Anti N-Methyl-D-Aspartate Receptor (NMDR) Encephalitis in a 28-Year Old Female With Ovarian Follicular Cyst Presenting With Status Epilepticus

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ABSTRACT

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is a potentially fatal autoimmune condition where antibodies are produced and destroy NMDA receptors in the brain, thereby causing profound dysfunctional neurotransmission. This rare disease is often associated with a tumor, usually a teratoma.

A 28-year-old female previously diagnosed with seizure disorder presented with chronic history of neuropsychiatric symptoms leading to status epilepticus on the day of confinement. Investigation showed the presence of anti-NMDAR antibodies both in serum and cerebrospinal fluid. A right ovarian cyst was noted on ultrasound. Methylprednisolone and immunoglobulin were given followed by surgical removal of the ovarian cyst. Histopathology result showed a follicular cyst. The patient was discharged improved, and remained asymptomatic and seizure free. Repeat serum NMDAR antibody test was negative.

Early diagnosis and prompt treatment of patients with NMDA receptor encephalitis is lifesaving. Although mostly associated with an ovarian teratoma, the case reported a possible link between NMDAR encephalitis and benign ovarian cysts.

Keywords: Anti-NMDAR Encephalitis, Ovarian Follicular Cyst

INTRODUCTION

Anti-NMDAR encephalitis is an autoimmune disorder in which antibodies attack the N-methyl-D-aspartate (NMDA) receptors in the central neuronal synapses[1]. Initial symptoms can be neuro-psychiatric such as memory loss, hallucinations, delusions, catatonia and epileptic seizures[2]. As the condition worsens, level of consciousness decreases, apnea ensues, followed by autonomic dysfunction leading to cardio-pulmonary failure and death. Young women are commonly affected and an ovarian teratoma is associated in 60 percent of cases[3]. The presence of a tumor is associated with a better prognosis. Patients who underwent tumor resection and immunotherapy with corticosteroids, intravenous immunoglobulin, or plasma exchange alone or in combination have better chances of survival and recovery compared to patients without an identified tumor. There were reports of relapses specifically in cases where the etiology was not determined. Mortality is 7-10% and usually due to complications from a persistently vegetative state[4].

CASE PRESENTATION

A 28-year-old female had her first unprovoked seizure, a year prior to confinement. She was started on Lamotrigine

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100 mg tablet once a day and had no further attacks. However, her husband observed that she was becoming forgetful, irritable and had poor sleep. A week prior to admission she was diagnosed and treated for vaginosis. She also started to have breakthrough seizures described as versive head and eye movements towards the left followed by clonic - tonic movements of the left eye, left face, and left arm. Altered awareness was noted. Events lasted for 30 - 60 seconds, were recurrent and persisted for more than 30 minutes. In between attacks she was confused, repeatedly called her husband's name and repeating the same words. She had visual and auditory hallucinations.

