



## Fact Sheet: Pediatric Autoimmune Encephalitis

### What is Autoimmune Encephalitis?

Autoimmune encephalitis (Autoimmune encephalitides) is a rare group of treatable acquired central nervous system (CNS) disorders that cause inflammation of the brain. AE occurs when the immune system becomes activated and mistakenly attacks the brain. The immune system becomes mis-programmed causing an autoimmune response to occur. Some forms of AE, other than ADEM, are associated with the body's production of antibodies against certain targets within the brain. These auto-antibodies (aka antibodies) begin to attack healthy brain cells wrongly identifying them as foreign invaders causing brain inflammation.

There are several types of autoimmune encephalopathy that affect children and young people – the most common of which is acute disseminated encephalomyelitis (ADEM). The next most common type in children is anti-N-methyl D-aspartate (anti-NMDA) receptor encephalitis which remains the most identifiable autoimmune encephalitis in children. Despite the major advances in the field, a large proportion of children with suspected autoimmune encephalitis are seronegative, and these patients may have unidentified auto-antibodies or more likely other immune mechanisms. (4)

### How common is Autoimmune Encephalitis?

Autoimmune encephalitis has an incidence rate of 1.2 per 100,000 and is not as rare as previously thought. It is as prevalent as infectious encephalitis. Dramatic advances in discovery of biomarkers in AE has resulted in patients getting diagnosed faster.

### What causes Autoimmune Encephalitis?

AE may be triggered by infection (viral, bacterial, fungal) or cancer. Environmental factors and genetics may also play vital roles. The cause cannot be established in 40 to

50% of the cases. Most autoimmune encephalitides occur in patients with no apparent immunologic triggers, leading some investigators to postulate a genetic predisposition to these disorders. (6)

## What are the signs and symptoms?

Anti-NMDAR encephalitis (NMDARE) is the prototypic autoimmune encephalitis. Symptoms of the disease's clinical presentation is different and less known in young children than with adults where it is perfectly described. The first neurological symptoms observed in young children are seizures, especially focal seizure. 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. Teenagers and adults more often present with psychiatric symptoms, including agitation, hallucinations, delusions, and psychomotor slowing, (a visible slowing of physical and emotional reactions, including speech and affect), 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. 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). (6)

## How is it Diagnosed?

The diagnostic criteria for auto-antibody-negative but probable autoimmune encephalitis can be made when all four of the following criteria have been met:

1. Rapid progression (less than 3 months) of working memory deficits (short-term memory loss), altered mental status, or psychiatric symptoms
2. Exclusion of well-defined syndromes of autoimmune encephalitis (eg, typical limbic encephalitis, Bickerstaff 's brainstem encephalitis, acute disseminated encephalomyelitis)
3. Absence of well characterized auto-antibodies in serum and cerebral spinal fluid (CSF) obtained by lumbar puncture, and at least two of the following criteria: • MRI abnormalities suggestive of autoimmune encephalitis • CSF pleocytosis, CSF-specific oligoclonal bands or elevated CSF IgG index, or both\* • Brain biopsy showing inflammatory infiltrates and excluding other disorders (eg, tumor)
4. Reasonable exclusion of alternative causes (5)

## How is it treated?

For all types of autoimmune encephalitides, prompt immunotherapy has been associated with a favorable outcome; spontaneous clinical improvement is infrequent. The tenets of treatment that improve outcomes are: immune therapy is better than none, early treatment is better than late, and if a patient fails first line therapy second line therapy should be considered. In practice, most patients are treated with glucocorticoids, intravenous immune globulin, or plasma exchange (first line treatment), and if there is no clinical response, rituximab and/or cyclophosphamide (second line treatment) are used. Rituximab is usually effective in cases that do not respond as hoped, and it appears to reduce the risk of a clinical relapse, which accounts for its increasing use as an initial treatment. If long term immunosuppression is necessary, monthly cyclophosphamide, monthly tocilizumab, or q6m rituximab have been used. There is also some evidence for the use of bortezomib. It is important to point out that there are NO prospective clinical trials in any of these situations.

## Recovery

Long-term Neuropsychological outcomes:

Parents want to know, and need to be informed, about what things to look out for as their children are recovering. Because the presentation of this disease is so dramatic and there is such relief felt when the patient has made such a good recovery, we tend not to place an emphasis on lasting problems.

