

Anti Nmdar encephalitis

Dr jp,asst prof,ich,mch,kottayam

The syndrome

Antibodies against the NR1 subunit of the NMDAR (NMDAR antibodies) are associated with a characteristic syndrome that develops in several stages of illness and recovery, as first reported by Iizuka and colleagues¹⁷ and Sansing and colleagues.¹⁸

Encephalitis mediated by autoantibodies directed against the N-methyl-D-aspartate receptor (anti-NMDA receptor encephalitis) is a now well-described clinical entity in children and adults¹⁻⁴ and constitutes one of the most common causes of encephalitis in children.⁵ The syndrome is notable both for its often dramatic clinical presentation and for its typically favorable response to therapy. The syndrome of anti-NMDA receptor encephalitis includes some combination of neuropsychiatric symptoms, movement disorder, seizures, and/or autonomic dysfunction or vital sign instability, potentially progressing to coma and, in rare cases, death.²⁻⁴ In children, symptoms of abnormal behavior, speech disturbance, seizures (including status epilepticus⁶), and movement disorder seem to predominate.^{1,7} Approximately 40% of all reported patients with anti-NMDA receptor encephalitis are children (i.e., age < 18 years);⁴

What are the clinical features?

In young children, the behavioural change can be difficult to detect because they often present with temper tantrums, hyperactivity, or irritability as opposed to frank psychosis. In children, the first symptom to be recognised is often non-psychiatric—eg, seizures, status epilepticus, dystonia, verbal reduction, or mutism. Some behaviours are hypersexual and violent (for instance, kicking and biting caregivers and parents). Because of anxiety and insomnia, some children need intense sedation.¹²

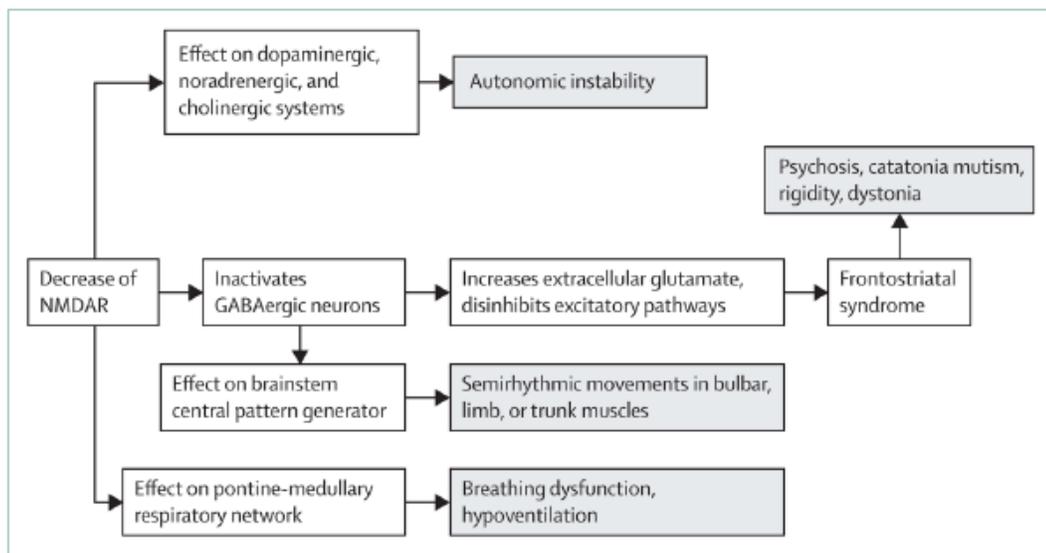
This initial phase of the illness is usually followed by decreased responsiveness that can alternate between periods of agitation and catatonia. At this stage, abnormal movements and autonomic instability are usual manifestations. Oro-lingual-facial dyskinesias are the most characteristic movements, but other types might occur simultaneously or alternate with limb and trunk choreoathetosis, elaborate motions of arms and legs, oculogyric crisis, dystonia, rigidity, and opisthotonic postures (see video recordings^{19–23}). The most frequent autonomic manifestations include hyperthermia, tachycardia, hypersalivation, hypertension, bradycardia, hypotension, urinary incontinence, and erectile dysfunction.⁸ Two women (aged 16 and 17 years) were thought to have Takotsubo cardiomyopathy (or stress cardiomyopathy) due to high blood pressure (JD, unpublished).

Hypoventilation, requiring respiratory support, occurs as the patient becomes comatose but can occur earlier when the level of consciousness is relatively preserved. In some cases the central origin of hypoventilation is noted when patients cannot be weaned from mechanical ventilation. While recovering, one patient needed nocturnal ventilatory support for 3 months. Autonomic

storms can fluctuate from tachycardia to bradycardia and longlasting cardiac pauses, which, in some patients, require a temporary pacemaker.¹⁸ A transient increase of intracranial pressure has been recorded in a few patients (JD, personal observation).

Motor or complex seizures develop at early stages of the disease. The overlap of abnormal movements and epileptic seizures can lead to under-recognition of the seizures or unnecessary escalation of antiepileptics for dyskinesias that are interpreted as seizures.²⁴ In general, the frequency and intensity of the seizures decrease as the disease evolves. However, seizures and status epilepticus can resurface at any time during the illness. Attempts to wean patients from sedation can result in status epilepticus.² During such stages, in which patients are usually managed in intensive care units, dissociative responses to stimuli are noted. For example, patients often resist eye opening but show little or no response to painful stimuli.¹⁷ This dissociative state is similar to that caused by NMDAR antagonists, such as phencyclidine or ketamine, which are called dissociative anesthetics.^{25,26}

Oversimplification of the disease into cortical and subcortical stages and the suggestion that patients without a tumour have a less impaired level of consciousness than do patients with a tumour²⁷ is (in our experience) highly inaccurate. Many symptoms with which a patient presents (such as anxiety, fear, bizarre or stereotypical behaviour, insomnia, and memory deficits) cannot be classified as cortical. Clinical examination of patients reveals a diffuse encephalopathy indicating dysfunction of subcortical structures, limbic regions, amygdalae, and frontostriatal circuitry. Patients without tumours have periods of unconsciousness and confusion that can be longer or worse than are those of patients with tumours.^{8,12,28}



The figure is based on data from animal models of pharmacological or genetic decrease of NMDAR (*N*-methyl-D-aspartate receptor). Each step has been shown in these models or in individuals treated with antagonists of NMDAR. The pronounced resemblance with the clinical features of anti-NMDAR encephalitis leads us to postulate that an antibody-mediated decrease of NMDAR predominantly inactivates GABAergic neurons (which are rich in NMDAR), leading to disinhibition of excitatory pathways and increase of extracellular glutamate. As a result patients develop a frontostriatal syndrome, which is characteristic of anti-NMDAR encephalitis. The complexity of orofacial and limb movements in patients with this disorder is probably explained by disinhibition of a brainstem central pattern generator that under normal conditions is tonically inhibited by the GABAergic system.⁸⁵ Because genetic disruption of NR1 causes hypoventilation,⁸⁰ a direct effect of the antibodies on the medullary-pontine respiratory network (nuclei of Kölliker-Fuse) might result in breathing dysfunction.⁸³ The presence of NMDAR in dopaminergic, cholinergic, and noradrenergic systems probably explains the autonomic manifestations (hypersalivation, hypertension, hyperthermia, cardiac dysrhythmia) that are also typical of NMDAR antagonists.²⁶ Figure adapted from Florance-Ryan and Dalmau⁸⁶ with permission from Wolters Kluwer Health. GABA= γ -amino-butyric acid.

what are the Diagnostic tests?

The cerebrospinal fluid (CSF) is initially abnormal in 80% of patients and becomes abnormal later in the disease in most other patients.⁸ Findings include moderate lymphocytic pleocytosis, normal or mildly increased protein concentration, and, in 60% of patients, CSF-specific oligoclonal bands. Most patients have intrathecal synthesis of NMDAR antibodies.^{3,8,27} Of 431 patients studied (412 with paired serum and CSF), we have not encountered a patient in whom antibodies were only present in serum. If diagnosis is delayed or patients have received treatment with plasma exchange or IV immunoglobulin, antibodies might be detected only in CSF.^{10,12}

Electroencephalograms (EEG) are abnormal in most patients, usually showing non-specific, slow, and disorganised activity sometimes with electrographic seizures.⁸ Slow, continuous, rhythmic activity in the delta-theta range predominates in the catatonic-like stage.¹² This activity is not associated with abnormal movements and does not respond to antiepileptic drugs. Monitoring with video EEG is important to diagnose and treat seizures appropriately.²⁴ One patient had non-convulsive status epilepticus that lasted for 6 months and required a pentobarbital-induced coma.³⁵ A prophylactic oophorectomy was done and a microscopic ovarian teratoma was detected; the patient recovered afterwards

Brain MRI is unremarkable in 50% of patients, and in the other 50%, T2 or FLAIR signal hyperintensity might be seen in the hippocampi, cerebellar or cerebral cortex, frontobasal and insular regions, basal ganglia, brainstem, and, infrequently, the spinal cord.² The findings are usually mild or transient and can be accompanied by subtle contrast enhancement in the affected areas or the meninges.

What is the **Sex, tumour association, and potential triggers of the immune response**

About 80% of patients with anti-NMDAR encephalitis are women. The detection of an underlying tumour is dependent of age, sex, and ethnic background.^{8,12} Figure 2 shows the distribution of 400 patients grouped by age and the presence or absence of a tumour. When compared with a previous series,⁸ these data show that, with increased awareness of this disorder, the disease is being more frequently recognised in younger teenagers and children. Analysis of these 400 patients confirms that the younger the patient, the less likely that a tumour will be detected, and that in female patients older than 18 years, the frequency of an underlying teratoma is much the same as we initially reported (webappendix p 1).⁸ Black women are more likely to have an underlying ovarian teratoma than are patients of other ethnic groups

what is the treatment outcome?

Treatment, outcome, and relapses

About 75% of patients with NMDAR antibodies recover or have mild sequelae; all other patients remain severely disabled or die.⁸ Management of anti-NMDAR encephalitis should initially focus on immunotherapy and the detection and removal of a teratoma. Most patients receive corticosteroids, intravenous immunoglobulins (IVIg) or plasma exchange as firstline of immunotherapy. These treatments have enhanced effectiveness and speed of action when patients have an underlying tumour that is removed.^{8,12,27} In patients without a tumour or with delayed diagnosis, additional treatment with second-line immunotherapy (a rituximab or cyclophosphamide, or both) is usually needed

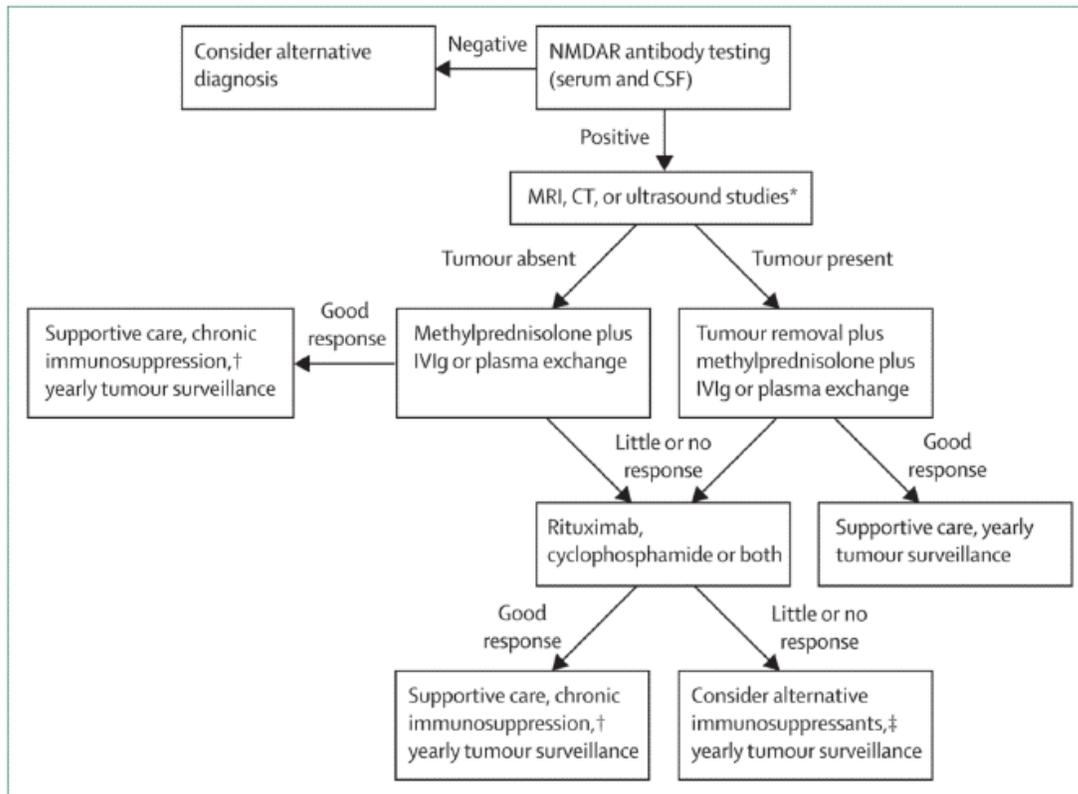


Figure 7. Proposed algorithm for the treatment of anti-NMDAR encephalitis

*In women, ultrasound of abdomen and pelvis, or transvaginal ultrasound (if age-appropriate); in men, testicular ultrasound. †Mycophenolate mofetil or azathioprine for 1 year. ‡Consider oral or intravenous methotrexate as an alternative immunosuppressant.¹⁰ Figure adapted from Florance-Ryan and Dalmau⁸⁶ with permission from Wolters Kluwer Health.

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what is **The process of recovery?**

Recovery from anti-NMDAR encephalitis occurs as a multistage process that happens in the reverse order of symptom presentation. Patients slowly wake from coma as their autonomic functions stabilise, respiration recovers, and dyskinesias subside; they are able to follow simple commands and can have appropriate interactions before they recover verbal functions. During this period patients can become psychotic and agitated again, calming as they recover further (JD, unpublished observations). Social behaviour and executive function symptoms are usually the last to improve, and recovery can be incomplete or delayed by many months.

For the acute stage of the disease, many patients need to be hospitalised for at least 3–4 months, followed by several months of physical and behavioural rehabilitation.^{8,12,17} Patients need close supervision to prevent incidents caused by inappropriate behaviour, impulsivity, disinhibition, and sometimes hyperphagia, hypersexuality, and hypersomnia.

Patients' symptoms might resemble those of patients with Klüver-Bucy syndrome (bulimia

What is the d/d

, Viral encephalitis is an early presumptive diagnosis, suggested by the acute neurological change, CSF pleocytosis, and occasional hyperthermia.⁵⁹ Three of our patients were suspected to have rabies because of the development of psychiatric symptoms, decreased consciousness, dystonic facial movements, hypersalivation, and autonomic instability (JD, unpublished). Ten of 20 children who had previously been enrolled in the California encephalitis project with a diagnosis of idiopathic encephalitis with psychiatric manifestations and dyskinesias had NMDAR antibodies.⁴¹ In a study⁵³ that examined patients who had previously been diagnosed with encephalitis lethargica, many with dyskinesias were shown to have NMDAR antibodies. There are several reported disorders,⁶⁰ mainly in paediatric studies,^{13,61–65} that were probably cases of anti-NMDAR encephalitis

what is the pathogenesis?

What is the Pathogenic mechanisms and effects of antibodies

Compelling clinical and laboratory evidence exists that anti-NMDAR antibodies are pathogenic. As previously discussed, antibody titres in CSF and, less often, in serum relate with clinical outcome. Furthermore, the reversibility of the disorder, irrespective of the duration of symptoms, suggests an immune-mediated neuronal dysfunction rather than irreversible degeneration. These features, coupled with the paucity of brain T-cell infiltrates, places this disorder in a category distinct from those that are mediated by complement or cytotoxic T-cell mechanisms.^{66,67} Although patients' antibodies are of the IgG1 and IgG3 classes,³⁷ and therefore capable of activating complement, autopsy and biopsy studies show deposits of complement in the tumour, but not in the brain, despite the presence of IgG in brain (EM-H, unpublished).² This occurrence is probably attributable to preservation of the blood-brain barrier and low concentrations of complement in the CNS

what is the Approach to diagnosis and proposal of a treatment strategy?

Anti-NMDAR encephalitis should be suspected in any individual, usually younger than 50 years and especially a child or a teenager, who develops a rapid change of behaviour or psychosis, abnormal postures or movements (mostly orofacial and limb dyskinesias), seizures, and variable signs of autonomic instability, hypoventilation, or both. Supportive findings include CSF lymphocytic pleocytosis or oligoclonal bands; electroencephalogram with infrequent spikes, but frequent, slow, disorganised, sometimes rhythmic activity that does not relate with most abnormal movements; and brain MRI that is often normal or shows transient FLAIR or contrast-enhancing abnormalities.

Antibody studies should be done in both serum and CSF. Such tests allow comparison of antibody concentrations during the course of the disease. Periodic screening of serum and

CSF is useful to assess the effects of treatment, especially in the CNS. All patients should be examined for the presence of an underlying tumour, mainly an ovarian teratoma or a testicular germ-cell tumour. The very low frequency of other tumours suggests that periodic whole-body screening, as recommended for classic paraneoplastic syndromes, is unnecessary.⁸⁸ However, we do recommend periodic screening for ovarian teratomas for at least 2 years, even if patients have recovered from encephalitis.¹⁷

what is the treatment?

On the basis of previous experience and data from this Review, a proposal for treatment is shown in figure 7. Although no standard of care exists, we prefer concurrent IVIg (0.4 g/kg per day for 5 days) and methylprednisolone (1 g/day for 5 days) to plasma exchange. Plasma exchange is more difficult to do in children, poorly cooperative patients, or patients with autonomic instability. If no response is seen after 10 days, we start second-line therapy. In adults, we use rituximab (375 mg/m² every week for 4 weeks) combined with cyclophosphamide (750 mg/m² given with the first dose of rituximab), followed by monthly cycles of cyclophosphamide. This treatment is discontinued when patients have had substantial clinical recovery, which is usually accompanied by a decrease of CSF and serum antibody concentrations. Paediatricians often use only one of these drugs—mostly rituximab. After substantial improvement, antiepileptics are not needed in most patients. Because relapses occur in 20–25% of patients, often in those without teratoma, in such patients we recommend continued immunosuppression (mycophenolate mofetil or azathioprine) for at least 1 year after initial immunotherapies are discontinued

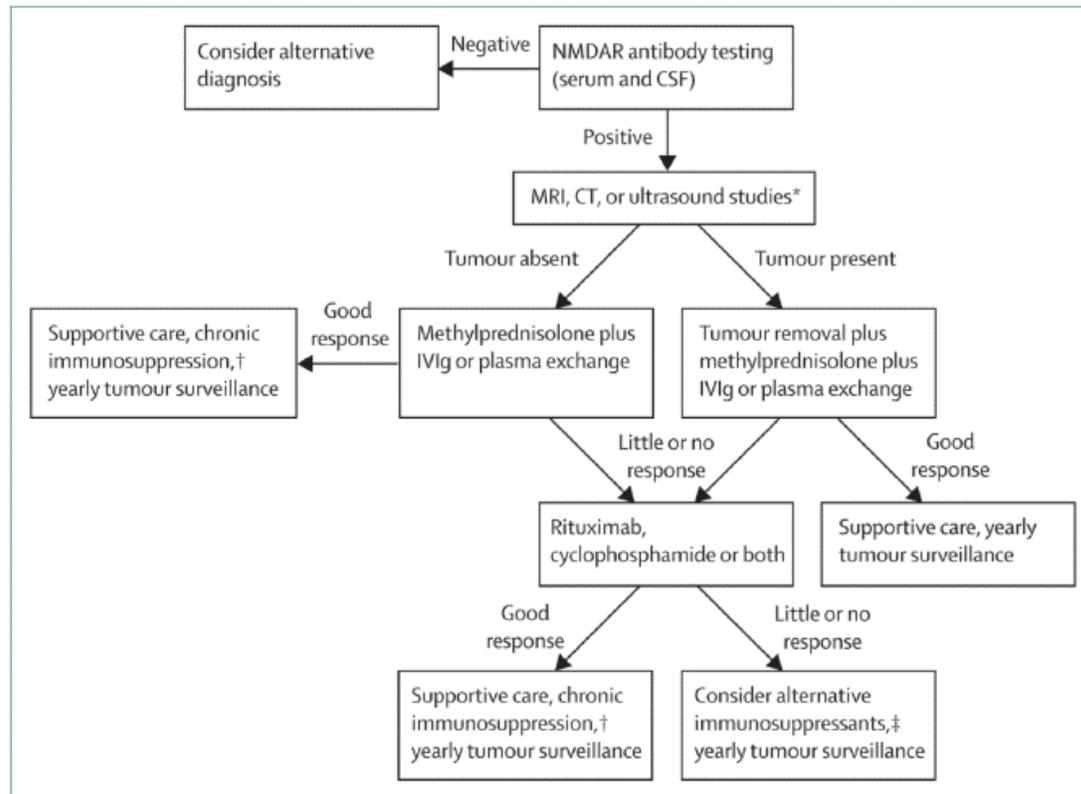


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