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ORIGINAL ARTICLE

# Autoimmune encephalitides

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## Abstract

**Objective:** To review the scientific literature on autoimmune encephalitides or encephalopathies, a specific form of autoimmunity against the central nervous system that is particularly prominent in pediatrics because it is involved in the differential diagnosis of acute viral encephalitis. **Methods:** We reviewed the epidemiology, clinical picture, and diagnostic and therapeutic management of autoimmune encephalitides on the basis of published papers over the past 5 years, which were selected using the keywords "autoimmune," "encephalitis," and "encephalopathy" in the PubMed and CAPES databases, in addition to reviewing recent editions of relevant books. **Results:** Patients of all age groups can be affected, and some case reports involved patients as young as 8 months. However, there is a predilection for children and young adults. Encephalitis due to antibodies against the N-methyl-D-aspartate receptor is the most prevalent type during childhood, affecting girls more often than boys, and is associated with underlying tumors in 40% of cases. The most common clinical features at onset in children younger than 12 years are movement disorder, seizures, and behavioral changes. Immunomodulatory therapy involves the administration of methylprednisolone and intravenous immunoglobulin, and plasmapheresis may also be administered. Either rituximab or cyclophosphamide is administered in refractory cases. **Conclusions:** The discovery of autoimmune encephalitides has changed our diagnostic and therapeutic approach to many neurological and psychiatric disorders. Early detection followed by timely therapy allows us to maximally increase the patient's chances of total recovery.

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## INTRODUCTION

Until the early 2000s, non-infectious cases of encephalitis were associated with neoplasms of the lung, testis, ovary, breast, thyroid, and thymus. The clinical picture included amnesia, psychiatric symptoms, sleep disturbances, and epileptic seizures, and most affected individuals were aged 50–70 years[1]. The immune pathophysiology involved the production of antibodies against intraneuronal antigens, including Hu, Ma2, and CV2/CRMP5, as well as effects on the mesial temporal lobe. Therefore, the condition was designated as paraneoplastic limbic encephalitis[2].

Then, a succession of studies described a new category of non-infectious encephalitis that affects both adults and children and is mediated by antibodies against neuronal surface receptors or synaptic proteins[3]. In 2003, cases of encephalitis due to antibodies against the voltage-gated potassium channel (VGKC)[4] were reported. In 2007, Dalmau et al. diagnosed encephalitis secondary to antibodies against the N-methyl-D--aspartate (NMDA) receptor, and most of the affected patients presented with ovarian teratomas[5]. In 2012, it was reported that 12 children with antibodies against the dopamine D2 receptor (D2R) presented with movement disorders and psychiatric symptoms[3]. In total, 16 autoantibodies were identified, and these cases were not necessarily associated with tumors, particularly in pediatric patients. Therefore, this condition was denominated as autoimmune encephalitis. Some authors prefer using the term autoimmune encephalopathy[6,7].

Subsequently, it was shown that in many cases of anti-VGKC encephalitis, antibodies were actually directed against more specific antigens, including leucine-rich glioma--inactivated protein 1 (LGI1) and contactin-associated protein 2 (Caspr2)[8,9].

Autoimmune encephalitides or encephalopathies represent a specific type of autoimmunity against the central nervous system (CNS), and they differ from traditional neuroinflammation originating from primary disorders such as multiple sclerosis or disorders secondary to neurodegeneration[7]. In contrast to the classical cases of paraneoplastic encephalitis, the prognosis may be more favorable after immunotherapy and, where appropriate, tumor excision[10].

The complex and heterogeneous clinical picture varies according to the age of the patient, distribution of the involved neuronal antigens, and presence of an underlying neoplasm. The disease affects memory, cognition, and behavior in varying degrees, as these functions depend on the normal function of neurotransmitter receptors, ion channels, and neuronal surface proteins that participate in synaptic transmission[6].

Autoimmune encephalitides (AIEs) are particularly relevant in pediatrics because they are involved in the differential diagnosis of acute viral encephalitis[10]. The California Encephalitis Project examined samples from 20 patients with a clinical picture suggestive of acute encephalitis but without viral etiology and concluded that 50% of the patients were positive for anti-NMDA receptor antibodies[10]. Therefore, pediatricians should become familiar with AIEs because they often have to consider the diagnostic hypothesis of these treatable diseases.

