J Pediatr Neurosci. 2014 May-Aug; 9(2): 145–147.

doi:  [10.4103/1817-1745.139322](https://dx.doi.org/10.4103%2F1817-1745.139322)

PMCID: PMC4166838

PMID: [25250071](https://www.ncbi.nlm.nih.gov/pubmed/25250071)

**Anti-N-methyl-D-aspartate receptor encephalitis: A case report and review of the literature**

[Satnam Kaur](https://www.ncbi.nlm.nih.gov/pubmed/?term=Kaur%20S%5BAuthor%5D&cauthor=true&cauthor_uid=25250071), [Monica Juneja](https://www.ncbi.nlm.nih.gov/pubmed/?term=Juneja%20M%5BAuthor%5D&cauthor=true&cauthor_uid=25250071), [Devendra Mishra](https://www.ncbi.nlm.nih.gov/pubmed/?term=Mishra%20D%5BAuthor%5D&cauthor=true&cauthor_uid=25250071), and [Silky Jain](https://www.ncbi.nlm.nih.gov/pubmed/?term=Jain%20S%5BAuthor%5D&cauthor=true&cauthor_uid=25250071)

Department of Pediatrics, Maulana Azad Medical College, Lok Nayak Hospital, New Delhi, India

**Address for correspondence:** Dr. Satnam Kaur, Department of Pediatrics, Maulana Azad Medical College, Lok Nayak Hospital, New Delhi - 110 002, India. E-mail: [ni.oc.oohay@cod\_ks](mailto:dev@null)

Anti-N-methyl-D-aspartate receptor encephalitis is a well characterized immune-mediated encephalitis. It is increasingly being recognized as one of the common causes of encephalitis, but is frequently misdiagnosed especially in resource-constrained settings. With a simple test available to diagnose the disorder and prospects of good recovery following early immunotherapy, the disorder should be kept as a differential diagnosis in patients presenting with unexplained behavioral/psychiatric symptoms and progressive encephalopathy with movement disorders.

**Keywords:**Encephalitis, immune-mediated encephalitis, N-methyl-D-aspartate receptors

**Introduction**

Encephalitis has numerous and varied causes, but in resource-constrained settings, most cases are assumed to be infectious in etiology. Despite infections being a common cause, immune-mediated encephalitis is increasingly being recognized as a significant contributor to encephalitis cases (20-30%).[[1](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/?report=printable" \l "ref1),[2](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/?report=printable" \l "ref2)] Apart from acute disseminated encephalomyelitis (ADEM) (immune-mediated encephalitis predominantly affecting white matter), a number of a immune-mediated encephalitis predominantly affecting the grey matter have been described recently. In fact, a number of cases previously labeled as “encephalitis of unknown cause” have been found to have immune-mediated etiology.[[2](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/?report=printable" \l "ref2),[3](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/?report=printable" \l "ref3)]

Here, we report a case of anti-N-methyl-D-aspartate receptor encephalitis (anti-NMDAR encephalitis), followed by discussion of on immune-mediated encephalitis. The main purpose of our case report is to increase awareness regarding the immune-mediated encephalitis, especially anti-NMDAR encephalitis.

[Go to:](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/?report=printable)

