Joint Submission

A case of NMDA receptor encephalitis in a 20-year-old female with ovarian teratoma

Introduction:

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is a relatively new disorder with rapidly growing literature on its pathophysiology, with a well-defined set of clinical features. The findings of this disorder have modified the diagnostic method to clinical conditions such as catatonia, subacute memory disturbances, seizures, abnormal movements, and limbic encephalitis. In addition, it has also lead to the recognition of various other immune mediated encephalitides such as AMPA receptor, GABAB-R, and LGI1. At first, NMDAR encephalitis was thought to be exclusively by a paraneoplastic disorder, occurring in young females in association with ovarian teratomas. The associated syndrome has been described as changes in mood, behavior, and personality, resembling acute psychosis\textsuperscript{1}. It usually progresses to include seizures, decreased level of consciousness, dyskinesias, autonomic instability, and hypoventilation. The younger the patient is, the less likely he or she is to have any associated tumor. In addition, black females are more likely to have a teratoma than any other ethnic groups. Studies have also shown that patients with Asian or African origin are more likely to have this condition. Cases with other tumors such as testicular germ cell tumor, teratoma of mediastinum, small cell lung cancer, Hodgkin lymphoma, ovarian cystadenofibroma, and neuroblastoma have also been reported\textsuperscript{3}. However, with recent studies, it has been shown to be present with or without tumor and can arise in children and young adults including males and females. Herpes simplex viral encephalitis (HSVE) is the only preceding infection that has been shown in 20% of the patients with NMDAR encephalitis. In many instances, an etiology is not identified and majority is autoimmune based. According to the California Encephalitis Project (CEP), 65% of patients are under the age of 18 years\textsuperscript{5}. Here we present a case of 20-year-old Caucasian female with no prior inpatient psychiatric hospitalizations presenting to the emergency department with disorganized mood, agitated and aggressive behavior.

Objective:

- Primary objective: The primary objective of the case study is to give an opportunity to develop an approach to diagnose first episode of psychosis.
- Secondary objective: The secondary objective is to reinforce the understanding of NMDA encephalitis, its diagnostic criteria and treatment.

Case Presentation:

A 20-year-old previously healthy Caucasian female, university student was brought to the New Bridge Medical Center (NBMC) emergency department (ED) after exhibiting out of character behavior with symptoms of mood liability, disorganized speech, intermittent
agitation, and aggression over the course of two weeks. She was performing well in the university until she failed a midterm and reported depressive symptoms, such as low mood, helplessness, worthlessness, and low self-esteem, to her family. Thereafter, she exhibited symptoms of mania, such as hyperactivity, feeling of euphoria after engaging in a relationship with her male friend, flight of ideas, and persistently elevated mood for approximately three days. She was brought to Robert Wood Johnson Hospital ED due to above mentioned symptoms. She was started on low dose of Risperdal 0.25mg and discharged with recommendations to follow up with her private psychiatrist.

She responded well to the anti-psychotic treatment and after one week, her family brought her to the private psychiatrist for a follow up. The private psychiatrist suggested to start a long acting intramuscular (IM) injectable (LAI); however, she started acting bizarre, crying and speaking incoherently at the office visit. 911 was called and she was brought to NBMC ED involuntarily. Upon arrival in the ED, the patient was put into physical restraints and was given Ativan 2mg due to her agitated and aggressive behavior. Upon questioning the family in the ED, they denied any previous history of traumatic brain injury, recent travel, sick contacts, and ingestion of new foods or medications. The family reported that the patient had been partying with her male friend and suspected that she might have ingested an illicit drug.

The patient was afebrile and had stable vital signs. Complete blood count (CBC), comprehensive metabolic profile (CMP), thyroid stimulating hormone (TSH), beta human chorionic gonadotropin (b-HCG), acetaminophen level, alcohol level, salicylate level, vitamin B12 level, syphilis screening (VDRL), urinalysis (UA), urine toxicology, and computed tomography (CT) scan of the head did not reveal any abnormalities. She was determined medically cleared and was admitted to the inpatient psychiatric service for management of acute psychosis. Upon psychiatric assessment, the patient was internally preoccupied with little recollection of past events and was perseverating on graduating from college. She was started on Risperdal M-tab 1mg twice daily, Haldol 5mg every six hours as needed for agitation, Ativan 2mg IM every six hours as needed for anxiety, and Benadryl 50mg every six hours as needed for extrapyramidal (EPS) symptoms.

