AE requires positivity of neuronal antibodies [24].

Once a patient is diagnosed with AE, a prolonged screening for underlying neoplasm should necessarily be performed (Figure 4). Identification and then treatment of an underlying malignancy (chemotherapy or tumor resection), either before or together with immunotherapy, is essential for neurological improvement [24].

AE is among the potentially treatable etiologies of encephalitis [20]. First line immunotherapy includes IV methylprednisolone, started either with plasmapheresis or IV polyvalent immunoglobulins [20,24]. Choice between the two is based on expertise practice [20]. Concomitant tumoral removal (if identified) should be performed. It is recommended that immunotherapy should be started as soon as diagnosis is suspected, even if confirmation of autoantibody status is still ongoing [28]. Indeed, early treatment of AE has been associated with better prognosis [24].

After 2-3 weeks of treatment, absence of clinical improvement should indicate the initiation of second-line therapies that include Rituximab (a B-cell depletion agent,) or cyclophosphamide [20,24].

AE is usually monophasic; however, relapses may occur and in these situations second-line therapies minimize the risk of relapse (Figure 4) [29]. As it was mentioned above, predictive factors of relapses are not yet specified. Moreover, appropriate maintenance therapy regimen for AE is not yet well-established. It is mainly based on steroid-sparing agents during the first two years after diagnosis, with the main goal is to prevent relapses (Figure 5) [20].
Figure 5: Diagram of immunotherapy for AE. Legend: AE=Auto-immune encephalitis; AZA=Azathiprine; IV MP = intravenous methylprednisolone; MMF=Mycophenolate mofetil; RTX=rituximab.
Conclusion

The knowledge of AE should be increased among neurologists but also among non-neurology professionals, and especially among health professionals dealing with young women, since this is the most affected age group beside children.

At presentation of encephalitis at any age, both viral and autoimmune etiologies should be suspected. Clinical presentation may be overlapping in the first stages between NMDA encephalitis (or others types of AE) and infectious etiologies. An Early recognition of the underlying cause is crucial since treatments are different.

Early investigations should target the two entities together. Once diagnosis of AE is made, specific immunotherapy should quickly be initiated along with screening for an associated tumor. In fact, early identification and correct treatment of AE ensures better prognosis. However, future randomized studies are needed to better standardize the therapeutic approach, especially for long-term therapy of AE.

Non neurology professionals, especially health professionals dealing with young women, should be aware of AE entity, which is more frequently observed in young women as well as children. Its occurrence after abortion is possible. Prompt and adequate treatment leads to improved outcome and may be a protective factor against relapse.

Specific pathomechanisms related to the physiological changes in pregnancy, the way to use immunomodulator treatments as well as the obstetrical care should be better determined in the future.

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All authors report none of conflict interest.

Patient consent for publication

Written informed consent for publication was obtained from the patient.
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