**Case Report**

A 9-year-old developmentally normal girl child was admitted with a history of abnormal behavior for 3 days and inability to sleep for 2 days. She was apparently well 7 days back when she had a flu-like illness that lasted 4 days. Following an asymptomatic period of 2 days, she suddenly started talking irrelevantly with periods of normal behavior in between. Over next 3 days, she became increasingly restless, agitated and anxious, and did not sleep for 2 consecutive nights before presenting to the hospital. She was having hallucinations, delusions and hyper-religiosity. There was no inadvertent drug intake, abdominal pain, dark colored urine, jaundice, dog bite or stressful life event. At admission, she was oriented to place and person but not time. She was having inappropriate speech and was restless and agitated. Rest of the examination (including neurological) was unremarkable. Liver function tests, serum ammonia, and lactate were within normal limits. Neuroimaging done on day 3 of admission was unremarkable. Cerebrospinal fluid (CSF) examination including herpes simplex virus serology was normal. Over next 2 days, child developed features of catatonia in the form of echolalia, echopraxia and keeping limbs in bizarre postures, followed by gradually decreasing verbal output that progressed to complete mutism by day 6. She stopped interacting with parents and indicating her needs. On day 6, she had multiple episodes of left sided complex partial seizures (interictal electroencephalography (EEG) revealed a slow background). Next day, she started having abnormal movements in the form of oro-facial dyskinesias (grimacing, chewing, tongue thrusting, lip smacking, frowning), dystonias (progressing to the dystonic storm) and choreoathetoid movements of limbs that were difficult to control. No evidence was found for Wilson's disease. Repeat magnetic resonance imaging (MRI) done on day 10 of admission [[Figure 1a](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/figure/F1/)] revealed T2 hyperintensities in bilateral thalamus and cerebellar hemisphere (left > right). In view of the presentation with psychiatric symptoms followed by development of catatonia, seizures, encephalopathy, abnormal movements with normal CSF and nonspecific MRI findings, possibility of autoimmune encephalitis was kept. Testing for serum anti-NMDAR antibodies was requisitioned (which subsequently came positive), and methylprednisolone was started. CSF evaluation for antibodies could not be done because of financial constraints. Contrast-enhanced computed tomography abdomen to look for ovarian teratoma was normal. Repeat MRI brain [[Figure 1b](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/figure/F1/)] showed decreased hyper-intensity as compared to the previous scan with some cortical atrophy mainly in the temporal region. Subsequently, she received two courses of intravenous immunoglobulin (IVIG). After the second course of IVIG, involuntary movements decreased, though she continued to be unresponsive to surroundings with intermittent visual fixation and following. She also started having stereotypic movements (pelvic thrusting, floating of hands into the air, writhing movements of extremities) and periods of hyperthermia. In view of poor response to IVIG and steroids, she was given 4 doses of rituximab at weekly intervals. Gradually, her sensorium improved, abnormal movements abated, and she started following simple commands. Follow-up MRI on day 63 showed diffuse cerebral atrophy [[Figure 1c](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/figure/F1/)]. At last follow-up, 6 months after onset, she has rare abnormal movements, no seizures, near normal speech in response to questions (but reduced spontaneous speech output) and improved cognition.

[Go to:](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/?report=printable)

**Discussion**

Immune-mediated encephalitis (predominantly affecting the grey matter, thus excluding ADEM) can be broadly divided into three groups – paraneoplastic encephalitis associated with onconeural antibodies (paraneoplastic neurological syndromes [PNS]); autoimmune encephalitis associated with antibodies to neuronal cell surface proteins (neuronal surface antibody syndrome [NSAS]); encephalitis strongly suspected to be immune-mediated, but immune mechanisms still not fully elucidated (e.g., opsoclonus myoclonus syndrome, Rasmussen encephalitis, Hashimoto encephalopathy, etc.).[[4](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/?report=printable" \l "ref4),[5](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/?report=printable" \l "ref5)]

Paraneoplastic neurological syndromes are rare (overall affect <1% of patients with cancers), associated with the presence of onconeural antibodies and usually precede the diagnosis of cancer. Criteria for diagnosis of PNS were established by PNS Euronetwork in 2004.[[6](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/?report=printable" \l "ref6)] Neuronal cell loss in PNS is mediated by cytotoxic T-cells that are probably directed against the target antigens of accompanying antibodies. Thus, onconeural antibodies are just markers for immune-mediated process and are not pathogenic. These disorders do not usually respond to immunotherapy, though disease progression can be slowed with effective tumor therapy.

Neuronal surface antibody syndrome are associated with antibodies to cell surface proteins expressed in neurons. These antibodies are pathogenic and target receptors and cell surface proteins involved in synaptic transmission, plasticity or neuronal excitability. Main NSAS described are anti-NMDAR encephalitis and limbic encephalitis. Though, these disorders can be associated with tumors, they are frequently nonparaneoplastic, especially in pediatric age group, and they respond to immunotherapy with a good chance of substantial recovery. Compared with PNS, these disorders are not rare. In fact, in a long-term study, frequency of anti-NMDAR encephalitis exceeded that of any individual viral encephalitis.[[2](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/?report=printable" \l "ref2)]