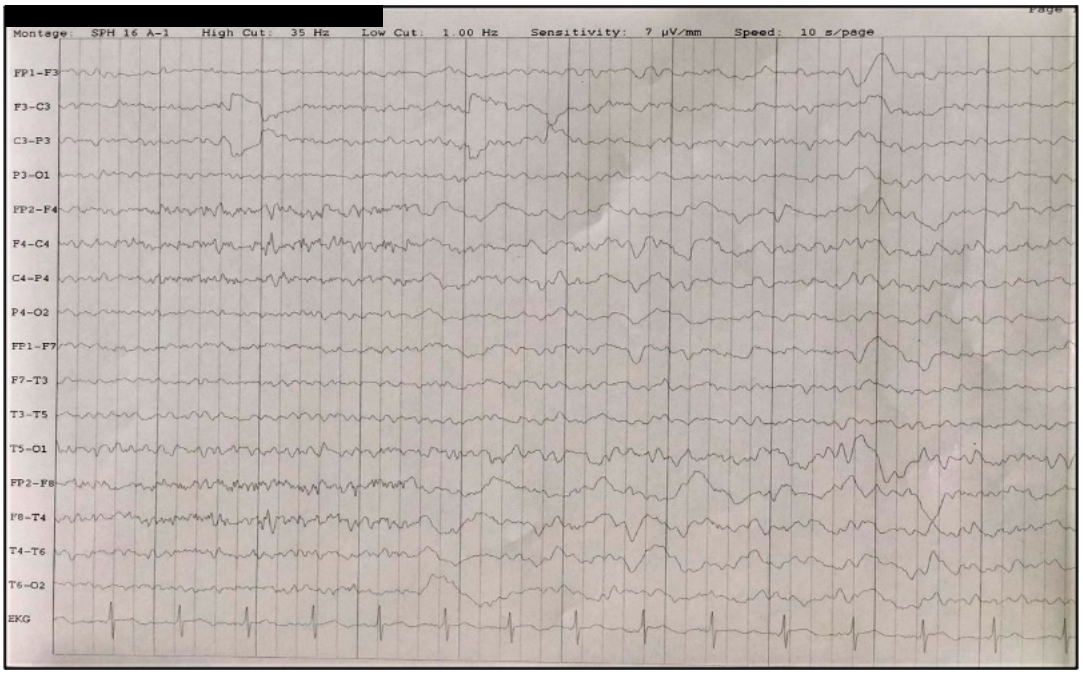
A 6-hour Video Electroencephalogram was done to characterize the behavior and showed focal epileptiform activity coming from the right frontal region with spread and theta–slow background activity indicative of an underlying mild diffuse cerebral dysfunction of non-specific etiology (Figure 1). There were episodes of confusion and echolalia, but no EEG correlate was noted. Cranial CT scan with contrast and Cranial MRI with contrast revealed no intracranial or neurovascular lesions.

Complete Blood Count, Electrolytes, Creatinine, Liver Enzymes, Anti–Nuclear Antibodies (ANA) and C–Reactive Protein (CRP) were unremarkable. Lumbar puncture and CSF analysis were normal. CSF HSV 1 assay was negative. NMDAR encephalitis was highly considered thus serum and CSF NMDAR antibody test were done. The results were positive for NMDAR antibody both for serum and CSF.

Tumor markers were unremarkable. Whole abdomen ultrasound and Chest X-ray did not reveal any masses. Thyroid function tests were normal. A trans-vaginal ultrasound showed a right multi-locular ovarian cyst measuring 3 cm x 2 cm x 2.2 cm.

The patient's seizures stopped after she was started on Levetiracetam 500 mg IV twice a day, Phenytoin 100 mg IV three times a day and Topiramate 50 mg tablet at 1 tablet once a day. Methylprednisolone 1 gm IV per

Figure 1: Focal epileptiform activity coming from the right frontal region with spread, theta – slow background activity.



day for 3 days and Intravenous Immunoglobulin (IVIG) infusion 400mg/kg/day for 5 days were started. After initiation of immunotherapy, she became more responsive and cooperative with lesser hallucinations and disorientation to time and place. However, she had no recollection of the events. After immunotherapy, she underwent right salpingo-oophorectomy with intra-operative findings showing the right ovary converted to a 4x4 cm mass with cystic component (Figure 2). Three independent, board certified pathologists were requested to examine the specimen and all of them made a final histo-pathologic report of a follicular cyst (Figure 3).

The patient was discharged seizure - free and asymptomatic after two weeks of confinement. Anti-seizure medications and oral prednisone were tapered off during her regular clinic follow up. A year after her illness, her repeat serum NMDAR antibody test result was negative. She remains asymptomatic and without neurologic deficit.

DISCUSSION

This is a confirmed case of anti – NMDAR encephalitis whose neuro-psychiatric symptoms dramatically improved after

Figure. 2. Right ovary converted to a 4x4 cm mass with cystic component, brownish pinpoint lesions noted at the periphery of the ovarian cyst.

