ECRONICON OPEN ACCESS

EC NEUROLOGY
Case Report

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

Smit Shah[1]*, Pooja Shah[2], Ramkrishna Makani[3] and Stacy Doumas[4]

[1]4th Year Medical Student, Rutgers Robert Wood Johnson Medical School, USA

[2]Department of Psychiatry, Delaware Psychiatric Center, USA

[3]Deparment of Child and Adolescent Psychiatry, Children's Hospital of Philadelphia, USA

[4]Deparment of Psychiatry, Jersey Shore University Medical Center, USA

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

Received: December 20, 2017; **Published:** February 14, 2018

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.

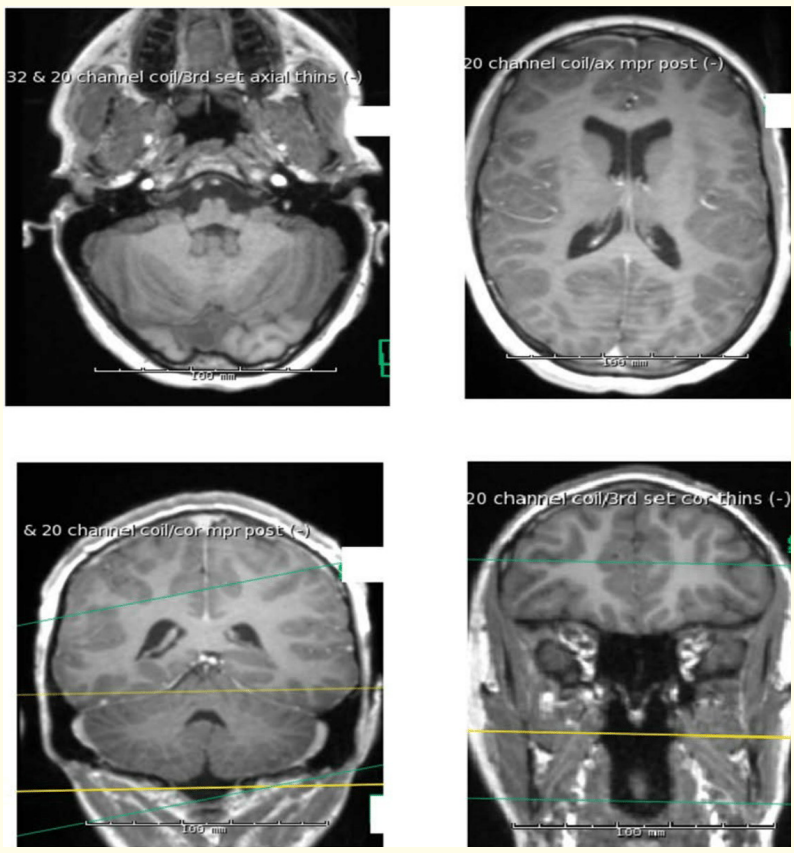

Figure 1: *Mild focal narrowing at the superior aspect of the cerebral aqueduct with mildly prominent lateral ventricular size. Right ventricle appears to be slightly enlarged as compared to left ventricle. There is mild deformity of the third ventricle on the left, likely due to indentation from asymmetrically 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.*

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-occurence [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 gluaminergic synaptic function by decreasing glutamate receptors in the neurons specifically in highly NMDA receptor rich areas like hippocampus [26].