Mental status examination at the time of the evaluation illustrated a 20-year-old Caucasian female who appeared disheveled. Her speech was soft with normal rate, rhythm, volume, and amount. Her mood was “anxious” and the affect was blunted, and was incongruent with the stated mood. Her affect range was labile. Her thought process was circumstantial with significant thought blocking. She was internally preoccupied. There was no evidence of auditory or visual hallucinations during the interview. Her judgment was poor and her insight was minimal. She was oriented to time, place, and person. Her mini mental status examination was normal.

The patient had no prior history of inpatient psychiatric hospitalization, suicidality or homicidality, self mutilatory behavior, legal charges, aggressive/assaultive behavior, depressive,
 manic, psychotic, and anxiety symptoms. In addition, there was no reported history of physical, emotional, and sexual abuse. No access to guns or firearms was reported.

The patient stayed in the psychiatric unit for approximately two days and refused to take Risperdal. No other medication was suggested at that time as she did not exhibit any psychotic symptoms. Thereafter, the patient started to develop high grade fever, decreased oral intake, and psychomotor retardation. Second set of labs including CBC with differential, CMP, and UA were performed and medicine department was consulted. The labs revealed leukocytosis (19,000/mm³), without any apparent signs of acute infection. The serial review of vital signs illustrated autonomic instability (specifically tachycardia/bradycardia, fluctuations in blood pressure, and high fever). The patient was transferred to medicine department for further work-up of her leukocytosis and catatonic state. She was started on aggressive intravenous (IV) rehydration and supportive management. The patient was initially started on Rocephin IV empirically which was then switched to oral Recephein 2gm twice daily and vancomycin 1gm twice daily for possible differential diagnosis of meningitis but was later discontinued due to a negative lumbar puncture. In addition, Ativan 1mg IV every 8 hours was started and antipsychotic medications were discontinued as the patient appeared catatonic. Nueroleptic Malignant syndrome (NMS) was in the differential diagnosis; however, her creatine phosphokinase (CPK) levels were within normal limits. She was started on Dantrolene 50mg three times daily with a plan to up-titrallte to Dantrolene 100mg four times daily if unresponsive.

Her electrolytes revealed severe hypokalemia, despite replacement of her potassium levels. Due to the fever and the hypokalemia, the CT scan of abdomen and pelvis was performed which showed a large right ovarian teratoma. Findings on the CT scan and acute psychiatric condition lead the clinicians to think of possible NMDAR encephalitis diagnosis. Patient was started on high dose steroids (methylpredinsone 1gm) with improvement of her catatonic state. In addition, the patient was transferred to tertiary hospital for the removal of the teratoma and further work-up for NMDAR encephalitis. Our case discussion will present with the course of illness, diagnostic criteria, pathophysiology, complications, and treatment modalities that can be used for NMDAR encephalitis.

**Laboratory Studies (over the span of 10 days in NBMC):** (N= Normal; H= High; L= Low; RBC= Red blood cells; WBC= white blood cells; MRI= magnetic resonance imaging; CT= computed tomography)

**Electrolytes (mEq/L):**

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<th>Day 8</th>
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<tr>
<td>Na⁺</td>
<td>143</td>
<td>143</td>
<td>138</td>
<td>140</td>
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<td>K⁺</td>
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<td>3.2</td>
<td>2.9 (L)</td>
<td>3.0 (L)</td>
<td>2.8 (L)</td>
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<td>2.7 (L)</td>
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<tr>
<td>Mg²⁺</td>
<td>1.8</td>
<td>1.5 (L)</td>
<td>1.8</td>
<td>1.4 (L)</td>
<td>1.7</td>
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Complete Blood Count with differential:

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<tr>
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<tr>
<td>Neut</td>
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<tr>
<td>Lymph</td>
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WBC- white blood cell count; Neut- neutrophil count; Lymph- lymphocyte count

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<thead>
<tr>
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<th>Day 2</th>
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<th>Day 6</th>
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<tr>
<td>CKI</td>
<td>227 (H)</td>
<td>215 (H)</td>
<td>633 (H)</td>
<td>297 (H)</td>
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CKI- creatine kinase isozyme

Creatine Phosphokinase (CPK): Within normal limits

CA 125: Day 8: 94 (H)

CA 19: Day 8: 11 (Normal)

Alpha-Fetoprotein (AFP) tumor marker: Day 8: 3.6 (N)

Cerebrospinal Fluid Analysis (CSF): Day 3: Color: colorless; Clarity: clear; CSF RBC: 2/µl; CSF WBC: 3/µl; Protein: 25 mg/dL; Glucose: 62 mg/dL. Culture and gram stain: negative

Imaging Studies:

Day 1: Chest x-ray: Normal findings with no evidence of infiltrate and mass.

Day 2: MRI of the brain: T1 and T2-weighted sequences demonstrated no abnormalities in midline structures, no evidence of acute ischemia, and normal signal void in carotid arteries.

Day 7: CT scans of abdomen and pelvis with and without contrast: Complex mass arising from pelvis to the umbilicus measuring 15 x 10 x 10 cm suggesting a dermoid neoplasm. Recommendations for pelvic ultrasound were suggested.
Day 8: Pelvic ultrasound: Transabdominal imaging demonstrated a large complex mass extending superior from the uterus measuring at least 16 x 8 x 14 cm containing cystic and solid components. Suspicion of an ovarian teratoma was made and gynecology was consulted.

Day 9: MRI of the pelvis: T1 and T2-weighted sequences without contrast showed a large complex mass extending from the superior aspect of the uterus measuring at least 14 x 7 x 13 cm containing both cystic and solid features. The lesion measured 10 x 9 x 7 cm. Pelvic mass appeared to be arising from the right ovary suggesting a possible ovarian teratoma.

Discussion:

NMDAR encephalitis was initially discovered as a syndrome of memory deficits, psychiatric symptoms, decreased level of consciousness, and hypoventilation in 2005 in four young women with ovarian teratomas. NMDAR encephalitis seems to have distinct and usually predictable phases of illness. These phases include: 1) prodrome and initial psychiatric symptoms, 2) neurologic complications, 3) recovery and relapse, and 4) late-phase cognitive and behavioral sequelae. An understanding of these stages can help anticipate patient’s needs and medical management. Studies have shown that approximately 70% of patients experience a viral-like prodrome including headache, lethargy, upper respiratory symptoms, nausea, diarrhea, myalgias, and fever. These symptoms ensue around five days prior to the onset of behavioral changes. There are usually no neurologic symptoms during this time. Psychiatric manifestations vary and include delusional thought content, perceptual disturbances, and disorganized thoughts and behaviors. In addition, patients specifically exhibit agitation, mood lability, paranoid ideation, bizarre behavior with personality changes. Majority of patients also get combative and aggressive. Patients are typically evaluated initially by a psychiatrist. While psychotic symptoms are commonly seen in adults; in contrast, manic symptoms such as irritability, hyperactivity, and hypersexuality are seen in pediatric populations. Cognitive deterioration, abnormal speech, and confusion are also seen. Patients experience progressive decline in speech and language. These abnormalities include alogia, echolalia, mutism, perseveration and mumbling. The initial psychiatric phase lasts usually 1-3 weeks.

