

# Ovarian Teratoma presenting as Anti NMDAR Antibody Negative Limbic Encephalitis

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## Abstract

Anti NMDA receptor (NMDAR) antibody mediated limbic encephalitis is the most common type of autoimmune encephalitis. Nearly half of the females presenting with anti NMDAR encephalitis have associated ovarian teratoma. Almost all of them have positive anti NMDAR antibody. Here we present a case of ovarian teratoma associated limbic encephalitis, with clinical picture typical of anti NMDAR mediated encephalitis, who was found to be negative for the antiNMDAR antibody. Clinicians should not defer from investigating a case of suspected anti NMDAR encephalitis for ovarian teratoma, even if antibody is negative.

## Introduction

The incidence of autoimmune encephalitis is increasing with improved recognition of clinical syndromes and diagnostic testing of various neuronal cell surface antibodies. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is the most common autoimmune encephalitis, which presents with classical clinical features. The classic presentation of this syndrome is a subacute encephalopathy with core clinical features of encephalopathy, psychiatric symptoms, cognitive symptoms, seizures and extrapyramidal movement disorder often associated with inflammatory CSF. About 43 % of Anti NMDA encephalitis women have associated ovarian teratoma.<sup>1</sup>

We report a case of clinically typical case of anti NMDAR encephalitis with negative antibody screening for NMDAR- ab, who was found to have associated ovarian teratoma and had remarkable clinical improvement with removal of the tumour.

## Case Report

We report the case of a 24 year old unmarried female, studying for Chartered Accountancy who presented with altered behavior, irrelevant talk and fever for 10 days. To begin with, she spent one whole night scribbling in a diary and sending irrelevant messages to friends in the mobile phone. She was talking irrelevant things and was angry, restless and pacing about. Following this, the patient developed delusions and hallucinations. She claimed that

she could see media personnel in her room with cameras. She tried to drive them away, saying they are there to harm her. She was scared and would shut herself in her room. She started repeating religious verses. Later on, her word output decreased progressing to mutism.

About a week later, patient developed orofacial dyskinesia in the form of jaw opening and closing, chewing, facial grimacing and lip pouting. Patient continued to be catatonic and mute. Meanwhile occasional fever spikes persisted.

On examination the patient was mute and there was no eye-to-eye contact during conversations. She kept her eyes tightly closed, was grimacing to pain but not obeying commands. The blood pressure recordings and pulse rate fluctuated over a wide range. She had orthostatic hypotension and was sweating profusely. She had generalized rigidity with exaggerated tendon reflexes and extensor plantar response.

She was started on acyclovir suspecting viral encephalitis. However cerebrospinal fluid showed no cells with normal protein and sugar. MRI brain didn't reveal any abnormality. EEG showed generalized slowing. HSV polymerase chain reaction (PCR) was negative and acyclovir was discontinued. Serum and CSF samples were tested negative for antibodies against voltage-gated potassium channel and NMDARs. Serum paraneoplastic panel of neuronal antibodies were also

negative. Ultrasonogram abdomen was essentially normal. A thorough work up for fever including vasculitic profile was normal. However in view of her neuropsychiatric symptoms, fever, catatonia, orofacial dyskinesia and autonomic instability, the possibility of autoimmune encephalitis was strongly considered. So methylprednisolone 1g intravenous for 5 days followed by intravenous immunoglobulins (0.4 g/kg/day) was started.

With a strong suspicion of autoimmune encephalitis, with a possible paraneoplastic association, her computerized tomography (CT) scan of the abdomen was done, even though ultrasonogram was normal. CT scan showed a cystic lesion arising from her left ovary suggestive of teratoma. In view of such strong clinical possibility and the paraneoplastic association, the cerebrospinal fluid study was repeated which showed nervous system specific autoimmunity in the form of an unclassified antibody, but anti NMDAR-ab was again negative. She underwent a left ovarian cystectomy and histopathology of the tumor specimen revealed benign mature cystic teratoma.

Her autonomic instability reduced over the next three days and rigidity and fever decreased by one week. By the end of the first week, she was able to talk with her family members and ask for food and water. By the 10th day, she was making eye-to-eye contact during conversations with good word output. By the 20th day, she was well oriented, had no rigidity and could walk normally. By the end of two months, she was performing her household chores and school work easily.