## DEFINITION

AIEs are a group of treatable inflammatory CNS diseases that affect individuals from all age groups[8] who were previously healthy in most cases[11]. These diseases occur more frequently in immunocompetent than in immunocompromized individuals[12]. AIEs involve conspicuous neuropsychiatric symptoms and are associated with IgG antibodies against cell surface proteins, ion channels, or receptors[13]. AIEs are recognized as an increasing cause of encephalitis and fall into the broader group of neuroimmune disorders[11].

Anti-NMDA receptor encephalitis is the prototypical AIE in pediatrics, and 40% of patients manifest this condition before the age of 18 years[7]. Dalmau et al.[5] described 12 female cases, all of which were associated with neoplasms, and 10 cases were associated with ovarian teratomas. Three patients presented with short-term memory loss, followed by psychiatric symptoms and altered consciousness. The other patients presented with a psychiatric syndrome, which delayed diagnosis. Eleven patients had generalized or partial epileptic seizures. Other clinical manifestations appeared later, such as movement disorders (dystonia, dyskinesia of the face and/or arms, choreoathetosis, and catatonia-like episodes), hypoventilation, dysautonomia, and sleep disorders[5]. Antibodies are directed against the NR1 subunit of the NMDA receptor[14].

AIE should be suspected when the patient presents at least three of the following manifestations[11]:

- Epileptic seizures
- Psychiatric symptoms or behavioral changes
- Movement disorders
- Cognitive regression or memory deficits
- Speech disturbances
- Dysautonomia

## EPIDEMIOLOGY

Patients of all age groups may be affected, with reported patients being as young as 8 months. However, there is a predilection for children and young adults. Anti-NMDA receptor encephalitis is the most common type of encephalitis in childhood, predominantly affecting female individuals[15].

It is estimated that the annual incidence of all types of encephalitis is 5–8 cases per 100,000 individuals, and the etiology is not identified in 40%–50% of cases. Some studies suggest that autoimmune disorders are the third most common cause of encephalitis after viral infections and acute disseminated encephalomyelitis (ADEM). It is estimated that the latter represents 15% of the cases of acute encephalitis in children[16].

A prospective study conducted in Britain found that the incidence of anti-NMDA receptor encephalitis is 0.85 per million children per year[17]. A Dutch study reported that the incidence of anti-LGI1 encephalitis is 0.83 per million people, representing the second most common AIE[13]. Nevertheless, genetic/racial factors may play a role, because a study conducted in Olmsted, Minnesota, United States, found that the incidence of AIE is 2.8 per 100,000 person-years in individuals with African ancestry, compared with 0.7 per 100,000 person-years in Caucasians[18].

Two triggering factors that are well characterized for AIE are neoplasms and viral encephalitis. It is believed that either the implicated tumors contain neural tissue or tumor cells express neural proteins that elicit the production of autoantibodies. Moreover, herpes encephalitis can produce antibodies against the NMDA receptor or other neuronal surface proteins, which triggers choreoathetosis in children a few weeks after the onset of acute viral encephalitis[13].

## CLASSIFICATION

AIEs are classified according to the autoantibody detected in the cerebrospinal fluid (CSF) and/or serum. Sixteen autoantibodies have been identified to date considering all age groups; they often cause unique clinical conditions and have variable epidemiology (Table 1)[7,13].

Some authors include conditions previously described in the AIE group, such as ADEM, Hashimoto encephalopathy, optic neuromyelitis, opsoclonus–myoclonus–ataxia syndrome, and Bickerstaff's brainstem encephalitis[7,18-20].

## PATHOGENESIS

Individuals become susceptible to autoimmune diseases when there is a loss of tolerance to autoantigens, with subsequent deregulated activation of T and B cells. The activation and proliferation of B cells that differentiate into autoantibody-secreting plasmocytes play a crucial role in the pathogenesis of AIEs[21].

In AIEs associated with antibodies against cell surface antigens, the antibodies have direct access to the epitopes and modify the structure and function of the target protein. However, in encephalitis associated with antibodies against intracellular antigens, the antibodies do not reach the epitopes; therefore, cytotoxic T cells cause autoimmune insult[13].

The pathogenic mechanism of autoantibodies involves cross-linking and receptor internalization, complement activation, and antigen destruction. In addition, the subclass of pathogenic IgG autoantibodies is responsible for several clinical consequences. In anti-NMDA receptor encephalitis, antibodies are primarily of the IgG1 class and do not trigger complement activation or T-cell infiltration. In contrast, antibodies against LGI1 and Caspr2 are predominantly of the IgG4 class and cause complement activation and neuronal loss[21].