Early psychiatric changes are followed by changes in the level of consciousness, sometimes development of catatonic-like state with mutism and eyes open, while others present with increased level of agitation. Neurologic complications also include abnormal movements, such as orofacial dyskinesia, dystonic posturing, as well as autonomic instability (i.e. hyperthermia, tachycardia/bradycardia, hypotension/hypertension), and hypoventilation. In children, abnormal movements are a frequent part of the presenting picture; instead of occurring later in the disease process. In adults, hypoventilation, a common complication of this condition, occurs which is usually central in origin and often requires an average of two months of ventilator support. Seizures are also a major feature of NMDAR encephalitis and have increased intensity and frequency earlier in the course of disease. As a matter of fact, studies have shown that >25% of female patients between ages of 18-45 with new onset epilepsy had anti-NMDA receptor antibodies, with no other cause for seizures identified.
The process of recovery is the reversal of the phases of illness mentioned above and can take up to 3-4 months of hospitalization. Autonomic and respiratory functions improve first, and cognitive and psychiatric functions improve the slowest. Compare to other synaptic encephalitides, the relapse rate of this syndrome is relatively low (i.e. ~20-25%) and can occur with medication noncompliance.

Approximately 85% of patients make a full recovery after a long course of rehabilitation. However, some patients do have deficits in executive function, impulsivity, behavioral disinhibition, and abnormal sleep patterns. Prolonged psychiatric abnormalities have not been well described in larger studies; however, individual case reports demonstrated persistent symptoms. For instance, in one case report, patient continues to have limited cognitive abilities after one and a half year of initial disease manifestation; and had gradual improvement two year post-recovery. Some patients have prolonged symptoms resembling Kluver-Bucy or Klein-Levin syndromes with symptoms such as hypersexuality, hyperphagia, hypersomnia, irritability, and blunted affect. Amnesia seems to be a common symptom for the entire phase of acute illness and memory deficits may persist.

Suggested diagnostic criteria for NMDAR encephalitis is listed as (all three criteria must be met):

1) Rapid onset (<3 months) of at least four of the six following major groups of symptoms:
   a) Abnormal behavior or cognitive dysfunction
   b) Speech dysfunction
   c) Seizures
   d) Movement disorder, dyskinesias, or rigidity/abnormal postures
   e) Decreased level of consciousness
   f) Autonomic dysfunction or central hypoventilation

2) At least one of the following laboratory results:
   a) Abnormal electroencephalogram (EEG) (focal or diffuse slow or disorganized activity, epileptic activity, or extreme delta brush)
   b) CSF with lymphocytic pleocytosis and elevated protein or oligoclonal bands

3) Reasonable exclusion of other disorders

The most definitive or confirmatory diagnosis is the presence of IgG anti-NR1 (also called GluN1) antibodies in CSF with the presence of one or more of the six major groups of symptoms, after reasonable exclusion of other disorders.

The reversible loss of NMDARs and the resulting synaptic dysfunction may cause the memory, behavior, and cognition deficits, which are hallmarks of anti-NMDAR encephalitis. There is a direct correlation between clinical consequence and antibody titers, which are usually higher in CSF than serum due to the intrathecal antibody production. One study has shown the extreme delta brush pattern on EEG is associated with more prolonged illness.
MRI is usually normal or shows transient fluid-attenuated inversion recovery (FLAIR) or contrast-enhancing irregularities in cortical (brain, cerebellum), or subcortical (hippocampus, basal ganglia, white matter regions).³

The condition is facilitated by autoantibodies that target NMDA receptors in the brain. NMDA receptors are ligand-gated cation channels and play a vital role in synaptic transmission. These receptors are different parts of NR1 subunits that bind glycine and NR2 subunits that bind glutamate. Hyperfunctioning of NMDA receptors causing excitotoxicity is thought to be the mechanism for epilepsy, dementia, and stroke; however, decreased activity of NMDA receptors lead to symptoms of schizophrenia.⁷ Studies have shown that patients’ antibodies decrease the surface density and synaptic localization of NMDAR via antibody mediated capping and internalization without affecting other synaptic proteins.⁶ The antibodies have been attributed to the functional blocking of NMDA receptor in presynaptic GABA-mediated interneurons of the thalamus and frontal cortex, leading to a decreased release of GABA. The consequence is disinhibition of postsynaptic glutamatergic transmission, excessive release of glutamate in the prefrontal cortex, and glutamate and dopamine dysregulation that might contribute to development of schizophrenia-like psychosis and bizarre dyskinesias in NMDAR encephalitis.⁸ Future studies will focus on the circuit-level dysfunction caused by patients’ antibodies in hippocampus and other brain regions to begin to connect synaptic and circuit dysfunction with the behavioral abnormalities that are hallmarks of this disorder.⁹

