Anti N-Methyl D-Aspartate Receptor Encephalitis: Case Report and Literature Review

Smit Shah1*, Pooja Shah2, Ramkrishna Makani3 and Stacy Doumas4

14th Year Medical Student, Rutgers Robert Wood Johnson Medical School, USA
2Department of Psychiatry, Delaware Psychiatric Center, USA
3Department of Child and Adolescent Psychiatry, Children’s Hospital of Philadelphia, USA
4Department of Psychiatry, Jersey Shore University Medical Center, USA

*Corresponding Author: Smit Shah BA, 4th Year Medical Student, Rutgers Robert Wood Johnson Medical School, USA.


Abstract
Anti N-methyl D-aspartate Receptor Encephalitis (ANRE) is a rare autoimmune disorder that is induced by autoantibody formation against NMDA receptors in the Central Nervous System. Clinical presentation of ANRE ranges from progressive psychosis, seizures, and memory deficits to catatonia and severe autonomic instability. ANRE poses as a huge diagnostic dilemma for clinicians due to significant overlap in clinical symptoms along with other causes of encephalitis including bacterial, viral, fungal, parasitic and lupus cerebritis. In this paper, we discuss a case of ANRE along with imaging studies. Furthermore, we also perform literature review of various studies of ANRE and their corresponding medical management.

Keywords: Epilepsy; Encephalitis; Pathophysiology; Teratomas; Autoimmune

Abbreviations
CBC: Complete Blood Count; CMP: Complete Metabolic Panel; TSH: Thyroid Stimulating Hormone; IVIG: Intravenous Immunoglobulin; CSF: Cerebrospinal Fluid; LP: Lumbar Puncture; EEG: Electro Encephalogram; MRI: Magnetic Resonance Imaging; CNS: Central Nervous System; ANRE: Anti NMDA Receptor Encephalitis; T4: Thyroxine; NMDA: N-Methyl D-Aspartate; UDS: Urine Drug Screen; CT: Computerized Tomography

Introduction
Anti NMDA Receptor Encephalitis (ANRE) is a rare autoimmune disorder which is induced by autoantibody formation against N-methyl D-Aspartate (NMDA) receptors in the central nervous system (CNS) [1]. NMDA receptors are basically glutamate responsive receptors which play a pivotal role in synaptic plasticity and memory function [1]. Clinical presentation of ANRE ranges from progressive psychosis, seizures, memory deficit to catatonia and autonomic instability [1]. In patients with ANRE, most common cause of death is systemic failure secondary to autonomic instability [1,2]. Interestingly, ANRE is often associated with malignancies and tumors including ovarian teratomas and testicular germ cell tumors [3]. ANRE poses as a huge diagnostic dilemma for clinicians due to significant overlap in clinical symptoms with other causes of encephalitis including bacterial, viral, fungal and parasitic. In addition, conditions like lupus cerebritis need to be excluded as well due similar clinical symptomatology. Onset of symptoms can be vague ranging from nonspecific flu like symptoms to severe behavioral changes including agitation, paranoia, psychosis and violent behavior [1]. Recovery can be challenging as the symptoms regress in the reverse order of occurrence. A high index of suspicion should be maintained when encountering patients that present with admixture of psychiatric and neurological symptoms like seizures and catatonia. A delay in identifying the underlying etiology and administration of appropriate treatment can often be detrimental leading to significant mortality secondary to autonomic instability.
Materials and Methods

Deidentified patient information was obtained from hospital records. Studies with respect to ANRE were reviewed via online PubMed search.

Case Report

History of present illness: Our patient is a 14-year-old female with a significant past medical history of choroid plexus cyst who presented to the emergency department with chief complaint of new onset seizures. Patient reportedly had a total of five witnessed seizure episodes in the past twelve hours followed by sixth seizure in the emergency room.

Past Medical History: Choroid plexus cyst at birth, no recent history of head trauma or illnesses.

Past Psychiatric History: None.

Past Family History: No family history of epilepsy or seizures.

Surgical History: None.

Allergies: None.

Medications: None.

