

Diagnostic evaluation of autoimmune encephalitis

Weerathunga DN¹

Journal of the Ceylon College of Physicians, 2024, **55**, 68-77

Abstract

Autoimmune encephalitis (AIE) is a complex neurological condition characterized by brain inflammation caused by autoantibodies targeting neuronal surface antigens or synaptic receptors resulting in direct antibody-mediated neuronal dysfunction. The aetiology of AIE includes malignancies and viral infections. However, significant proportion of these patients have no identifiable trigger.

The clinical presentation of AIE is varied, ranging from memory deficits and psychiatric symptoms to seizures and movement disorders. The diagnosis is typically based on a combination of supportive clinical features and diagnostic tools such as EEG, MRI, and CSF findings. The detection of antibodies confirms diagnosis of specific autoimmune encephalitis syndromes.

Early recognition and prompt treatment of AIE are crucial, as delayed intervention can result in permanent neurological damage. The primary treatment approach is immunotherapy, along with screening for underlying malignancies. With the evolving knowledge on different antibodies and their associated syndromes, it is important for clinicians to have a high degree of suspicion and rule out other differentials to ensure timely and appropriate diagnosis. Furthermore, the use of appropriate diagnostic criteria can help minimize delays in starting treatment.

This review provides an overview of the current understanding of AIE, with a focus on pathophysiology, clinical presentation, diagnostics, and treatment modalities, specifically for the most

commonly encountered types of AIE associated with cell surface and synaptic antibodies.

Key words: Autoimmune encephalitis (AIE), Neuronal cell surface antibodies (NSAbs), NMDAR, LGI 1, Limbic encephalitis

Introduction

Encephalitis, also known as inflammation of the brain, was previously believed only to be caused by infections or paraneoplastic processes. However, since the identification of antibodies against cell surface antigens, specifically the NMDAR antibody in 2007, antibody-mediated encephalitis has emerged as a potentially treatable form of the condition. Since then the incidence of autoimmune encephalitis (AIE) has steadily increased, with a population-based study revealing it to be the most common cause of encephalitis among those under 30 years of age, surpassing viral encephalitis.¹ The incidence of AIE has risen from 0.4 cases per 100,000 person-years in 1995-2005 to 1.2 cases per 100,000 in the 2006-2015 period.² This can be attributed to the growing knowledge of the condition over the last two decades, leading to the discovery of various antibodies and the diagnosis of more cases.

Although AIE is more commonly seen in young females, it can occur in individuals of any age, including children. While potential triggers for the condition have been identified, such as malignancies and certain viral infections, some studies have also suggested genetic or HLA associations that may make individuals more susceptible. However, further evidence is needed to confirm these associations.³

¹Consultant Neurologist, District General Hospital, Chilaw, Sri Lanka.

Correspondence: e-mail: dulmini.dn@gmail.com

 <https://orcid.org/000-0002-8345-495>



This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

The terminology used around AIE might be confusing due to certain overlapping terminologies in the literature to describe these syndromes, including antibody mediated encephalitis, paraneoplastic encephalitis or immune encephalitis. However, it is important to note that these noninfectious immune mediated encephalitides can be broadly classified into three main groups based on their underlying pathophysiology.

1. Autoimmune encephalitis due to antibodies against cell surface or synaptic antigens. As these pathogenic antibodies cause reversible neuronal damage, they respond well to immune therapy if started early.
E.g.: Anti NMDAR, LGI 1, AMPA, GABA A, GABA B, CSPR 2, DPPX, mGluR5 receptor antibodies.
2. Paraneoplastic encephalitis due to antibodies against intracellular antigens. This type is typically associated with a malignancy and has a poor response to immune therapy.
E.g.: anti Hu, Ma, Ri, CRMP5
3. Other immune mediated syndromes with encephalitic presentation. This group of patients also demonstrate a response to immune therapy.
E.g.: Hashimoto's encephalitis, Myelin oligodendrocyte glycoprotein antibody disease (MOGAD), Acute disseminated encephalomyelitis (ADEM), Bickerstaff encephalitis.

This review will primarily focus on antibody-mediated encephalitis, specifically those with antibodies targeting cell surface and synaptic antigens.