Although follow-up is often reported as “good” following pediatric anti-NMDAR encephalitis, many patients have significant cognitive problems and fatigue that persist several years after apparent recovery, even up until adolescence, resulting in academic achievement problems and lower quality of life. It is essential that patients and caregivers are aware of these problems and to consider early neuropsychological counseling. (1)

Neuropsychiatric evaluations can assist teachers and parents in understanding what cognitive challenges exist and how they will need to be supported in school. The student should qualify for an Individualized education plan (IEP). It may appear the person is doing well yet a neuropsychiatric evaluation may reveal unknown struggles. Being aware of apathy and passivity in children recovering is too often neglected and can lead to school dropout. Challenges in school performance commonly seen are word finding difficulties, attention and concentration, anxiety and impulsiveness; dyslexia and indecisiveness affects a lower percentage of students. (3) Children do improve but parents and caregivers should not underestimate the burden these lasting cognitive and behavioral challenges are for them.

Rehabilitative efforts should include physical and occupational therapy as well as strategies that focus on cognitive and neuropsychiatric impairments. The challenges are not finite with autoimmune encephalitis as several areas of the brain may be affected. AE is a global process affecting the central nervous system rather than a person who received a traumatic brain injury on a specific area of the brain.

## Relapse

Relapses are fortunately uncommon in autoimmune encephalitis. At this time, a relapsing course widening spectrum of CNS inflammatory disorders of the CNS can be anticipated in approximately 12% of anti-NMDAR encephalitis cases within 2 years. The frequency of clinical relapse in the encephalitides associated with antibodies against NMDAR, AMPAR, LGI1, CASPR2, or DPPX ranges from 12 to 35%. (6) Children with anti-MOG antibody-associated disease have a relapse rate of approximately 30%, typically with ADEM, optic neuritis or myelitis. Relapses often occur when immunotherapy is reduced or discontinued. There is anecdotal evidence that cases of anti-LGI1 or anti-NMDAR encephalitis can relapse many years after the first episode. Relapses may herald recurrence of the associated tumor or a tumor that was missed in the initial episode. Immunotherapy and treatment of the tumor, if it was missed initially, usually result in improvement. Relapses tend to be less severe and can be mono-symptomatic, such as isolated seizures or movement disorder, unlike the initial episode when many symptoms appeared. The relapse rate has reduced since the initial descriptions of the disease, possibly due to the increasing use of second-line therapies and chronic immune suppression, which may be altering the natural history of disease. (4)

1. Long-term neuropsychological outcome following pediatric anti-NMDAR encephalitis <https://n.neurology.org/content/90/22/e1997.long>
2. Initial clinical presentation of young children with N-methyl-D-aspartate receptor encephalitis [https://www.ejpn-journal.com/article/S1090-3798\(17\)31851-2/fulltext](https://www.ejpn-journal.com/article/S1090-3798(17)31851-2/fulltext)
3. In the Clinic-Autoimmune Encephalitis Persistent Cognitive, Neuropsychological Deficits After Anti-NMDAR Encephalitis Require Therapy, Study Suggests Neurology Today By Gina Shaw June 7, 2018 [https://journals.lww.com/neurotodayonline/Fulltext/2018/06070/In\\_the\\_Clinic\\_Autoimmune\\_Encephalitis\\_\\_Persistent.7.aspx](https://journals.lww.com/neurotodayonline/Fulltext/2018/06070/In_the_Clinic_Autoimmune_Encephalitis__Persistent.7.aspx)
4. Autoimmune encephalitis in children clinical phenomenology, therapeutics, and emerging challenges [https://journals.lww.com/co-neurology/Citation/2017/06000/Autoimmune\\_encephalitis\\_in\\_children\\_clinical.20.aspx](https://journals.lww.com/co-neurology/Citation/2017/06000/Autoimmune_encephalitis_in_children_clinical.20.aspx)
5. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol 2016; 15:391–404. Graus F, Titulaer MJ, Balu R, et al.

6. Antibody-Mediated Encephalitis Josep Dalmau, M.D., Ph.D., and Francesc Graus, M.D., Ph.D

Created in collaboration with International Autoimmune Encephalitis Society and Neurologist, Michael Sweeney, M.D. Louisville, Kentucky

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