Lab work and Imaging

Complete blood count (CBC), comprehensive metabolic panel (CMP), thyroid stimulating hormone (TSH), Free T4 were within normal limits. Urine drug screen (UDS) was positive for acetaminophen, ibuprofen and diphenhydramine. Electrocardiogram (EKG) was within normal limits and computed tomography (CT) scan of head was negative. Magnetic resonance imaging (MRI) of brain was grossly normal.

Additional clinical management

Neurology was consulted and patient was admitted on neurology service for twenty four hours of observation. Treatment was started using intravenous immunoglobulin, methylprednisolone, rituximab, diazepam, lorazepam as needed and diphenhydramine as well. Baclofen and botox injections were added to the regimen as well. Diagnosis of seizure was made and patient was discharged next day with a scheduled outpatient appointment within one week.

Patient was seen by a neurologist in outpatient setting after five days. Here, patient’s mother disclosed that patient was sleeping maximum of forty five minutes since last three days. In addition, patient was reportedly having worsening emotional lability and hallucinations. Consequently, outpatient neurology referred patient to the emergency room for psychiatry and neurology evaluation. Psychiatry evaluation was performed. Patient was found to have acute psychotic symptoms that were waxing and waning in nature. So a potential diagnosis of delirium was made and medical admission was recommended for further work up. Patient was admitted on pediatric floor. CBC, CMP, UDS, TSH and urine pregnancy test were done; all of which were normal. A repeat head CT was done which was read as normal. MRI and its corresponding findings are demonstrated in figure 1.

Figure 1: Mild focal narrowing at the superior aspect of the cerebral aqueduct with mildly prominent lateral ventricular size. Right ventricle appears to be slightly enlarged as compared to left ventricle. There is mild deformation of the third ventricle on the left, likely due to indentation from asymmetrically prominent left thalamus. The fourth ventricle is normal in size. Basal cisterns are patent. There is mild focal narrowing at superior aspect of the cerebral aqueduct of Sylvius.
Anti N-Methyl D-Aspartate Receptor Encephalitis: Case Report and Literature Review

Patient was transferred to neurology service. Further medical work up with presumed diagnosis of encephalitis was done. Lumber puncture (LP) and electroencephalogram (EEG) were performed. Anti-NMDA receptor antibodies and oligoclonal bands found in cerebrospinal fluid (CSF) and serum were positive which suggested anti-NMDA receptor encephalitis. Oncology was consulted to rule out any malignancy including ovarian teratoma. After thorough medical work up including a pelvic ultrasound, no malignancy or tumors were found. Further management included interdisciplinary teams including general pediatrics, neurology, psychiatry, physical and occupational therapy and nutrition consults. With this approach, patient’s condition started improving slowly, along with her mental status. Catatonia resolved and patient became less agitated. Patient’s psychotic symptoms started resolving in first week and returned to baseline by two weeks post treatment.

Patient stayed on neurology service for about one month and then transferred to rehabilitation unit where patient stayed about seventy days. Patient was discharged with regular outpatient neurology follow up. Last follow up was done in November 2017 during which patient’s condition was significantly improved with better sleep and appetite. In addition, patient was reportedly, functioning at baseline in home environment. However, patient still has memory and balance problems at times which have improved over the past few months. Patient is currently receiving diazepam, melatonin, polyethylene glycol as standing medications and acetaminophen as needed.

Discussion

Anti NMDA (Anti-N-methyl-D-aspartate) receptor encephalitis (ANRE) is a lesser recognized progressive neuropsychiatric disorder with a wide array of clinical presentations. Neuropsychiatric symptoms includes cognitive dysfunction, motor dysfunction and autonomic instability along with severe aggression at times. In addition, prodromal symptoms include headache and low-grade fever in weeks preceding clinical symptoms mimicking a viral illness [4]. Additional, psychiatric symptoms are consistent with new onset psychosis, hallucinations, delusions and catatonia which could be confused with schizophrenia.

From studies conducted by Steiner., et al. and Zandi., et al. ANRE was found to be accountable for 5 - 10% cases of first onset psychosis [5,6]. Symptoms of autonomic instability and rigidity compel us to consider a diagnosis of medication induced neuroleptic malignant syndrome which should be ruled out before proceeding to additional clinical management [7]. Dyskinetic movements and orofacial dyskinesias can be misinterpreted for seizures and tardive dyskinesias [8]. Due to a significant overlap in symptoms between ANRE and other disorders like seizure disorders, lupus cerebritis it is important to exclude them as well. Cystic teratomas, which are one of the most commonly known benign ovarian malignancies in women are associated with ANRE. With a rise in the incidence of ANRE, identification of underlying ovarian or testicular lesions is important to ensure no co-occurrence [9-11].