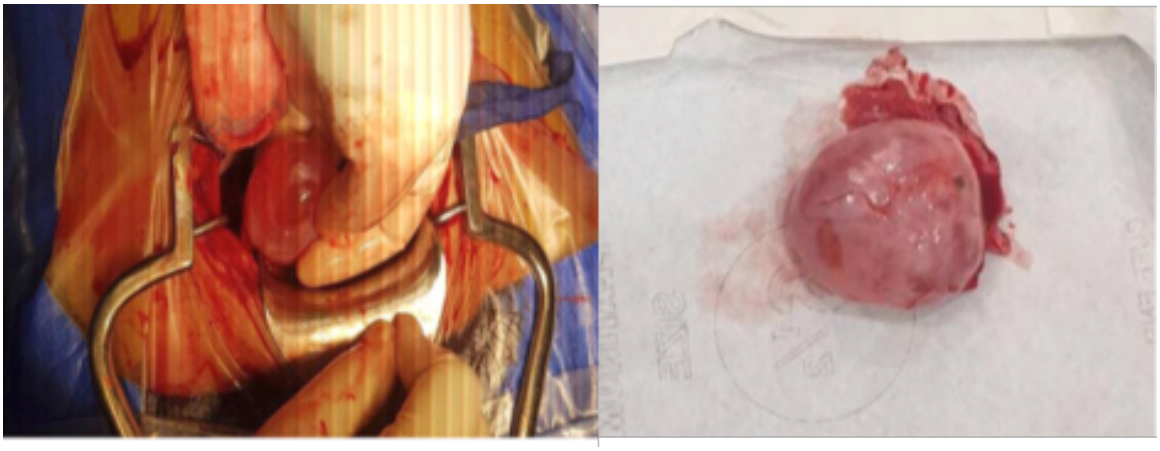
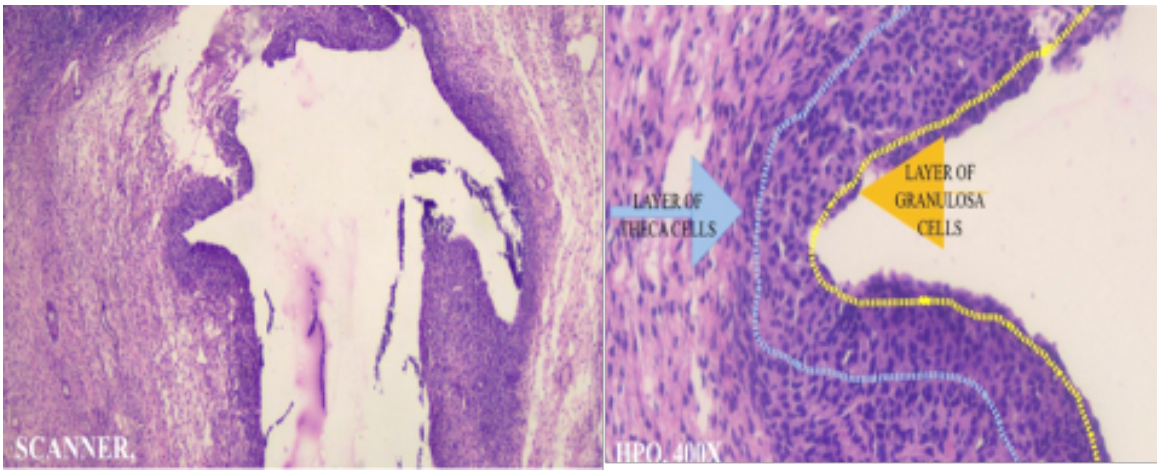


Figure 3. Cut shows a unilocular cyst with tan – red smooth inner wall. Cyst Wall measuring from < 0.1 – 1 cm Follicular Cyst.



immunotherapy and surgical removal of a benign ovarian cyst. Anti-NMDAR encephalitis is a relatively rare diagnosis. Incidence is unknown. NMDA receptors play an important role in synaptic transmission by binding with glutamate, glycine and serine in the post synaptic cleft and facilitating influx of cations thereby initiating cascade of events important in regulating memory and behavior[5]. Consequently, these lead to symptoms of NMDAR encephalitis such as memory loss, mutism, seizures, language dysfunction, insomnia, delusions and hallucinations[6].

