NMDA Receptor Antibody Associated Encephalitis: Unexplained Encephalitis
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Introduction
N-methyl D-aspartate (NMDA) receptors are glutamate receptors and responsible for controlling memory function and synaptic plasticity.1 Activation of these receptors requires binding with glutamate or aspartate. These receptors are present in the limbic system, hypothalamus, and forebrain.2 Binding of antibodies to these receptors lead to their removal from synaptic sites, thus leading to changes in functions.3,4 Under-activity of these receptors is linked to development of psychotic symptoms as seen in schizophrenics and also in patients on PCP (angel dust) or ketamine.3,5
NMDA-receptor antibody encephalitis was first seen in young women with underlying ovarian teratoma.6 Recent reports have shown that only 60% of patients have underlying tumor and the rest are idiopathic.7,8 The disease is known to effect young women predominantly (< 50 years) more than males,2 but cases involving children as young as eight months to two years also have been reported.7,9 Neoplasm is seen rarely in children and adolescents.10

Case Report
Liaison service was consulted regarding a 26-year-old female. She presented to the emergency room with acute onset of aphasia, auditory hallucinations, and agitation. She reported that the voices were instigating her to kill her own children. This patient was transferred from another hospital where she was admitted for difficulty in speaking and agitation.

The patient had a history of anxiety and depression. She recently was started on clonazepam (1 mg every 8 hours) and hydroxyzine (25 mg TDS PRN) after her selective serotonin re-uptake inhibitors were discontinued due to anticipation of possible serotonin syndrome.

The patient denied having a history of alcohol or substance abuse. In the ER, she was agitated and aggressive and had to be put on haloperidol (5 mg IV) and lorazepam (2 mg). Her vitals were normal and physical examination was unremarkable. The patient was not oriented. Her mental status was notable for incoherent speech, echolalia, and agitation. She was put in 4-point restrain.

Routine lab investigation revealed a significant increase in blood glucose. Cerebrospinal fluid (CSF) analysis showed mild pleocytosis. Chest x-ray, electro-cardiogram, and electro-encephalography were normal.

The patient was transferred to neurology because of the altered mental status. She continued to have frequent episodes of agitation and confusion. Her speech was
largely incoherent and showed significant mood lability. The psychiatry consult team remained involved in this patient’s care, offering treatment for psychiatric symptoms, and helping in diagnostic formulation.

No diagnostic clarity was achieved. She had a broad differential diagnosis including serotonin syndrome, schizophrenia, mood disorders, neuroleptic malignant syndrome, autoimmune disorders, and endocrine disorders. Causes, such as infection and inflammation, were considered. Throughout her stay, her metabolic panel was unremarkable, except blood glucose levels were elevated. Screening for autoimmune disorder also was negative.

On hospital day 15, the patient was started on methylprednisolone with a presumptive diagnosis of NMDA encephalitis. CSF analysis confirmed the presumed diagnosis (elevated IgG index). Plasmapheresis was included in her management. The following day, her agitation decreased and slowly her symptoms resolved. She responded to simple commands and formed simple sentences.

**Discussion**

Anti-NMDA receptor encephalitis is potentially lethal, but reversible if recognized early.\(^8\) It was considered as part of paraneoplastic syndrome,\(^4\) but recently a number of cases have been reported which are not associated with neoplasia.\(^4,8\) It should be suspected in young patients (especially females) who present with psychiatric symptoms, autonomic instability, hypoventilation, and movement disorders.\(^8,11\)

**Pathogenesis.** Tumors (ovarian, testicular, mediastinal) that express ectopic NMDA receptors or infections (Epstein-Barr virus, herpes simplex virus, mycoplasma, influenza A and B, chlamydia via molecular mimicry) activate specific antibody mediated immune responses, resulting in formation of memory B cells that can cross the blood brain barrier.\(^8\) Memory B cells produce NMDA receptor antibodies that bind to the receptors and internalize it resulting in loss of inhibition of excitatory pathway.\(^6,9\)

Clinically, the disease is divided into three stages.\(^9,12,13\) In the prodromal stage, patients experience fever, headache, fatigue, and lethargy. In the second stage, the patient develops behavioral abnormalities, impulsivity, confusion, stupor, and fluctuating consciousness. Patients often are presented to the psychiatrist or admitted with a diagnosis of schizophrenia, drug abuse, or acute psychosis. Autonomic instability is the third stage. The patient develops bradycardia, tachycardia, fluctuating blood pressure, heart block, and hypoventilation.

If anti-NMDA receptor encephalitis is suspected, NMDA antibody titres in CSF and serum should be evaluated, followed by screening for tumor (whole body CT scan, chest x-ray) or infections (complete blood count with differential, urinalysis, CSF viral PCR, and cultures).\(^2,14\) In most cases, lumbar puncture shows elevated CSF IgG index with mild pleocytosis as compared to viral encephalitis.\(^15\) Brain magnetic resonance imaging may show mild cortical or subcortical increased signal on fluid attenuated inversion recovery sequence.\(^14,15\) Anti-NMDA receptor encephalitis is confirmed by screening NMDA antibody titers in serum and CSF. The titers of antibodies are higher in CSF than in serum indicating intrathecal synthesis.\(^11\)

**Management.** The goal of initial management should be resolution of psychiatric symptoms, plasmapheresis, plasma exchange, immunosuppression (steroids, immunoglobulins), and removal of tumor if present.\(^8,9,12\) However, there is lack of information on specific management of psychiatric symptoms. In case of poor clinical response or relapse, rituximab (monoclonal antibody that depletes B cell)
Psychotropic medications used to control behavioral symptoms include haloperidol, atypical antipsychotics (olanzapine, risperidone, ziprasidone), and benzodiazepines.

Given the complex nature and presentation of this disorder, a multidisciplinary approach (psychiatry, neurology, and surgery) is required. There is slow but continuous improvement and the majority of patients make a good recovery.8-10 Patients are at risk of relapse so long term therapy and surveillance is required.

Conclusion

Anti-NMDAR encephalitis is a common cause of encephalitis. Its relative frequency is close to some common infectious etiologies for encephalitis like HSV-1 in young individuals.6,11 There has been an increase in reporting of anti-NMDAR encephalitis in recent years. Therefore, it is important to keep it high on the differential diagnosis. This will avoid unnecessary diagnostic and treatments cost and help in timely diagnosis and effective treatment. More research is required to clarify the exact pathogenesis and best treatment.

References


Keywords: encephalitis, NMDA receptors, neuronal plasticity, paraneoplastic syndromes