Since the discovery of NMDAR antibodies, the understanding of this condition has greatly improved and numerous new antibodies have been identified. Among these, NMDAR antibody-mediated encephalitis is the most frequently reported form of autoimmune encephalitis. Limbic encephalitis, which involves LGI 1, AMPA, and GABA A antibodies, is also common, with LGI 1 being the most prevalent type. Other important cell surface antibodies associated with autoimmune encephalitis include GABA B, CSPR2, DPPX, mGluR, and glycine receptor. Additionally, anti IGLON5, a cell adhesion protein antibody, has been linked to abnormal Tau protein deposition. These antibodies trigger an immune response that directly affects neuronal function. However, early treatment can reverse this dysfunction.⁴

Anti-GAD65 is another important antibody which could cause stiff person syndrome, progressive

encephalomyelitis with rigidity and myoclonus (PERM) or limbic encephalitis. The pathophysiology of this antibody is uncertain as GAD is an intracellular synaptic protein which is hypothesised to transiently migrate to the surface and bind with extracellular antibodies. This process triggers pathological T cell mediated immunity. Unlike in classic paraneoplastic encephalitides with intracellular antibodies, this syndrome does not have a direct relationship to malignancies and shows partial response to immunotherapy.⁵ The antibody could be detected in 1% of the general population and 80% of patients with type 1 diabetes mellitus. However, titers of 100-1000 times higher than in diabetes favors central nervous system associated disorders.⁶

The clinical presentation of autoimmune encephalitis is diverse, with symptoms such as memory deficits, psychiatric symptoms, seizures and movement disorders. Unlike classic paraneoplastic encephalitis, in which a malignancy is usually present, AIE may or may not be associated with malignancies. The diagnosis of AIE relies on a combination of factors, including clinical presentation, electroencephalography, cerebrospinal fluid analysis, and imaging. The confirmation of specific antibodies is important in identifying specific autoimmune encephalitis syndromes.

The primary treatment for autoimmune encephalitis is immunotherapy, which may include corticosteroids, intravenous immunoglobulin, or plasma-pheresis. In some cases, second-line immunosuppressants may be necessary. It is important to screen for malignancies in the management of these conditions. The prognosis of AIE varies widely, with some individuals making a full recovery while others may experience lasting deficits or relapses. Long-term management often requires a multidisciplinary approach.

Clinical features

Clinical suspicion of AIE arises when a patient presents with acute or subacute onset of psychiatric symptoms, cognitive decline, sleep disorders, seizures, or movement disorders. These symptoms can occur individually or in combination. Common clinical features associated with specific autoantibodies are described below.

Anti NMDAR encephalitis is more commonly found in young females and is associated with ovarian teratomas in over 50% of patients.⁴ Other reported associations include breast, neuroendocrine, pancreatic, sex cord stromal, testicular germ-cell, and small-cell lung cancers. While some cases have been

linked to viral triggers such as HSV, others have no identifiable trigger. Patients with anti-NMDAR encephalitis typically experience a viral-like prodrome followed by neuropsychiatric symptoms such as delusions, visual and auditory hallucinations, mood instability, irritability, mutism, and catatonia. Almost all patients with this type of AIE develop psychiatric manifestations. In the first few weeks to months of the illness, patients may also experience seizures, movement abnormalities (particularly oro-facial dyskinesia), cognitive decline, executive function deficits, and memory impairment. In severe cases, central hypoventilation, dysautonomia, and coma may occur, potentially leading to death if left untreated. EEG can be abnormal in about 90% of patients with nonspecific slowing. A more characteristic occurrence of extreme delta brush in this background was observed in some patients. MRI changes can only be seen in about 30% of the patient population and show nonspecific FLAIR signal changes in cortical, subcortical, basal ganglia, cerebellar or brainstem.⁴

It is important to note that there is a common association between HSV and NMDAR encephalitis. HSV infection can trigger NMDAR encephalitis in approximately 20% of infected patients, and both types of encephalitis often share similar characteristics.⁴ Therefore, if a patient develops new onset or worsening neuropsychiatric symptoms following herpes simplex encephalitis (HSE), two differential diagnoses to consider are post-viral NMDAR encephalitis and HSE relapse. Differentiation can be achieved by analysing the cerebrospinal fluid (CSF), where positive NMDAR antibodies and negative HSV PCR are seen in the former, and vice versa in HSE relapse.

Anti LGI 1 limbic encephalitis is the most commonly encountered AIE in adults over 50 years and is the second most common type in all ages. It is more commonly found in males in their 60s.⁷ Patients with anti LGI 1 encephalitis typically present with seizures, particularly fascio-brachial-dystonic seizures, psychiatric manifestations, and memory impairment. Some patients may also experience sleep disorders. Approximately 65% of these patients may exhibit mild to moderate hyponatremia. While about half of the LGI 1 patients may have a normal MRI, the remaining half and the majority of other limbic encephalitis cases show increased FLAIR signal in the bilateral medial temporal lobes.

Other types of autoimmune limbic encephalitis include Anti AMPAR encephalitis, which has a

presentation similar to NMDAR encephalitis but with medial temporal changes in MRI.⁴ Approximately 50-60% of these cases are associated with malignancies such as lung, breast, or thymus cancer. Anti GABA B R encephalitis is another cause of limbic encephalitis. This type typically presents with seizures and behavioral abnormalities. The presentation can be severe with refractory seizures or status epilepticus. Over half of the patients may have associations with malignancies, especially small cell carcinoma of the lung.