## CLINICAL PICTURE

The primary clinical manifestation of AIE is encephalopathy, which is characterized by confusion, disorientation, behavioral changes, or cognitive dysfunction[7]. The initial symptoms are often headache or diarrhea, as well as flu-like symptoms, and although most patients with acute viral encephalitis have fever, 50% of patients with AIE present this symptom at onset or during the course of the disease, which may lead to the suspicion of an infectious etiology[12]. In fact, the clinical manifestations of AIE and viral encephalitis are similar, at least initially. Nonetheless, specific clinical and demographic factors help with differential diagnosis (see below)[18].

Other clinical manifestations vary according to the autoantibody involved (Table 1). The presence of movement disorders, psychosis, and restlessness suggests the development of anti-NMDA receptor encephalitis and should encourage the institution of early immunotherapy while waiting for the autoantibody test results[8].

A recent study involving 500 patients found that the most common initial clinical manifestations in children younger than 12 years were movement disorders, epileptic seizures, and abnormal behavior, including restlessness, aggression, mood swings or personality changes, and sudden onset of anger attacks[14].

A unique condition is the development of choreoathetosis a few weeks or, in a few cases, a few months after herpes encephalitis; choreoathetosis occurs in 20% of cases. In this clinical context, the detection of anti-NMDA receptor antibodies in the CSF is mandatory[20].

AIEs also include limbic encephalitis, which is usually manifested as confusion, behavioral changes, epileptic seizures, and inability to form new memories[13]. Further details on limbic encephalitis will not be provided in this review because this condition predominantly affects patients older than 45 years.

Some autoantibodies are associated with distinctive clinical pictures. Examples other than anti-NMDA receptor antibodies are as follows[3,7-9,21]:

- anti-gamma-aminobutyric acid A receptor → status epilepticus
- anti-D2R → basal ganglia encephalitis or Tourette syndrome
- anti-GAD65 → stiff-person syndrome
- anti-glycine receptor → progressive encephalitis with rigidity and myoclonus
- anti-Caspr2 → neuromyotonia
- myelin oligodendrocyte glycoprotein (MOG) → ADEM
- anti-metabotropic glutamate receptor 1 → cerebellar ataxia
- anti-metabotropic glutamate receptor 5 → Ophelia syndrome

**Table 1.** Autoantibodies and clinical picture of autoimmune encephalitis

| Autoantibody | Median age (range) | Sex ratio (M:F) | Clinical presentation | Clinical syndrome | Notes |
|---|---|---|---|---|---|
| NMDA receptor | 21 years (2 months–85 years) | 1:4 | Dyskinesia, epileptic seizures, behavioral changes, psychosis, dysautonomia | Anti-NMDA receptor encephalitis | Prolonged evolution<br>Responds to immunotherapy in 60% of cases |
| AQP4 | — | — | Similar to ADEM in younger children | Optic neuromyelitis | Recurrent evolution |
| MOG | — | — | — | Encephalitis<br>Optic neuritis<br>Myelitis<br>ADEM | Detected in 50% of children with ADEM |
| VGKC | — | — | — | Limbic encephalitis<br>Morvan syndrome | Rare in children<br>A positive radioimmunoassay titer should be interpreted with caution |
| LGI1 | 64 years<br>(31–84 years) | 2:1 | Amnesia, faciobrachial dystonic seizures, hyponatremia | Limbic encephalitis | — |
| Caspr2 | 66 years | (25–77 years) | 9:1 | Amnesia, insomnia, dysautonomia, ataxia, neuropathic pain | Limbic encephalitis |
| Morvan syndrome | Not reported in children | | | | |
| Contactin-2 | — | — | — | Limbic encephalitis<br>Morvan syndrome | Not reported in adults |
| D2R | 6 years<br>(2–15 years) | 1:1 | Parkinsonism, dystonia, psychiatric symptoms | Basal ganglia encephalitis<br>Tourette syndrome | Not reported in adults |
| GlyR | — | — | — | PERM<br>SPS | Rare occurrence |
| GABAb receptor | 61 years<br>(16–77 years) | 1.5:1 | Epileptic seizures, amnesia, confusion | Limbic encephalitis | Severe epileptic seizures |
| GABAa receptor | 40 years<br>(2 months–88 years) | 1:1 | Epileptic seizures, confusion, behavioral changes | Encephalitis<br>Status epilepticus | Presence of anti-TPO and anti-GAD65 antibodies is possible |
| DPPX | 52 years<br>(13–76 years) | 2.3:1 | Confusion, diarrhea, weight loss | Encephalitis | Associated with diarrhea |
| mGluR1 | — | — | Cerebellar ataxia, Hodgkin's lymphoma | Limbic encephalitis | Not reported in children |
| mGluR5 | 29 years<br>(6–75 years) | 1.5:1 | Hodgkin's lymphoma | Limbic encephalitis | — |
| AMPA receptor | 56 years<br>(23–81 years) | 1:2.3 | Confusion, amnesia, psychiatric symptoms | Limbic encephalitis | Not reported in children<br>Frequent recurrence |
| GAD65 | — | — | — | SPS | Very rare in children |