Study Authors	Type of Study	Number of Patients	Clinical Presentation	Significant Findings	Optimal Treatment
Armangue T., *et al*.	Retrospective Cohort Study	20	Dyskinesias or seizures, alteration in movements and speech patterns.	Positive blood or CSF NMDAR antibodies.	Steroids, intravenous immunoglobulin or plasma exchange, rituximab or cyclophosphamide
Baizabal-Carvallo J., *et al*.	Case Study	9	Movement disorders including: chorea, stereotypic movement, extremity dystonia, facial/oromandibular dystonia, opisthotonus, athetosis, and tremor	Positive blood or CSF NMDAR antibodies.	Immunotherapy for all patients except one patient that was treated with tetrabenazine.
Florance N., *et al*.	Prospective Cohort Study	81	Behavioral or personality change, seizures, sleep disturbance, dyskinesia, dystonia, autonomic instability, hypoventilation. Women (not all) had ovarian teratomas as well.	Serum samples were positive for NMDAR antibodies.	Immunotherapy, tumor removal in cases with Ovarian Teratomas.
Gable M., *et al*.	Retrospective Cohort Study	24	Hallucinations, Seizures, Movement disorders, aphasia, Autonomic instability	CSF findings with (+) NMDAR antibodies, EEG and MRI Anomalies.	1st Line Therapy: Plasma exchange, intravenous immunoglobulin, and/or steroids. 2nd Line Therapy: Rituximab alone or in combination with cyclophosphamide.
Hacohen Y., *et al*.	Prospective Cohort Study	48	Behavioral Difficulty, Cognitive Problems, Seizures, Motor difficulties.	Serum samples were positive for NMDAR antibodies.	Immunotherapy.
Kurian M., *et al*	Case Study	1	Symptoms of depression followed by psychomotor slowing, progressive gait instability, and opsoclonus-myoclonus syndrome.	MRI: Normal CSF: (+) Anti-NMDAR antibodies EEG: Generalized slowing of activity with left-sided predominance with any epileptiform changes.	Plasmapheresis
Philips O. *et al*.	Prospective cohort study	46	Functional and memory impairment	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.	Steroids followed by neurocognitive testing.
Raha S., *et al*.	Case Series	4	Neuropsychiatric and extrapyramidal symptoms	Positive blood or CSF NMDAR antibodies.	IVIG, Steroids and/or ACTH
Smith J., *et al*.	Case Study	1	Acute migraine followed by subacute progressive myoclonus, opsoclonus, and encephalopathy.	MRI: (+) Leptomeningeal enhancement in cerebellar folia and subsequent T2 hyperintensities in the periventricular regions and amygdala CSF: (+) IgG NMDAR antibodies	IV Methylprednisolone followed by plasmapharesis
Titulaer M., *et al*.	Multi-institutional observational study	577	Initial symptoms were related to anomalies in behavior, speech, cognition and seizure disorder	Serum samples were positive for NMDAR antibodies. All patients were screened for systemic tumors specifically Ovarian Teratomas in females.	1st Line immunotherapy was administration of steroids, IVIg or plasma exchange alone or combined; 2nd Line immunotherapy included rituximab or cyclophosphamide alone or combined.
Titulaer M., *et al*.	Observational Cohort Study	661	Behavioral, cognition and memory symptoms	Positive blood or CSF NMDAR antibodies.	1st Line Therapy: IVIG 2nd Line Therapy: Rituximab or Cyclophosphamide.
Wright S., *et al*.	Prospective Surveillance Study	31	Behavioral changes, neuropsychiatric symptoms, seizures and movement disorders	Positive blood or CSF NMDAR antibodies.	1st Line Therapy: Steroids, IVIG, Plasma exchange. 2nd Line Therapy: Other immunotherapy.

Literature Review Table 1 [5-14, 26].

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 work up, 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

1. Kayser MS., *et al*. "Frequency and characteristics of isolated psychiatric episodes in anti-NMDA receptor encephalitis". *JAMA Neurology* 70.9 (2013): 1133-1139.

2. Iizuka T., *et al*. "Anti-NMDA receptor encephalitis in Japan: Long-term outcome without tumor removal". *Journal of Neurology* 70.7 (2008): 504-511.

3. Seki M., *et al*. "Neurological response to early removal of ovarian teratoma in anti-NMDAR encephalitis". *Journal of Neurology, Neurosurgery, and Psychiatry* 79.3 (2008): 324-326.

4. Dalmau J., *et al*. "Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies". *Lancet Neurology* 7.12 (2008): 1091-1098.

5. Steiner J., *et al*. "Increased prevalence of diverse N-methyl-D-aspartate glutamate receptor antibodies in patients with an initial diagnosis of schizophrenia: specific relevance of IgG NR1a antibodies for distinction from N-methyl-D-aspartate glutamate receptor encephalitis". *JAMA Psychiatry* 70.3 (2013): 271-278.

6. Zandi M., *et al*. "Disease-relevant autoantibodies in first episode schizophrenia". *Journal of Neurology* 258.4 (2011): 686-688.