While the pathogenesis of ANRE is unclear, many different theories have been hypothesized in recent research [12,13]. In a study conducted by Stein-Wexler et. al., major histological findings on examination of brain biopsies of ANRE patients included microgliosis, B cell and plasma cell proliferation [12,13]. As discussed previously, with behavioral and personality changes being the most common presenting symptoms in majority of ANRE cases, it is not surprising to find prominent microglial activation localized in the hippocampus that are responsible for emotional processing and are closely connected to the limbic circuitry [12,13]. Additionally, molecular studies have found antibodies against NR-1 subunit of NMDA receptor as a major target for auto-antibody formation. NR1 is heavily expressed in different areas of brain [12,13]. However, from recent studies, NR1 seems to be expressed more in neuronal limbic circuitry, specifically the hippocampus [12,13]. This can potentially explain high emotional instability in ANRE patients along with different neuropsychiatric manifestations [12,13].

From recent studies (Table 1), we can see that majority of patients regardless of initial presentation can be successfully treated with methylprednisolone, intravenous immunoglobulin or plasmapheresis. However, in treatment refractory cases, novel secondary therapies like tetrabenazine, rituximab and cyclophosphamide have shown significant improvement and recovery [14-25]. Reversibility of ANRE after treatment has been explored in mice studies. In a study by Moscato., et al. NMDA receptor density was dramatically reduced in the hippocampus of rats infused with patients’ NMDA receptor antibodies. Such studies can potentially explain why NR1 antibodies reversibly glaminergic synaptic function by decreasing glutamate receptors in the neurons specifically in highly NMDA receptor rich areas like hippocampus [26].
<table>
<thead>
<tr>
<th>Study Authors</th>
<th>Type of Study</th>
<th>Number of Patients</th>
<th>Clinical Presentation</th>
<th>Significant Findings</th>
<th>Optimal Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Armangue T, et al.</td>
<td>Retrospective Cohort Study</td>
<td>20</td>
<td>Dysesthesia or seizures, alteration in movements and speech patterns.</td>
<td>Positive blood or CSF NMDAR antibodies.</td>
<td>Steroids, intravenous immunoglobulin or plasma exchange, rituximab or cyclophosphamide.</td>
</tr>
<tr>
<td>B послал- Карвилью, J., et al.</td>
<td>Case Study</td>
<td>9</td>
<td>Movement disorders including: chorea, stereotypic movement, difficulty dystonia, facial/oculomandibular dystonia, opisthotonus, ataxia, and tremor</td>
<td>Positive blood or CSF NMDAR antibodies.</td>
<td>Immunotherapy for all patients except one patient that was treated with intrabenzine.</td>
</tr>
<tr>
<td>Florance N, et al.</td>
<td>Prospective Cohort Study</td>
<td>81</td>
<td>Behavioral or personal- ity change, seizures, deep disturbance, dyskinetia, dystonia, autonomic instability, hypoventilation. Women (not all) had ovarian teratomas as well.</td>
<td>Serum samples were positive for NMDAR antibodies.</td>
<td>Immunotherapy, tumor removed in cases of ovarian Teratomas.</td>
</tr>
<tr>
<td>Gale M, et al.</td>
<td>Retrospective Cohort Study</td>
<td>24</td>
<td>Hallucinations, seizures, Movement disorders, aphasia, Autonomic instability</td>
<td>CSF findings with (+) NMDAR antibodies, EEG and MRI Anoma- lay.</td>
<td>1st Line Therapy: Plasma exchange, immunoglobulin, and/or steroids.</td>
</tr>
<tr>
<td>Hanrahan S, et al.</td>
<td>Prospective Cohort Study</td>
<td>48</td>
<td>Behavioral Difiiculty, Cognitive Problems, Sensitivity, Motor difficulties.</td>
<td>Serum samples were positive for NMDAR antibodies.</td>
<td>Immunotherapy.</td>
</tr>
<tr>
<td>Karacan M, et al.</td>
<td>Case Study</td>
<td>1</td>
<td>Symptoms of depression followed by psychomotor slowing, progressive gait instability, and opucionous-myoclonus syndrome.</td>
<td>MRI: (+) Anti-NMDAR antibodies, EEG Generalized slowing of activity with left-sided pre- dominance with any opliquetions changes.</td>
<td>Steroids followed by neurocognitive testing.</td>
</tr>
<tr>
<td>Philipp O, et al.</td>
<td>Prospective cohort study</td>
<td>46</td>
<td>Functional and memory impairment</td>
<td>Non-recovered patients showed widespread superficial white matter damage in comparison to recovered; increased damage to superficial white matter in non-recovered patients specifically in frontal and temporal lobes.</td>
<td>Phlebopheresis.</td>
</tr>
<tr>
<td>Raha S, et al.</td>
<td>Case Series</td>
<td>4</td>
<td>Neuropsychiatric and en- tropyragal symptoms</td>
<td>Positive blood or CSF NMDAR antibodies.</td>
<td>IVIG, Steroids and/or ACTH.</td>
</tr>
<tr>
<td>Smith J, et al.</td>
<td>Case Study</td>
<td>1</td>
<td>Acute migraine followed by subacute progressive myoclonus, opucionous, and encephalopathy.</td>
<td>MRI [+] Leptomeningeal enhancement in cerebellar folia and subcortical T2 hyperintensities in the periventricular regions and amygdala CSF: (+) IgG NMDAR antibodies.</td>
<td>5-Methylpred- nison followed by plasmapheresis.</td>
</tr>
<tr>
<td>Titlaier M, et al.</td>
<td>Multi-institu- tional observa- tional study</td>
<td>577</td>
<td>Initial symptoms were related to anomalies in behavior, speech, cognition and seizure disorder</td>
<td>Serum samples were positive for NMDAR antibodies.</td>
<td>1st Line Immunotherapy non administration of steroids, IVIG or plasma exchange alone or combined;</td>
</tr>
<tr>
<td>Titlaier M, et al.</td>
<td>Observational Cohort Study</td>
<td>661</td>
<td>Behavioral, cognition and memory symptoms</td>
<td>Positive blood or CSF NMDAR antibodies.</td>
<td>1st Line Therapy: IVIG.</td>
</tr>
</tbody>
</table>