Legend: —, data unavailable; AQP4, aquaporin 4; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; Caspr2, contactin-associated protein 2; D2R, dopamine D2 receptor; DPPX, dipeptidyl peptidase-like protein 6; GABA, gamma-aminobutyric acid; GAD65, glutamic acid decarboxylase; GlyR, glycine receptor; LGI1, leucine-rich glioma-inactivated protein 1; MOG, myelin oligodendrocyte glycoprotein; PERM, progressive encephalomyelitis with rigidity and myoclonus; SPS, stiff-person syndrome; TPO, thyroperoxidase. Source: Lim et al.[7]; Dale et al.[8]; Dalmau and Graus[13].

Encephalopathy secondary to autoimmune thyroiditis, i.e., Hashimoto encephalopathy, is linked to the production of antibodies against thyroperoxidase and manifests in children and adolescents in an acute or subacute form as epileptic seizures, psychosis, chorea, tics, coma, migraine-like headache, or acute focal neurologic dysfunction. Disease evolution can be progressive or relapsing/remitting, and the mean age of onset in children is 12–14 years[22].

It should be noted that in 5% of patients, the clinical picture remains monosymptomatic—for example, with psychiatric manifestations only[13].

Although in some patients, AIEs have a monophasic course, in many patients, recovery takes a long time or the disease recurs frequently[7].

## CLINICAL INVESTIGATION

The clinical investigation of suspected AIE should include brain magnetic resonance imaging (MRI); lumbar puncture with cell count, biochemical tests, culture, Gram staining, and oligoclonal bands; electroencephalogram; polymerase chain reaction for the most prevalent viral agents, including herpes simplex virus, enterovirus, and varicella-zoster virus, and in immunocompromized patients, cytomegalovirus, human herpesvirus 6, and Epstein–Barr virus; arbovirus serology; HIV testing; and quantification of autoantibody titers in the CSF and serum[18].

The presence of signal abnormalities in the medial temporal lobes in T2-weighted and FLAIR MRI, without significant contrast uptake, is suggestive of AIE. However, it should be noted that epileptic seizures and viral infection may produce similar findings[12]. The rate of abnormal brain MRI results varies widely in different studies, from 11% to 83%; therefore, the diagnosis of AIE should not be excluded on the basis of a normal MRI scan[23]. Other studies have reported that abnormal brain MRI occurred in 30% of the cases, with a hyperintense signal in the cortical, subcortical, or cerebellar regions[13]. A few studies evaluated the use of positron emission tomography and observed frontal and temporal hypermetabolism and parietal and occipital hypometabolism in cases of AIE, even when the brain MRI was normal[23].

The search for an underlying tumor depends on the patient's age and sex and the type of autoantibody[12]. For instance, in anti-LGI1 encephalitis, which is associated with hyponatremia in 65% of cases, underlying tumors are rare; however, 50%–60% of cases of anti-GABAb receptor encephalitis are caused by cancer[13]. Forty percent of patients with anti-NMDA receptor encephalitis have tumors, and this rate is increased to 58% in women aged 18–45 years[6]. The youngest patient with anti-NMDA receptor encephalitis associated with an underlying tumor was 7 years old at presentation[24]. Tumor screening should ideally include MRI scans of the chest, abdomen, and pelvis[15].

Electroencephalogram (EEG) usually does not show AIE-specific changes. Nonetheless, the prominent presence of delta brushes suggests anti-NMDA receptor encephalitis. Other findings may help with the differential diagnosis, and sometimes, the EEG tracing reveals subclinical epileptic seizures or non-motor status epilepticus[20].