## Discussion

Anti NMDAR encephalitis, a well-recognized autoimmune encephalitis

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with autoantibodies to the NR1 subunit of NMDA receptor was first described by Dalmau et al.<sup>3</sup> Clinicians should consider antibody testing in patients presenting with acute encephalitis. In a UK study of encephalitis presenting to district hospitals,<sup>4</sup> 16 of the 44 patients (36%) without an identifiable infectious aetiology, had autoantibodies to either NMDAR (9 patients) or VGKC complexes (7 patients), making autoimmunity the third highest association with acute encephalitis. Furthermore, in a series of patients from the Queen Square intensive care unit, around a fifth of the patients with encephalopathies had NMDAR-abs.<sup>5</sup>

About 43% of anti NMDA encephalitis women have associated ovarian teratoma. The frequency of ovarian teratomas was 56% in women > 18 years old, but only 31% in women < 18 years old.<sup>1</sup> The pathogenesis involves autoimmune over expression of NR2 subunits by nerve tissues in the teratomas that lead to a break in the immune tolerance. Associated factors such as a prodromal viral-like illness and genetic factors may play additional roles in the initiation of the immune response.<sup>6</sup> Rarely, tumours such as testicular teratomas and small cell lung cancers have also been associated with this entity.<sup>7</sup>

In those patients with ovarian or other tumours, the syndrome responds to immunotherapy once the tumour is removed; later removal can be associated with poor outcome.<sup>8,19</sup>

Previous studies have shown a universal association of anti NMDAR-ab in all patients with ovarian teratoma associated with limbic encephalitis.<sup>2</sup> Only very rarely, ovarian teratomas with autoimmune encephalitis have presented without anti NMDAR-ab. In our patient, even though the clinical picture was classical of the anti NMDAR encephalitis, antibody testing was negative on two occasions both in the serum and CSF. Sensitivity for NMDA receptor antibodies was higher for CSF (100%) than for serum (86%).<sup>10</sup>

Rarely, AMPA receptor mediated encephalitis can be associated with ovarian teratoma.

Patients with AMPA receptor antibodies develop acute limbic dysfunction that can be associated with prominent psychiatric symptoms. The

disorder most commonly affects middle-aged women. Most patients present with the subacute onset of confusion, disorientation and memory loss with or without seizures. About 70% of patients will have an underlying tumour in the lung, breast or thymus.<sup>11</sup> Romana Höftberger, Agnes van Sonderen et al<sup>12</sup> reported 22 patients with autoimmune encephalitis associated with AMPA receptor antibody, among which two patients had ovarian teratoma.

In our patient, even though the clinical presentation was different from that reported in literature,<sup>11,12</sup> the possibility of AMPA receptor antibody mediated encephalitis cannot be ruled out. Unfortunately AMPA receptor antibody testing could not be done in our patient because of non-availability.

Sadahisa Okamoto, Teruyuki Hirano, Yukitoshi Takahashi<sup>13</sup> reported a rare case of ovarian teratoma associated limbic encephalitis who had autoantibodies to glutamate receptor (GluR) in the CSF. This was a case of 35-year-old woman with altered consciousness and was initially diagnosed as non-herpetic encephalitis. Her signs and symptoms improved with acyclovir and steroid pulse therapy. However, after the treatment, an ovarian tumour was discovered, and autoantibodies to GluR were detected in the CSF.

Andrew D. Smith, Lawrence Samkoff et al<sup>14</sup> reported a woman in her mid-20s who presented with fever, headache, encephalopathy and predominant ataxia and later found to have ovarian teratoma and antiNMDA antibody was negative in that patient. Marina Frasset, Luis Bataller et al<sup>15</sup> reported a patient with AQP4 antibody positive longitudinally extensive transverse myelitis (LETM) revealing ovarian teratoma. The teratoma expressed the AQP4 antigen, providing a possible paraneoplastic link between both diseases.

These case reports may suggest that ovarian teratoma can also present with cerebellar ataxia and longitudinally extensive transverse myelitis other than the picture of LE and those patients presenting with LE associated with ovarian teratoma need not always have anti NMDAR antibody as previously thought.

It is important to realize that there are patients whose syndromes appear

to be identical to the established phenotypes, but who are negative on the tests currently available. Moreover, many autoantibodies to specific neuronal proteins are only beginning to be unravelled in patients with otherwise unexplained subacute onset of neurological symptoms, with or without MRI and CSF evidence of inflammation. In all of these patients, immunosuppressive treatments should be seriously considered, once the alternate possibilities are reliably ruled out.

## Conclusion

The case is presented to high light the fact that the neurophysicians should not defer from investigating for ovarian tumour in patients with strong clinical suspicion of autoimmune encephalitis, even if anti NMDAR antibody is negative.

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