Early recognition of this condition is critical because outcomes are best in patients treated early in the course of disease. There are different treatment options including immunosuppression and tumor resection when indicated. Death and progressive neurologic decline can occur without treatment. Intravenous (IV) methylprednisolone should be the initial treatment and either IV immunoglobulin G (IVIG) or plasma exchange should be considered. These treatment options work best in cases where an underlying tumor has been removed. The use of plasma exchange is challenging in agitated patients or in cases with autonomic instability, and IVIG is usually preferred in these patients. Second line treatment modalities include rituximab, cyclophosphamide, or both; when there is no improvement from initial treatment or no underlying tumor. Based on clinical observations, rituximab with steroids and IVIG or plasma exchange is becoming the initial treatment. In addition, for patients without a tumor (in whom relapse is common), continued immunosuppression with mycophenolate mofetil or azathioprine is recommended for at least one year and periodic screening for an ovarian tumor over two years.² Despite the treatment, 25% of patients remain severely disabled or die; mortality is estimated to be 4%.

There is a general consensus that began to emerge on management of neurologic symptoms, however, control of psychiatric manifestations is at times more difficult to achieve. Several interventions have been tried during the course of disease, ranging from high dose neuroleptics to electroconvulsive therapy (ECT). Physicians’ personal experiences and literature review has suggested that in many cases, high-dose dopamine blockade actually exacerbates
dyskinetic and dystonic movements when used in an agitated patient; however, it is unclear whether this originates from excessive blockade in what is usually a neuroleptic naïve patient. Medications that are sedating, such as anticholinergics, benzodiazepines, and valproic acid; and more sedating antipsychotics such as quetiapine or chlorpromazine have proven helpful in many cases. Some reports have also suggested that trazodone and clonidine are helpful adjuncts for managing sleep. ECT has been tried effectively in a minority of patients, however, the improvement is usually partial or transient and treatment of underlying etiology is almost uniformly required. Patients with comorbid or isolated mood symptoms, such as lability and/or mania, showed improvement with mood stabilizers like valproic acid. Valproic acid also gives the added benefit of seizure prophylaxis and intravenous formulation.²

Transplacental transfer of IgG anti-NMDAR antibodies has been documented in serum of babies born to mothers with NMDAR encephalitis.³ However, the effect of these autoantibodies on the fetus is not well described and might be variable. Case reports have demonstrated short-term fetal outcome ranging from normal to early neonatal death. Nevertheless, close prenatal monitoring and measurement of antibody titers is suggested in women with a history of NMDAR encephalitis.

Conclusion:

This patient presented with symptoms of mood lability, disorganized speech, intermittent agitation, and aggressive behavior. NMDAR encephalitis can present with or without teratoma and can occur in both males and females. The differential diagnosis includes acute psychosis or schizophrenia, malignant catatonia, neuroleptic malignant syndrome, viral encephalitis, and encephalitis lethargica. This intricate disorder involves proper management and coordinated care between different medical specialties. Symptoms can be purely psychotic in nature at first, suggesting that NMDAR encephalitis can be misdiagnosed as a primary psychiatric illness. Diagnosis can be confirmed by the detection of IgG antibodies to NR1 subunit of the NMDA receptor in CSF. High dose steroids and IVIG are used as initial treatment in addition to tumor removal if applicable, while immunotherapy is used as secondary treatment. Further studies are needed to examine and recognize the psychiatric manifestations in depth, and how to provide optimal care in the early phases of the illness. In addition, patients need to be followed up after the prolonged recovery process.
References:


