



NMDAR-antibody Encephalitis:

The major role of our immune system is to recognize and get rid of infection. But sometimes some components of the immune system, called antibodies, may instead react with proteins in our own body causing an autoimmune disease. When this reaction is against proteins in the brain it is called autoimmune encephalitis. If the brain protein is the N-methyl-D-aspartate (NMDA) receptor, the condition is termed NMDA-receptor antibody encephalitis, or anti-NMDAR encephalitis. These antibodies disrupt normal brain signaling and cause brain swelling, or encephalitis. Essentially the immune system is attacking the brain.

Anti-NMDA receptor encephalitis is a neurologic disease first identified by Dr. Josep Dalmau and colleagues at the University of Pennsylvania in 2007. Initially thought to be rare, this progressive multistage encephalopathy is now the most commonly identified form of autoimmune encephalitis and most frequently recognized on clinical grounds. It was first described as a paraneoplastic phenomenon in young females with an ovarian teratoma. The Ab target was then confirmed as the extracellular domain of the NR1 subunit of the NMDA receptor.



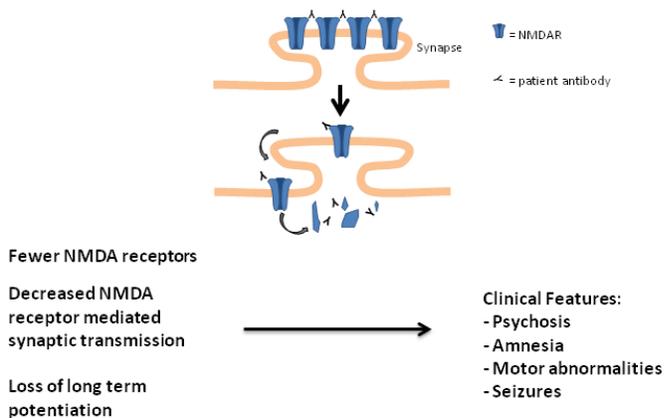
The clinical spectrum associated with NMDAR-Abs includes adult and pediatric, male and female, paraneoplastic and non-paraneoplastic patients (with and without tumor). Anti-NMDAR encephalitis is now the most common Autoimmune Encephalitis in younger patients predominantly children and young adults (median age, 21 years), with a predominance of cases in females (4:1) that becomes less evident after the age of 45 years. Up to 58% of affected young female patients of reproductive age, between the ages of 18-45, have an ovarian teratoma (extragonadal teratomas are a rare cause); in men and children, the association with tumors is less frequent. The disorder is a differential diagnosis to be considered in *any* patient presenting with subacute alterations of cognition, behavior and amnesia.

SYMPTOMS:

Anti-NMDAR (N-methyl-D-aspartate receptor) encephalitis has a characteristic clinical syndrome in most patients. Symptoms of psychosis and memory impairment are commonly the initial findings with abnormal movements, seizures, and depressed level of consciousness emerging later. Patients may experience the psychotic symptoms again as they wake from coma, a phenomenon analogous to the psychotic symptoms seen after recovery from phencyclidine anesthesia (Phencyclidine, also known as PCP or "angel dust", is an NMDAR antagonist developed as an anesthetic but is not used due to the high risk of psychosis).

Young children typically present with insomnia, seizures, abnormal movements, or a change in behavior such as irritability, temper tantrums, agitation, and reduction of verbal output. Abnormal movements may occur early in the disease course, especially in children, who generally have more motor symptoms and fewer psychiatric symptoms than adults. The movement disorder is often the most distinctive single feature of the condition. This may resemble dystonia or chorea, with writhing and fixed abnormal postures of the limbs and involves stereotyped, complex, prolonged orofacial, and limb movements which are often refractory to drugs usually used to treat chorea and dystonia. Seizures, dysautonomia, (when the autonomic nervous system functions abnormally, it is not a single disease process), central hypoventilation (inadequate ability to breathe), and sleep pattern alterations.

Teenagers and adults more often present with psychiatric symptoms, including agitation, hallucinations, delusions, and catatonia, which may lead to hospital admission for psychosis. The disease progresses in a period of days or weeks to include reduction



of speech, memory deficit, orofacial and limb dyskinesias, seizures, decreased level of consciousness, and autonomic instability manifested as excess salivation, hyperthermia, fluctuations of blood pressure, tachycardia, or central hypoventilation. Bradycardia and cardiac pauses are infrequent but require a temporary pacemaker in some patients. One month after disease onset, regardless of the symptoms at presentation, most children and adults have a

syndrome that combines several of the above-mentioned symptoms; in approximately 5% of patients, the disease may remain monosymptomatic (e.g., psychiatric symptoms).