The detection of autoantibodies in the appropriate clinical context confirms the diagnosis. In patients suspected of having anti-NMDA receptor encephalitis, antibody titers in the CSF are more sensitive and specific; however, serum titers are more sensitive in cases wherein there is suspicion of a disease associated with anti-MOG antibodies. Therefore, the current recommendation is quantifying antibody titers in the CSF and serum whenever possible[8]. In anti-NMDA receptor encephalitis, the conversion to a positive antibody titer occurs first in the CSF and then in the serum[6].

Another relevant issue is the laboratory technique used for identifying autoantibodies. Many laboratories use immunohistochemistry for screening because it can detect antibodies against several antigens; however, it cannot identify specific antibody targets. Therefore, cell-based assays (CBAs) are recommended for detecting antibodies against neuronal surface antigens. Some studies recommend using both immunohistochemistry and CBAs with the CSF and serum during the investigation of a suspected case of AIE[21].

However, these serological tests are expensive, inaccessible (the equipment used is available only in a few laboratories), and time-consuming, with a typical waiting period of several weeks[21]. Some diagnostic criteria do not require the need to quantify antibody titers to establish the presumptive diagnosis (see below), which allows the prompt institution of appropriate treatment[20]. Nevertheless, confirmation of the diagnosis by serology is always desirable, given the severity of the clinical picture and the aggressiveness of treatment.

## DIAGNOSIS

The discovery that several potentially treatable forms of encephalitis originate from autoantibodies has modified the diagnostic investigation of patients with a clinical picture suggestive of encephalitis[12]. Early diagnosis and diligent treatment are the primary approaches to maximize the chances of full recovery[18].

The diagnostic criteria defined by Graus et al. (2016) employ three diagnostic categories: possible, probable, and definitive[20]. According to these authors, a definitive diagnosis can be established when four criteria are satisfied:

1. Subacute onset (less than 3 months previously) of operational memory deficits, epileptic seizures, or psychiatric symptoms suggestive of limbic system involvement.
2. Brain MRI shows bilateral abnormalities in T2--weighted images or FLAIR, restricted to the medial temporal lobes.
3. At least one of the following changes: CSF pleocytosis (leukocyte count, >5 cells per $mm^3$) or EEG showing epileptic activity or slow waves restricted to the medial temporal lobes.
4. Other possible causes have been reasonably excluded.

In cases wherein one of the first three criteria is not satisfied, definitive diagnosis is only established after detecting antibodies against onconeural, synaptic, or cell surface proteins[20].

The specific diagnostic criteria for anti-NMDA receptor encephalitis, the most common form of encephalitis in pediatrics, are described in Table 2.

**Table 2.** Diagnostic criteria for anti-NMDA receptor encephalitis

| Probable anti-NMDA receptor encephalitis |
|---|
| The diagnosis is established when the following three criteria are satisfied: |
| 1. Rapid onset (less than 3 months previously) of at least four of six major symptom groups: |
| • Abnormal behavior (psychiatric symptoms) or cognitive dysfunction |
| • Speech disorder (verbiage, verbal reduction, mutism) |
| • Epileptic seizures |
| • Movement disorder, dyskinesia, or stiffness/abnormal postures |
| • Reduced level of consciousness |
| • Autonomic dysfunction or central hypoventilation |
| 2. At least one of the following test results: |
| • Abnormal EEG (focal or diffuse slowing or disorganized activity, epileptic activity, or extreme delta brush) |
| • CSF with pleocytosis or oligoclonal bands |
| 3. Reasonable exclusion of other disorders |
| It is also possible to establish the diagnosis in the presence of three of the symptom groups mentioned in item 1 together with systemic teratoma. |
| **Definitive** anti-NMDA receptor encephalitis |
| The diagnosis is confirmed in the presence of one or more of the six major groups of symptoms + positive IgG antibody titers against the GluN1 subunit of the NMDA receptor in the CSF or serum after reasonable exclusion of other disorders. |

Source: Graus et al.[20]

## DIFFERENTIAL DIAGNOSIS

The most important differential diagnosis is that between AIE and acute viral encephalitis, although their clinical picture may be indistinguishable[12]. ADEM, other inflammatory parainfectious or postinfectious forms of encephalitis, exogenous intoxication (particularly in children younger than 5 years), and neuroleptic malignant syndrome should also be considered[24]. Moreover, other infections can mimic viral encephalitis, including those due to *Legionella* sp., *Bartonella henselae* (the cause of cat-scratch disease), *Mycoplasma pneumoniae*, and certain fungi and parasites[16].