Anti-NMDAR encephalitis is a well characterized syndrome and is most frequent of all the disorders discussed above. In a recent population based study done in England, anti-NMDAR encephalitis constituted 4% of all the cases of encephalitis.[[1](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/?report=printable" \l "ref1)] Majority of cases occur in females (about 80%), and disorder is more frequent in young teenagers and children.[[7](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/?report=printable" \l "ref7)] Frequency of tumor association (mostly teratoma) depends on age, sex and ethnicity, being more common in adult black women. Tumor detection is less likely in younger patients and men. Tumors other than teratoma are uncommon (2%).[[7](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/?report=printable" \l "ref7),[8](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/?report=printable" \l "ref8)]

Antibodies against NR1 subunit of NMDAR cause a reversible decrease in NMDAR cluster density in postsynaptic dendrites in titer dependent fashion resulting in a characteristic neuropsychiatric syndrome that evolves in several stages of illness and recovery. The decrease in NMDAR receptor density is reversible upon removal of antibodies and explains good response to tumor removal and immunotherapy even in patients with severe symptoms.[[9](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/?report=printable" \l "ref9)] What triggers the immune response is not clear but a genetic and racial predisposition to autoimmunity has been suggested.

Illness begins with a prodromal phase of low grade fever, and nonspecific features followed, usually within 2 weeks, by a prominent “psychiatric phase” characterized by anxiety, insomnia, bizarre behavior, delusions, hyper-religiosity, mania, visual/auditory hallucinations. Language problems, varying from reduced verbal output and echolalia to complete mutism, are common. Short term memory loss is frequent, though difficult to assess because of psychiatric symptoms and speech problems. Neurological phase follows the psychiatric phase and is characterized by decreased responsiveness that may alternate with periods of agitation and catatonia. Abnormal movements and autonomic instability predominate in this phase. Orofacial dyskinesias are particularly striking. Other abnormal movements include choreoathetosis, complex and stereotypic movements, dystonic posturing, episodic opisthotonus, oculogyric crisis. Autonomic manifestations include hyperthermia, tachycardia, hypersalivation, bradycardia, hypotension, and hypoventilation. Compared to adults, autonomic manifestations are less severe in children.[[8](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/?report=printable" \l "ref8)] Seizures are common. Recovery occurs in reverse order of symptom presentation and usually there is complete amnesia for the entire event.[[9](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/?report=printable" \l "ref9)]

Cerebrospinal fluid is abnormal (lymphocytic pleocytosis, normal or mild increase in proteins, oligoclonal bands) in most of the patients.[[7](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/?report=printable" \l "ref7),[8](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/?report=printable" \l "ref8),[9](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/?report=printable" \l "ref9)] EEG abnormalities are found in all the patients in the form of nonspecific slow and disorganized activity, sometimes with electrographic seizures.[[7](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/?report=printable" \l "ref7),[8](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/?report=printable" \l "ref8),[9](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/?report=printable" \l "ref9)] Brain MRI is unremarkable in 50% patients. In other 50%, it may show nonspecific hyperintensities in cortical/subcortical areas and cerebellum, sometimes with contrast enhancement in the affected areas or meninges. Serial MRIs may show cerebral atrophy, but this is at least partly reversible over years.[[7](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/?report=printable" \l "ref7)] Definitive diagnosis is established by demonstrating antibodies against NR1 subunit of NMDAR in CSF/sera of patients.

Management of NMDAR encephalitis includes immunotherapy and detection and removal of teratoma, if present. First line immunotherapy includes IVIG, methylprednisolone and plasma exchange. Concurrent use of IVIG and methylprednisolone as first line treatment followed by rituximab (4 doses at weekly intervals) with or without cyclophosphamide in case of poor response at day 10 is the suggested treatment.[[7](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/?report=printable" \l "ref7)] Additional courses of IVIG/methylprednisolone/plasma exchange have been suggested to be useful if both CSF and serum antibody titers remain high.[[10](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/?report=printable" \l "ref10)] Chronic immunosuppression with mycophenolate moeftil or azathioprine for 1-year is recommended for patients without teratoma and those requiring second line immunotherapy. Methotrexate can be used as an alternative immunosuppressant in case of poor response to first and second line treatment. Yearly surveillance for teratoma for at least 2 years is recommended.

Recovery from this disease is slow (months-years) but 75% patients show complete/substantial recovery.[[7](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/?report=printable" \l "ref7),[8](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/?report=printable" \l "ref8),[9](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/?report=printable" \l "ref9)] Outcome is better with early diagnosis and treatment.[[7](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/?report=printable" \l "ref7),[10](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/?report=printable" \l "ref10)] Relapses can occur in 20-25% patients and are more common in idiopathic cases and with delayed diagnosis.[[7](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/?report=printable" \l "ref7),[8](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/?report=printable" \l "ref8),[9](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/?report=printable" \l "ref9),[10](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/?report=printable" \l "ref10)]

To conclude, anti-NMDAR encephalitis is one of the common causes of encephalitis, has distinctive clinical features and is potentially reversible if diagnosed early and treated appropriately.

[Go to:](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/?report=printable)

**Footnotes**

**Source of Support:** Nil

**Conflict of Interest:** None declared.

[Go to:](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/?report=printable)

**References**

1. Granerod J, Ambrose HE, Davies NW, Clewley JP, Walsh AL, Morgan D, et al. Causes of encephalitis and differences in their clinical presentations in England: A multicentre, population-based prospective study. Lancet Infect Dis. 2010;10:835–44. [PubMed: 20952256]

2. Gable MS, Sheriff H, Dalmau J, Tilley DH, Glaser CA. The frequency of autoimmune N-methyl-D-aspartate receptor encephalitis surpasses that of individual viral etiologies in young individuals enrolled in the California Encephalitis Project. Clin Infect Dis. 2012;54:899–904. [PMCID: PMC3297648] [PubMed: 22281844]

3. Prüss H, Dalmau J, Harms L, Höltje M, Ahnert-Hilger G, Borowski K, et al. Retrospective analysis of NMDA receptor antibodies in encephalitis of unknown origin. Neurology. 2010;75:1735–9. [PubMed: 21060097]

4. Zuliani L, Graus F, Giometto B, Bien C, Vincent A. Central nervous system neuronal surface antibody associated syndromes: Review and guidelines for recognition. J Neurol Neurosurg Psychiatry. 2012;83:638–45. [PMCID: PMC3348613] [PubMed: 22448032]

5. Armangue T, Petit-Pedrol M, Dalmau J. Autoimmune encephalitis in children. J Child Neurol. 2012;27:1460–9. [PMCID: PMC3705178] [PubMed: 22935553]

6. Graus F, Delattre JY, Antoine JC, Dalmau J, Giometto B, Grisold W, et al. Recommended diagnostic criteria for paraneoplastic neurological syndromes. J Neurol Neurosurg Psychiatry. 2004;75:1135–40. [PMCID: PMC1739186] [PubMed: 15258215]

7. 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;10:63–74. [PMCID: PMC3158385] [PubMed: 21163445]

8. Florance NR, Davis RL, Lam C, Szperka C, Zhou L, Ahmad S, et al. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Ann Neurol. 2009;66:11–8. [PMCID: PMC2826225] [PubMed: 19670433]

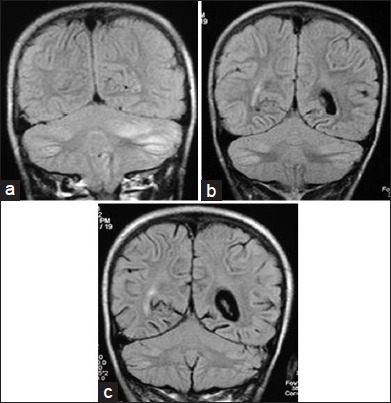
9. Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, et al. Anti-NMDA-receptor encephalitis: Case series and analysis of the effects of antibodies. Lancet Neurol. 2008;7:1091–8. [PMCID: PMC2607118] [PubMed: 18851928]

10. Florance-Ryan N, Dalmau J. Update on anti-N-methyl-D-aspartate receptor encephalitis in children and adolescents. Curr Opin Pediatr. 2010;22:739–44.[PubMed: 21045695]

[Go to:](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166838/?report=printable)

**Figures and Tables**

**Figure 1**



Serial magnetic resonance imaging brain showing (a) T2 hyperintensities in bilateral cerebellar hemispheres (left > right) (b) Mild cortical atrophy, more prominent in temporal lobes with decreased hyperintensities in bilateral cerebellar hemispheres (c) Diffuse cerebral atrophy