

# CASE REPORT

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## A RARE CASE OF OVARIAN TERTATOMA CAUSING ACUTE AUTOIMMUNE ENCEPHALITIS

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**ABSTRACT:** Anti-NMDA (N-methyl D-aspartate) receptor antibody encephalitis, also termed NMDA receptor antibody encephalitis, is an acute form of encephalitis caused by an autoimmune reaction primarily against the NR1 subunit of the NMDA receptor.<sup>[1]</sup> It is commonly associated with tumours, mostly teratomas of the ovaries, and is thus considered a paraneoplastic syndrome. However, there are a substantial number of cases without any tumour.<sup>[2]</sup> Here we are discussing a case of 24 year old lady presented in our medicine department with above disease.

**KEYWORDS:** NMDA receptor antibodies, ovarian teratoma, paraneoplastic encephalitis.

**INTRODUCTION:** Disease is seen mainly in children, with a median age of diagnosis of 21 years. Starts with prodromal symptoms-headaches, flu-like illness, or symptoms similar to an upper respiratory infection which may be present for weeks or months prior to disease onset. Progresses at varying rates and patients may present with a variety of neurologic symptoms-behavior changes are a common first symptom- increased agitation, paranoia, psychosis, and violent behaviors. Other common manifestations include seizures and bizarre, often rhythmic, movements mostly of the lips and mouth but also including pedaling motions with legs or hand movements resembling playing a piano. Some other symptoms typical during the disease onset include impaired cognition, memory deficits, and speech problems (including aphasia or mutism). As the disease progresses the symptoms become medically urgent and often include autonomic dysfunction, hypoventilation, cerebellar ataxia, hemiparesis, loss of consciousness, or catatonia. During this acute phase most patients require care in an Intensive Care Unit to stabilize breathing, heart rate, and blood pressure.

The condition is mediated by auto antibodies that target NMDA receptors in the brain. These are produced by cross reactivity with NMDA receptors in the teratoma –the possible 2 mechanisms described are firstly, increased serum NMDAR-antibodies than CSF antibodies, on average 10 fold higher. This strongly suggests the antibody production is systemic rather than in the brain / CSF. Passive access involves the diffusion of antibodies from the blood across a pathologically disrupted blood-brain barrier (BBB) mainly NMDA receptors in the teratoma. Exact pathophysiology is following acute inflammation of the nervous system. Intrathecal production (production of antibodies in the intrathecal space) may also be a possible mechanism. Once the antibodies have entered the CSF; they bind to the NR1 subunit of the NMDA receptor. There are 3 possible methods in which neuronal damage occurs.1.A reduction in the density of NMDA receptors on the post synaptic knob, due to receptor internalization once the antibody has bound.

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This is dependent on antibodies cross linking.2.The direct antagonism of the NMDA receptor by the antibody, similar to the action of typical pharmacological blockers of the receptor 3.The recruitment of the complement cascade via the classical pathway (antibody-antigen interaction). Membrane attack complex (MAC) is one of the end products of this cascade and can insert into neurons as a molecular barrel, allowing water to enter. The cell subsequently lyses.

Treatment involves removal of the tumour along with first line immunotherapy.

**CASE PRESENTATION:** A 24 year old P1L1, previous LSCS (big baby), LCB 3 years back and LMP 5/7/2014 presented to our medical ICU with complaints of vomiting, heaviness of head, altered behavior and speech & decreased sleep, along with abnormal movements of lips, visual and auditory hallucinations of 7 days duration and decreased urine output and fever of 2 days duration. She was admitted in a psychiatry hospital in view of above symptoms for 2 days, from there she was referred to our hospital as symptoms persisted and patient developed fever and decreased urine output. No h/o headache/palpitations/chest pain/pain abdomen/joint pains/bleeding/pulmonary TB. No significant past history or family history.

Physical examination - Patient not conscious or oriented, HMF –not normal, GCS –E2V1M3 PR-108/MT BP-140/100 mmhg, JVP not raised. Pupil's small and sluggishly reacting to light. Orofacial movements present, oral secretions +, rhythmic movements of both hands + Reflexes both plantar- flexor. Tone normal, no stiffness. Chest: b/l crepitation's +CVS: s1, s2 normal, no murmur. P/A: soft, no organomegaly or mass palpable

Local examination showed poor perineal hygiene and foul smelling discharge present, per speculum cervix could not be visualized. Digital vaginal examination cervix was felt normal, uterus anteverted, normal size, mobile with free fornices. No mass felt.

Routine blood investigations, RFT, LFT, TFT values were all normal. CSF study showed increased lymphocytes.CA 125, AFP, ANA, Beta HCG values were normal. LDH value was increased -2313 IU/L. Anti NMDA R antibody was positive. EEG done showed generalized slowing of background activity in the delta range suggestive of generalized electrophysiological dysfunction. CT Brain done was normal. MRI brain showed multiple confluent and focal altered signal intensity areas which are intense in T1 & T2 FLAIR with no diffusion restriction /blooming in GRE. Post contrast enhancement noted in B/L subcortical white matter. Another similar altered signal intensity area noted in left parahippocampal gyrus –s/o autoimmune encephalitis. USG Pelvis: Uterus –AV, normal size, ET-3.6mm. A mixed echoic lesion with solid and cystic areas ms 6.3 x 3.2 cm noted in the region of right adnexa. A solid area shows calcific foci and hyperechoic area s/o fat. Vascularity present in solid areas. Left adnexa shows a hyperechoic area (s/o fat)- 3.5 x 3.2 cm with multiple solid areas-suggestive of bilateral ovarian teratoma.