In this case, the presenting symptom was a seizure followed by subtle changes such as becoming forgetful, irritable and difficulty initiating and sustaining sleep. The florid psychiatric symptoms occurred with status epilepticus. A video-EEG was helpful in differentiating epileptic seizures from non-epileptic behavior, which can also mimic a focal seizure. It must be noted that in patients with NMDAR encephalitis both epileptic and non-epileptic events can co-exist.

The exact pathogenesis of Anti-NMDA receptor encephalitis remains indefinite. It is considered as an antibody-mediated encephalitis. In some reports, a prodromal "viral-like" presentation possibly sets off the autoimmune response. In this case, there was vaginosis prior to worsening of symptoms. The infection must have triggered an autoimmune response. The presence of antibodies both in the serum and CSF supports the theory that NMDAR is an immune mediated condition.

Aside from finding antibodies in the serum and CSF, other investigations include brain MRI, which can be negative in up to 50 to 70 percent of cases as in this case. EEG may show abnormal slowing but is nonspecific in 90 percent of patients. CSF studies show lymphocytic pleocytosis and normal to mild elevation of protein. Oligoclonal bands may be present in 60 percent of patients[7].

Immune modulation and tumor removal are the mainstay of treatment as what was done in this patient. There were no reports comparing methylprednisolone, plasmapheresis and IVIG infusion to determine which one is better. In this case, methylprednisolone and IVIG infusion were both used to expedite recovery. In some cases, second-line immunotherapy consists of Rituximab or Cyclophosphamide[8]. Antipsychotics and benzodiazepines are used in the treatment of seizures, psychosis and behavioral changes.

Ovarian teratomas accounted for 94% of all neoplasms linked with the formation of antibodies to the NMDA receptor[9]. Most of these reports were from international studies. In the Philippines, Munoz et al in 2014 and Seneres et al in 2016 reported one case each of NMDAR encephalitis associated with an ovarian teratoma. In all cases reported, tumor removal led to a faster clinical improvement.

What about a benign ovarian cyst? Sanmaneechai et al in 2013 reported a single case of NMDAR encephalitis in an adolescent girl with benign ovarian cystadenofibroma. After immunotherapy and cyst removal there was also full resolution of symptoms and disappearance of serum NMDAR antibodies. In this case report a follicular cyst was surgically removed. Follicular cysts are benign and are usually just observed but after a thorough discussion with the Obstetric and Gynecological service, it was decided to remove the cyst because of its large size (16 cm) and its possible association with the autoimmune encephalitis. Although, follicular cysts were not reported to have tissues that might express neuronal NMDA receptors, the improvement of the patient's condition after immunotherapy and surgical removal suggest a possible association. Furthermore, the repeat serum NMDAR antibody tests a year after showed negative results. This is the first report of such possible causal link between follicular cysts and NMDAR encephalitis. However, the decision to surgically remove a

follicular cyst routinely in cases of NMDAR encephalitis is not recommended until more evidence of this causal association are reported. Cardio-pulmonary support and appropriate nursing care is important to prevent complications and morbidity. The primary determinants of poor outcome, death, or relapse include high titers of antibodies, failure of cerebrospinal antibodies to decrease within 4 weeks of onset of syndrome, late initiation of treatment, a GCS of 8 or less at admission, presence of complications and admission to the intensive care unit[12].

CONCLUSION

This is a confirmed case of Anti-NMDAR encephalitis presenting with status epilepticus and the first reported case with possible causal link with an ovarian follicular cyst. The patient improved clinically and immunologically with immunotherapy and surgery. It is recommended that NMDAR encephalitis be considered in patients presenting with status epilepticus and neuro-psychiatric symptoms so that prompt treatment can be initiated. Finally, further study needs to be done to explore the association between NMDAR encephalitis and ovarian follicular cyst.

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