References:

Two major theories have been hypothesized to explain NMDA receptor antibodies access to brain parenchyma [12,17]: (1) Passive diffusion of antibodies across a disrupted blood brain barrier leading to increased antibody entry into CNS; (2) Intrathecal production of NMDA receptor with preserved blood brain barrier. Both theories have their own supporting evidence. For instance, patients with treatment refractory ANRE have responded well to cyclophosphamide and rituximab which supports the later theory [12,17]. However, patient with higher blood pressure and autonomic instability, can potentially have more extravasation of antibodies in CNS [12,17].

In summary, we have described basic pathophysiology along with case presentation of ANRE in addition to literature review of various clinical studies that have been performed in the recent past. As discussed in this case, the major takeaway points include a required detailed medical workup, psychiatry and neurology evaluation to rule out neuropsychiatry disorders. The neuropsychiatric presentation could further explain the pathophysiology of ANRE as depicted above in the discussion. NR1 and NR2 receptors in the CSF with associated clinical symptoms have a 100% specificity in early identification [26]. It is important to exclude other causes of encephalopathy. Given its association with ovarian teratomas, pelvic ultrasound helps identify the location of teratoma while maintaining a high index of suspicion. Medical management of ANRE would require interdisciplinary approach to help with acute phase of symptoms following maintenance phase and eventually intermediate to long term rehabilitation. During acute phase of treatment, caution should be warranted when using antipsychotics given the risk of developing possible neuroleptic malignant syndrome like symptoms namely altered mental status, autonomic instability and movement disorder. Immunosuppressive therapy in the form of steroids, intravenous immunoglobulin and plasma therapy are used in majority of cases along with supportive care and monitoring.

Conclusion
Thus in summary, we have described basic pathophysiology along with case presentation of ANRE, in addition to literature review of various clinical studies that have been performed in the recent past.

Conflict of Interest
None.

Bibliography
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