In adults with anti-NMDAR encephalitis, writhing movements of the face and limbs may be most prominent in the comatose phases of the illness. In anti-NMDAR encephalitis seizures may occur at any stage of the illness. Most patients develop these varied

symptoms within the first 4 weeks of their illness, often in a characteristic pattern. Symptoms may fluctuate rapidly.

MISDIAGNOSIS DUE TO PRESENTING SYMPTOMS:

The group of symptoms in anti-NMDAR encephalitis show substantial resemblance to those observed when the function of the same proteins is altered by genetic modification or pharmacologic antagonists. For example, many clinical features of anti-NMDAR encephalitis resemble those observed with the administration of noncompetitive NMDAR antagonists, ketamine (a short-acting drug with hallucinogenic effects) or phencyclidine (PCP also known as angel dust). It is for this reason that emergency room physician's mistake the culprit of the patient's symptoms to be drug induced as this is what they more commonly see in ER. However, the anti-NMDAR patient will test negative for a drug induced cause. Additionally, misdiagnosis of schizophrenia disorder and bipolar affective disorder can also occur as the group of presenting symptoms mimics these more common psychiatric disorders.

Intoxications such a neuroleptic malignant syndrome and serotonin syndrome may often present with similarities to autoimmune encephalitis. Conversely, patients with anti-NMDAR encephalitis may develop psychosis as an initial symptom and be treated with neuroleptics, then later show catatonia, rigidity, autonomic instability and altered level of consciousness; this pattern of findings may be mistaken for neuroleptic malignant syndrome. Autoimmune encephalitis therefore should enter into the differential diagnosis of any case of suspected neuroleptic malignant syndrome.

Patients with anti-NMDAR encephalitis may be particularly sensitive to strong dopamine antagonists, studies suggest an increased susceptibility to the adverse effects of these drugs (e.g., the neuroleptic malignant syndrome); the mechanisms underlying this complication are unknown. Attempts to avoid using these medications should be instituted.

The diagnosis of anti-NMDAR encephalitis is confirmed by the detection of CSF antibodies against the GluN1 subunit of the NMDAR; serum testing is less reliable, with false negative results in up to 14% of cases. Anti-NMDAR encephalitis often is present despite normal MRI findings. MRI of the head is abnormal in 30% of affected patients, mainly showing increased fluid attenuated inversion recovery (FLAIR) signal involving the cortical, subcortical, or cerebellar regions.

CAUSES:

Two potential triggers are tumors, and Herpes simplex encephalitis, and possibly other viral encephalitides, can trigger antibodies against the NMDAR. Some of the implicated tumors contain nerve tissue or the tumor cells express the neuronal proteins targeted by the autoantibodies, suggesting that the ectopic expression of these proteins may play a role in initiating the autoimmune response.

TREATMENT:

Treatment recommendations are based largely on retrospective series and expert opinion, since few clinical trials have been conducted. The current approach includes immunotherapy and removal of the immunologic trigger, such as teratoma or another tumor, when applicable. Early tumor treatment is particularly important in achieving a good outcome. In practice, most patients are treated with glucocorticoids, the antibodies themselves can be targeted for removal by plasmapheresis or intravenous gamma globulin, and if there is no clinical response, rituximab and cyclophosphamide are used. Rituximab is usually effective in refractory cases, and it appears to reduce the risk of a clinical relapse, which accounts for its increasing use as an initial treatment. Together these treatments change synaptic encephalitis from deadly disorders to diseases that can often have the patient enter recovery or at least control the disease, leading to minimal long-term disability in many patients. The process of caring for these patients requires patience and repeated evaluations to determine the proper degree of immune therapy needed at any given time.

The response to immune therapy is generally good, particularly if the more effective treatments are used promptly. However, treatment may take many months to reach its full effects, and some patients have persistent deficits, especially in the domains of memory and cognition. Autoimmune encephalitis may relapse, so follow-up care is important.

RECOVERY:

Perhaps the most important aspect of anti-NMDAR encephalitis is that it is amenable to treatment. This treatment may take several forms beyond symptomatic treatment of neurological symptoms. Patients with anti-NMDAR encephalitis commonly can recover from a totally unresponsive state to eventually resume a good quality of life. Recovery is slow and typically occurs in reverse of symptom onset. The most severe symptoms typically resolve first while the cognitive, behavioral, and memory problems take longer to resolve. Most patients will make a full recovery within two years of disease onset. Predictors of positive outcomes include presence of a tumor, patients without a tumor had a higher frequency of relapses than those with a tumor, quick diagnosis, and aggressive treatment including second line therapies. It is recommended that patients with a history of tumor have annual tumor screens up to 4 years.

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Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis

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