The degree of CSF pleocytosis is usually higher in viral encephalitides than in AIEs. One study found that the median white blood cell count was 90/mm$^3$ in enteroviral encephalitis, 56/mm$^3$ in herpetic encephalitis, and 22/mm$^3$ in anti-NMDA receptor encephalitis[10].

It is known that a large proportion of the patients suspected of having AIE remain seronegative. In addition, many presumptively diagnosed children present normal results in brain MRI and lumbar puncture and therefore fail to meet the diagnostic criteria described above. The so-called seronegative autoimmune encephalitis affects previously healthy children and children with Down syndrome or autism spectrum disorder[8].

## TREATMENT

Patients respond to interventions that decrease autoantibody titers either by stopping or suppressing autoantibody production with intravenous immunoglobulin (IVIg) and plasmapheresis or by attenuating the autoimmune production of pathogenic antibodies using steroids and other immunosuppressive agents. These interventions highlight the relevance of antibodies in disease pathogenesis[7,21].

It should be emphasized that there are no controlled clinical trials to support the current therapeutic strategy for AIE, but there is only limited evidence from the analysis of large retrospective case series[7].

The early excision of tumors, if present, is essential to achieve favorable outcomes[13].

After defining the presumptive diagnosis of AIE, immunological treatment is divided into three stages[7], including the following:

- Methylprednisolone, 30 mg/kg/day IV (maximum dose of 1 g/day) for 3–5 days, followed by oral steroids;
- IVIg, total dose of 2 g/kg at each course distributed over 2–5 days;
- Optionally, plasmapheresis, ideally before the administration of IVIg.

A clinical response is expected 1–2 weeks after initiation of treatment. The maintenance phase of the treatment is initiated if the response is favorable, with monthly IVIg courses for 3–12 months[8], long-term oral doses of steroids, and, if necessary, a steroid-sparing agent such as azathioprine or mycophenolate mofetil[7].

For subjects who remain severely symptomatic, in addition to the continuation of the first-line treatment, second-line treatment comprises the following:

- Rituximab, 375 mg/m$^2$ of body surface area, IV once weekly for 4 weeks or
- Cyclophosphamide, 1 g/kg IV once weekly for 6 months.

Rituximab is a monoclonal antibody against CD20, which is a glycoprotein found primarily on the surface of B cells. This broad-spectrum immunosuppressant acts by depleting naive and memory B cells. Circulating levels of B cells remain undetectable for 6–8 months after a course of treatment[21].

Cyclophosphamide is an alkylating agent that inhibits the proliferation of B and T cells, has potentially severe side effects, and should be used only in cases refractory to rituximab[21].

Of note, 20%–50% of patients with AIE have a poor response to second-line immunotherapy. In this context, other therapeutic strategies include restarting first-line therapies, intensifying second-line therapies (for example, with monthly doses of rituximab)[25], or using azathioprine or mycophenolate mofetil[21].

Third-line treatment incorporates new drugs such as tocilizumab, a monoclonal antibody directed against the interleukin 6 receptor, which has shown efficacy for rheumatoid arthritis and juvenile idiopathic arthritis[25]. Tocilizumab can have significant side effects, such as infection, neutropenia, and thrombocytopenia; therefore; its administration requires close monitoring[21]. Another drug that should be considered is bortezomib, a proteasome inhibitor that depletes plasmocytes[21]. However, experience with such drugs in pediatrics is limited.

Patients with AIE usually require intensive care unit admission and the assistance of a multidisciplinary care team. Complications such as thromboembolism, infections, and pressure ulcers should be prevented. In addition, the symptomatic treatment of epileptic seizures, dysautonomia, and dyskinesia helps to accelerate recovery[11].

## PROGNOSIS

The recovery rate, degree of residual neurological deficit, and relapse rate depend on the type of AIE[13]. Anti-NMDA receptor encephalitis is a severe disease with a mortality rate of 5%. Nevertheless, disease evolution is favorable in 81% of the cases[8].

The clinical course of anti-NMDA receptor encephalitis may be prolonged, probably because of the local production of antibodies by plasmocytes that remain in the brain for extended periods and because of the effects of antibodies on neuronal circuits[13].

## CONCLUSION

The discovery of AIE has changed the diagnostic and therapeutic management of many neurological and psychiatric syndromes[13], and the rapid advancement in scientific knowledge in the last 15 years has created new perspectives for effectively treating neuroimmune disorders.

Future research efforts should focus on identifying accessible AIE biomarkers and developing individualized therapeutic protocols for each autoantibody involved in AIEs.

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