7. Barry H., *et al*. "Anti-N-methyl-d-aspartate receptor encephalitis: review of clinical presentation, diagnosis and treatment". *British Journal of Psych Bulletin* 39.1 (2015): 19-23.

8. Dale RC., *et al*. "N-methyl-D-aspartate receptor antibodies in pediatric dyskinetic encephalitis lethargica". *Annals of Neurology* 66.5 (2009): 704-709.

9. Nokura K., *et al*. "Reversible limbic encephalitis caused by ovarian teratoma". *Acta Neurologica Scandinavica* 95.6 (1997): 367-373.

10. Okamura H., *et al*. "An acutely confused 15-year-old girl". *Lancet* 350.9076 (1997): 488.

11. Braverman J., *et al*. "Anti-NMDA-receptor encephalitis: A neuropsychiatric syndrome associated with ovarian teratoma". *Gynecologic Oncology Reports* 14 (2015): 1-3.

12. Moscato E., *et al*. "Mechanism underlying autoimmune synaptic encephalitis leading to disorders of memory, behavior and cognition: Insights from molecular, cellular and synaptic studies". *European Journal of Neuroscience* 32.2 (2010): 298-309.

13. Stein-Wexler R., *et al*. "Paraneoplastic limbic encephalitis in a teenage girl with an immature ovarian teratoma". *Pediatric Radiology* 35.7 (2005): 694-697.

14. Smith JH., *et al*. "N-methyl-D-aspartate Receptor Autoimmune Encephalitis Presenting With Opsoclonus-Myoclonus Treatment Response to Plasmapheresis". *Archives of Neurology* 68.8 (2011): 1069-1072.

15. Kurian M., *et al*. "Opsoclonus-myoclonus syndrome in anti-N-methyl-D-aspartate receptor encephalitis". *Archives of Neurology* 67.1 (2010): 118-121.

16. Hacohen Y., *et al*. "Paediatric autoimmune encephalopathies: Clinical features, laboratory investigations and outcomes in patients with or without antibodies to known central nervous system autoantigens". *Journal of Neurology, Neurosurgery and Psychiatry* 84.7 (2013): 748-755.

17. Florance N., *et al*. "Anti–N-Methyl-D-Aspartate Receptor (NMDAR) Encephalitis in Children and Adolescents". *Annals of Neurology* 66.1 (2009): 11-18.

18. Titulaer M., *et al*. "Treatment and prognostic factors for long-term outcome in patients with anti-N-Methyl-D-Aspartate (NMDA) receptor encephalitis: a cohort study". *Lancet Neurology* 12.2 (2013): 157-165.

19. Baizabal-Carvallo J., *et al*. "The spectrum of movement disorders in children with anti-NMDA receptor encephalitis". *Journal of Movement Disorders* 28.4 (2013): 543-547.

20. Titulaer MJ., *et al*. "Late-onset anti–NMDA receptor encephalitis". *Journal of Neurology* 81.12 (2013): 1058-1063.

21. Wright S., *et al*. "N-methyl-D-aspartate receptor antibody-mediated neurological disease: results of a UK-based surveillance study in children". *Archives of Disease in Childhood* 100.6 (2015): 521-526.

22. Gable M and Glaser C. "Anti-N-Methyl-D-Aspartate Receptor Encephalitis Appearing as a New-Onset Psychosis: Disease Course in Children and Adolescents within the California Encephalitis Project". *Pediatric Neurology* 72 (2017): 25-30.

23. Raha S., *et al*. "Nonparaneoplastic Anti-N-Methyl-D-Aspartate Receptor Encephalitis: A Case Series of Four Children". *Pediatric Neurology* 46.4 (2012): 246-249.

24. Armangue T., *et al*. "Pediatric Anti-NMDAR encephalitis-Clinical analysis and novel findings in a series of 20 patients". *The Journal of Pediatrics* 162.4 (2013): 850-856.

25. Phillips O., *et al*. "Superficial white matter damage in anti-NMDA receptor encephalitis". *Journal of Neurology, Neurosurgery, Psychiatry* (2017).

26. Anti-NMDA Receptor Encephalitis (2018).

Volume 10 Issue 3 March 2018