Case Report

# Anti-NMDA Receptor Encephalitis: A Rare but Important Auto-Immune Cause of Encephalitis

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**Abstract:** A previously healthy 30-year old lady presented with 1-day history of high grade fever and drowsiness. Five days prior to presentation, she developed insomnia and visual hallucinations of seeing unknown faces. Three days prior to presentation, she suffered from 5 episodes of generalized tonic colonic fits. On admission, she had a temperature of 102°F and GCS of 10/15 with no signs of meningeal irritation, no focal neurological deficit, normal deep tendon reflexes and down-going plantar reflex bilaterally. Her brain MRI scan showed mild hyper-intense signals in right cerebellum. Her CSF was tested for Anti-NMDA receptor antibodies which were positive. She was diagnosed as having Anti-NMDA Receptor Encephalitis and started on immediate Plasma Exchange with drastic improvement.

**Keywords:** Anti-NMDA receptor encephalitis, Anti-NMDA receptor antibodies, Plasma exchange, Antibiotic therapy, Meningeal, Autoimmune.

## INTRODUCTION

Anti-N-Methyl-D-Aspartate (NMDA) receptor encephalitis, an autoimmune encephalitis, is diagnosed by Anti-NMDA receptor antibodies which cause disruption in NMDA-receptor related synaptic transmission. At onset of disease, diagnosing Anti-NMDA receptor encephalitis is challenging as the clinical signs and symptoms overlap with other conditions such as viral encephalitis, primary psychiatric disorders, status epilepticus and organic movement disorders [1]. Anti-NMDA receptor encephalitis is seen predominantly in children and young adults [2]. The usual presentation of Anti-NMDA receptor encephalitis includes a prodromal phase followed by seizure or/and psychotic phase, catatonic unresponsive phase, hyper-kinetic phase and subsequently a recovery phase if adequately treated [3]. However some patients may not develop all the clinical features and the features may not appear in this sequence. Therefore, a high clinical suspicion is necessary to diagnose this disease timely and provide symptom-guided treatment in a critical/intensive care setting to improve the outcome of these patients [4].

## CASE PRESENTATION

A previously healthy 30-year old lady who presented with 1-day history of continuous high grade fever documented 102°F along with altered state of consciousness (drowsiness). There was no history of rigors, chills or night sweats. Five days prior to presentation, she was in her usual state of health when she developed insomnia and visual hallucinations of seeing unknown faces. Three days prior to presentation, she suffered from 5 episodes of generalized tonic clonic fits. Each episode lasted for 3-5 minutes associated with frothing of saliva, upward rolling of eyes, urinary incontinence and 1 episode of vomiting (leading to aspiration), followed by a post-ictal confusional state lasting 10-15 minutes. There was no history of oral or genital ulcers, skin rashes, joint pains, previous psychiatric or neurological manifestations. A school teacher by profession, she was married with 2 children and did not smoke or use illicit drugs. She was initially taken to a local GP clinic for management of the fits but at onset of fever and altered sensorium she was referred to our Tertiary Care Hospital. On examination, she had a temperature of 102°F and GCS of 10/15. On neurological examination, pupils were equally round and reactive to light. Signs' of meningeal irritation (Kernig and Brudzinski) were negative. There was no focal neurological deficit with normal deep tendon reflexes and down-going plantar reflex bilaterally. Examination of sensory, motor and cerebellar systems was limited as the patient was unable to follow commands. Respiratory rate was 18 per minute with normal vesicular breathing with bilateral coarse crepitations attributed to aspiration. Her oxygen saturation on room air was 80% which improved to 94% on 5L oxygen. Her precordial and abdominal examinations were normal.

On investigation, she had leukocytosis with TLC 14.1 x $10^9$/L with normal hemoglobin and platelet count. Her RFTs, LFTs and urinalysis were normal. She was admitted to the ICU on lines of meningo-encephalitis. Her brain MRI scan showed mild hyper-intense signals in right cerebellum as shown in

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Fig. (**1**). After doing a lumbar puncture, she was started empirically on intravenous acyclovir, ceftriaxone and vancomycin. CSF analysis showed TLC 250 cells/uL with 100% lymphocytes, RBC 0 cells/uL, Protein 22 mg/dl and Glucose 69 mg/dl with no organisms on Giemsa and AFB stain microscopy. Her blood, urinary and spinal fluid cultures did not grow any organism growth. Her condition, however, deteriorated and she was then given methylprednisolone pulse on suspicion of acute disseminated encephalomyelitis. She was intubated and put on mechanical ventilation. A repeat CSF analysis showed TLC 40 cells/uL with 100% lymphocytes, RBC 05 cells/uL, Protein 25.8 mg/dl and Glucose 99mg/dl with no organisms on Giemsa and AFB stain microscopy. Her CSF was tested for Anti-NMDA receptor antibodies using Enzyme-linked Immunosorbent Assay (ELISA) technique which were positive. A detailed autoimmune profile was ordered which showed negative ANA and ENA profile. Her echocardiography, chest and abomino-pelvic CT scan were

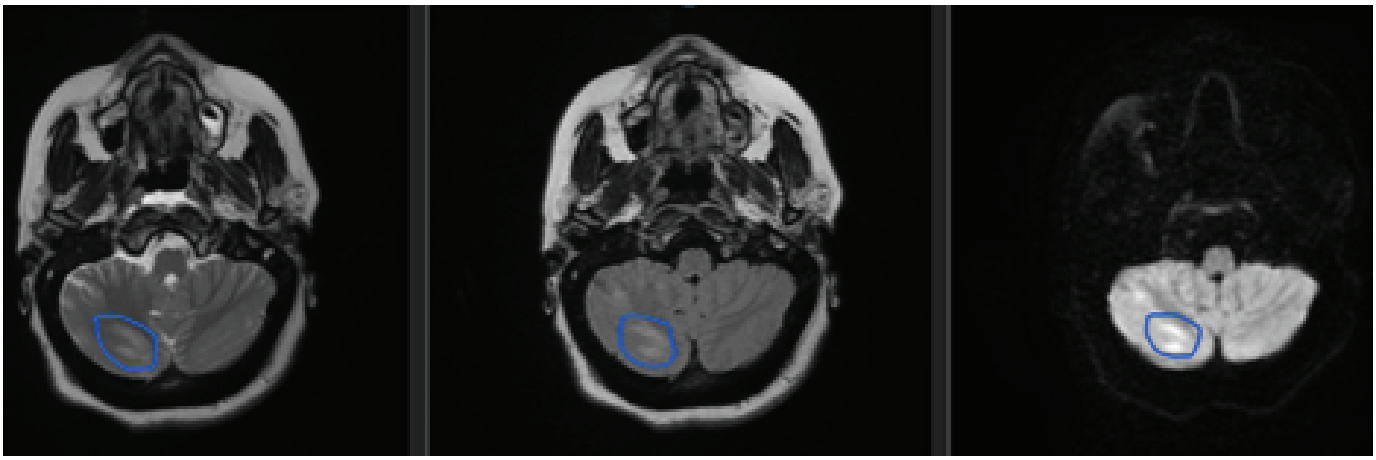

**Fig. (1).** MRI Scan Brain (with FLAIR) Showing Hyper-Intense Signals in Right Cerebellum.

within normal parameters. She was diagnosed as having Anti-NMDA Receptor encephalitis and started on immediate plasma exchange. Treatment with antiviral and antibiotics therapy was stopped once diagnosis of autoimmune disease was made. A total of 7 sessions of Plasma Exchange (2.0L each over 14 days) were done resulting in a drastic improvement. She was able to open eyes after first session, was following commands and extubated after 3rd session. By the 7th session she was able to stand and walk with assistance. A multidisciplinary management plan was formed incorporating neurology, psychiatry, physiotherapy and occupational rehabilitation. On follow up, she was markedly improved and able to do her vocational and avocational activities without assistance.

## DISCUSSION

The initial clinical presentation of Anti-NMDA receptor encephalitis may be non-specific and mimic other forms of encephalitis, primary psychiatric disorders, status epilepticus and organic movement disorders [1]. Dalmau *et al*. demonstrated that Anti-NMDA receptor encephalitis was more common in females (91%) and majority had psychiatric manifestations initially. Moreover, 59% patients had an underlying malignancy, with ovarian teratoma being the most common tumor in females [3]. Therefore, it is recommended that all female patients with Anti-NMDA receptor encephalitis be screened for ovarian tumors as tumor resection in these patients is the best treatment option. Our patient was worked up for a possible underlying malignancy but her CT scans (chest, abdomen, pelvis) did not show any evidence of malignancy. In Anti-NMDA receptor encephalitis, findings on MRI scan are variable and may include T2/FLAIR hyper-intense lesions in the temporal and frontal lobes, cerebellum, sub-cortical white matter and periventricular region along with lepto-meningeal and cortical contrast enhancement depending on the severity of disease. A poor prognostic marker on MRI scan is progressive cerebellar atrophy. In some patients the MRI scan may be normal therefore, it is necessary to test for Anti-NMDA receptor antibodies to confirm a diagnosis [3, 5-7].

Indications for admission to intensive/critical care in patients with Anti-NMDA receptor encephalitis include disturbed conscious level, refractory seizures, autonomic dysfunction and hyperkinetic status [8]. Diagnostic testing for Anti-NMDA receptor antibodies is not widely available and may take days to weeks before confirmation [9]. Therefore, prompt therapies based on the clinical features may be started as early as possibly when there is high clinical suspicion. First-line treatment options include intravenous methylprednisolone pulse therapy, intravenous immunoglobulin (IVIG) and plasmapheresis/plasma exchange therapy [9, 10]. In refractory cases, immune-modulation with cyclophosphamide and rituximab have been tired [1, 11]. Our patient did not respond to intravenous methylprednisolone therapy but responded well to plasma exchange therapy. Current literature

suggests that better outcomes are seen in patients who were started on therapy as soon as possible and in up to 75% patients full recovery may be seen [10, 11]. Titulaer *et al*. reported good outcome in 81% patients at 24 months' follow-up with early prompt treatment and no ICU admission being predictors of good prognosis. However, relapse may be seen in up to 25% and is more common in children [11, 12].

## CONCLUSION

In conclusion, high clinical suspicion is necessary to diagnose Anti-NMDA Receptor Encephalitis timely so that adequate treatment may be instituted in a critical/intensive care setting depending on the disease severity so that the prognosis may be improved.

## CONFLICT OF INTEREST

Declared none.

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## REFERENCES

[1] Lin KL, Lin JJ. Neurocritical care for Anti-NMDA receptor encephalitis. Biomed J 2020; 43(3): 251-8. doi: 10.1016/j.bj.2020.04.002.

[2] Florance NR, Davis RL, Lam C, *et al*. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Ann Neurol 2009; 66(1): 11-8. doi: 10.1002/ana.21756.

[3] Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol 2011; 10(1): 63-74. doi: 10.1016/S1474-4422(10)70253-2.

[4] Schneider R, Brüne M, Breuer TG, Börnke C, Gold R, Juckel G. Early Multidisciplinary intensive-care therapy can improve outcome of severe anti-nmda-receptor encephalitis presenting with extreme delta brush. Transl Neurosci 2019; 10: 241-3. doi: 10.1515/tnsci-2019-0039.

[5] Bacchi S, Franke K, Wewegama D, Needham E, Patel S, Menon D. Magnetic resonance imaging and positron emission tomography in anti-NMDA receptor encephalitis: A systematic review. J Clin Neurosci 2018; 52: 54-9. doi: 10.1016/j.jocn.2018.03.026.

[6] Iizuka T, Kaneko J, Tominaga N, *et al*. Association of progressive cerebellar atrophy with long-term outcome in patients with anti-n-methyl-d-aspartate receptor encephalitis. JAMA Neurol 2016; 73(6): 706-13. doi: 10.1001/jamaneurol.2016.0232.

[7] Lynch DR, Rattelle A, Dong YN, Roslin K, Gleichman AJ, Panzer JA. Anti-NMDA Receptor Encephalitis: Clinical Features and Basic Mechanisms. Adv Pharmacol 2018; 82: 235-60. doi: 10.1016/bs.apha.2017.08.005.

[8] Schubert J, Brämer D, Huttner HB, *et al*. GENERATE and IGNITE network. Management and prognostic markers in patients with autoimmune encephalitis requiring ICU treatment. Neurol Neuroimmunol Neuroinflamm. 2018 Oct 30;6(1):e514. doi: 10.1212/NXI.0000000000000514. PMID: 30568992; PMCID: PMC6278855.

[9] Peery HE, Day GS, Doja A, Xia C, Fritzler MJ, Foster WG. Anti-NMDA receptor encephalitis in children: The disorder, its diagnosis, and treatment. Handb Clin Neurol 2013; 112: 1229-33. doi: 10.1016/B978-0-444-52910-7.00045-3.

[10] Remy KE, Custer JW, Cappell J, *et al*. Pediatric Anti-N-Methyl-d-Aspartate receptor encephalitis: A review with pooled analysis and critical care emphasis. Front Pediatr 2017; 5: 250. doi: 10.3389/fped.2017.00250.

[11] Titulaer MJ, McCracken L, Gabilondo I, *et al*. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: An observational cohort study. Lancet Neurol 2013; 12(2): 157-65. doi: 10.1016/S1474-4422(12)70310-1.

[12] Poloni C, Korff CM, Ricotti V, *et al*. Severe childhood encephalopathy with dyskinesia and prolonged cognitive disturbances: Evidence for anti-N-methyl-D-aspartate receptor encephalitis. Dev Med Child Neurol 2010; 52(5): e78-82. doi: 10.1111/j.1469-8749.2009.03542.x.

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