Patient was treated with i/v methyl prednisolone 1 g i/v for 3days followed by immunoglobulin 20 g i/v for 2 days and other supportive treatments like eptoin, antibiotics and antivirals. She had multiple seizure episodes after admission and abnormal behavior persisted. Patient developed aspiration pneumonia during hospital stay following which she had saturation fall and required ventilator support. Since studies have shown that removal of tumour improves the patient's condition the patient was posted for surgery while on ventilator support only, but couldn't proceed with the surgery as the patient had cardiac arrest on the day of surgery.

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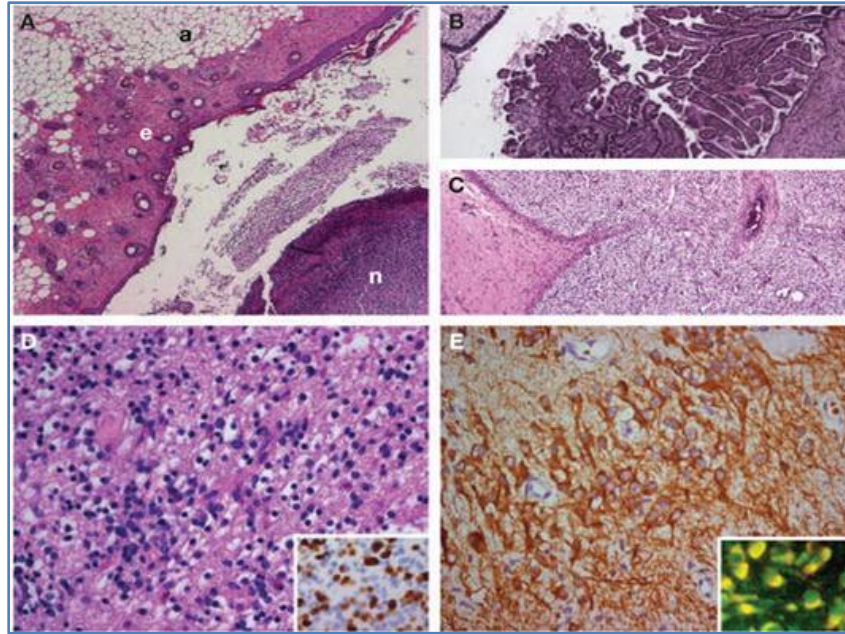
**DISCUSSION AND DIAGNOSIS:** The symptoms of this patient along with the MRI findings, CSF inflammatory features, and USG findings of bilateral ovarian mass raised suspicions of the presence of a type of paraneoplastic encephalitis that has recently been described in patients with teratoma<sup>[3]</sup>. The disorder associates with antibodies to NMDAR and affects young women, who are then often hospitalized for psychiatric care with diagnoses of acute schizophrenia, catatonia, drug abuse, or malingering. It is not until the patient develops seizures, autonomic instability, dyskinesias or a decreased level of consciousness that an organic illness is considered. Less frequently, patients present with severe short-term memory deficits resembling limbic encephalopathy. In the present case patient had positive Anti NMDA R antibody with bilateral ovarian mass with complex cystic and solid areas suggestive of terratoma.

**DIFFERENTIAL DIAGNOSIS:** In the present case, the CSF inflammatory abnormalities and MRI FLAIR hyper intensity in the patient's bilateral subcortical white matter and left parahippocambal gyrus were consistent with viral or autoimmune encephalitis.

**TREATMENT AND MANAGEMENT:** Treatment involves removal of the tumour along with first line immunotherapy. If a tumour is detected, long term prognosis is good with less chances of relapse. Patients with this disorder, however, usually require ventilator support and intensive care for seizures and autonomic instability, which can delay tumor removal. Treatment with methylprednisolone, plasma exchange or IVIg might result in partial neurological improvement or stabilization allowing resection, although the tumor could grow during the delay.<sup>[4]</sup> Second line immunotherapy includes rituximab, a monoclonal antibody that targets the CD20 receptor on the surface of B cells, thus destroying the self-reactive B cells. Cyclophosphamide has sometimes been proven to be useful when other therapies have failed. In some patients, tumor removal results in noticeable neurological improvement in a matter of days or after several weeks.

**CONCLUSION:** Paraneoplastic anti-NMDA receptor encephalitis is potentially lethal, but usually reversible if promptly recognized and treated. It should be suspected in young women with prominent psychiatric symptoms accompanied by seizures dyskinesias. The CSF usually shows inflammatory abnormalities, and the MRI can be normal, show transient cerebral cortical or cerebellar abnormalities, or show typical medial temporal lobe hyper intensities. The associated tumors are mature or immature teratomas, usually located in the ovary. Preliminary experience suggests that tumor resection, immunosuppressive treatment, intensive care, and physical therapy constitute the best treatment approach.

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- Histopathological studies of the patient's teratoma. (**A–C**) Areas of the tumor containing adipose tissue (a), epithelial tissue (e), and nervous tissue (n), all in the same section (panel A). Other areas contained choroid plexus (panel B), immature mesenchymal tissue (panel C), these findings are consistent with immature teratoma. (**D**) Area of the tumor with immature neurons and glial cells. Ki67 immuno staining (inset) shows extensive proliferative activity of the immature glial tissue (30–40% of the cells). (**E**) Immuno staining with microtubule-associated protein 2 (MAP2; a specific marker of neurons and processes) shows an area of immature neurons with an extensive network of neuronal processes. The patient's antibodies reacted with immature nervous tissue expressing N-methyl-D-aspartate receptors;

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