Anti GABA A R encephalitis also has a seizure predominant presentation with refractory seizures or status epilepticus. However, the MRI features are different, with Anti GABA B R showing medial temporal changes and Anti GABA A R showing more diffuse fronto-temporal cortical and subcortical changes. Anti GABA A R can be associated with thymomas.⁴

Antibodies against CASPR 2 antigen can affect both the central and peripheral nervous systems. The most common presentation is "Morvan syndrome," which includes neuromyotonia, pain, hyperhidrosis, weight loss, severe insomnia, and hallucinations. This condition may be associated with thymomas. Limbic encephalitis is another presentation of CASPR 2 disease.

Anti DPPX encephalitis shows a clinical triad of cognitive dysfunction, CNS hyperexcitability (myoclonus, seizures, exaggerated reflexes) and diarrhea with weight loss. Anti mGluR 5 encephalitis presents with cognitive decline and psychiatric symptoms of limbic encephalitis and could be associated with Hodgkin's lymphoma. Anti GlyR encephalitis may show progressive encephalomyelitis with rigidity and myoclonus (PERM) with an exaggerated startle response.⁸ Anti D2R is a rare form with clinical presentation of basal ganglia encephalitis.

Anti IGLON 5 is an antibody against cell adhesion proteins. This rare form of encephalitis is typically seen around 60 years of age, equally in males and females. They classically present with REM and NREM sleep disorders, cognitive decline, and bulbar symptoms. This type is usually not associated with malignancies.

Anti GAD65 encephalitis typically present with stiff person syndrome, progressive encephalomyelitis with rigidity and myoclonus (PERM) or limbic encephalitis.

Table 1. Clinical phenotypes and investigation profile of AIE

<i>Antibody</i>	<i>Median age (years)</i>	<i>Clinical phenotype</i>	<i>Typical investigation findings (if any)</i>	<i>Associated malignancies</i>	<i>Confirmatory test</i>
Anti NMDAR	21 F > M	• Viral prodrome • Neuropsychiatry symptoms • seizures • movement (characteristically) oro-facial dyskinesia	EEG common finding – background slowing specific finding – extreme delta brush MRI often normal can have nonspecific signal abnormalities in FLAIR	ovarian teratomas (50%) other; breast, neuroendocrin, pancreatic, sex cord stromal, testicular germ-cell, and SCLC viral triggers – commonly HSV	CSF and/ or serum cell based assay (CBA) (CSF superior than serum)
Anti LGI 1	56 M > F	Limbic encephalitis • seizures, (characteristically fascio-brachial-dystonic seizures) • psychiatric manifestations, memory impairment • sleep disorders	mild to moderate hyponatremia (in about 65%) MRI (normal in 50%) increased FLAIR signal in the bilateral medial temporal lobes	5-10% thymoma	Both CSF and Serum (CBA) *can detect in either CSF or serum separately
Anti AMPAR	64 F > M	Limbic encephalitis • presentation similar to NMDAR encephalitis	increased FLAIR signal in the bilateral medial temporal lobes	65% lung, breast, or thymus	CSF or serum CBA
Anti GABA B R	61	Limbic encephalitis • typically presents with seizures (some with refractory or status epilepticus) • behavioral & cognitive symptoms	increased FLAIR signal in the bilateral medial temporal lobes	>50% small cell carcinoma of the lung (SCLC)	CSF or serum CBA
Anti GABA A R	40	• seizures – frequently with refractory or status epilepticus • encephalopathy	MRI diffuse fronto-temporal cortical and subcortical changes	minority (<5%) with thymomas	CSF or serum CBA
Anti CASPR 2	66 M > F	1. Limbic encephalitis 2. “Morvan syndrome” (neuromyotonia, pain, hyperhidrosis, weight loss, severe insomnia, and hallucinations)	MRI increased FLAIR signal in the bilateral medial temporal lobes in limbic encephalitis	20-50% with thymomas	CSF or serum CBA

(Continued)

<i>Antibody</i>	<i>Median age (years)</i>	<i>Clinical phenotype</i>	<i>Typical investigation findings (if any)</i>	<i>Associated malignancies</i>	<i>Confirmatory test</i>
Anti DDPX	52	- cognitive dysfunction, CNS hyperexcitability diarrhoea with weight loss	MRI nonspecific changes in 30%	<10% with lymphoma	CSF or serum CBA
Anti mGluR 5	29	- cognitive decline - psychiatric symptoms	MRI nonspecific T2/FLAIR changes in temporal, parieto-occipital, cerebellum or thalamus	70% with Hodgkin's lymphoma	CSF or serum CBA
Anti GlyR	49	- progressive encephalomyelitis with rigidity and myoclonus (PERM) exaggerated startle response	EMG — hyper excitability (continuous motor activity)	<5% thymoma, lung or Hodgkin's lymphoma	CSF or serum CBA
Anti IGLON 5	65 M = F	- REM and NREM sleep disorders - cognitive decline - bulbar symptoms	MRI usually normal	usually not associated with malignancies	CSF or serum CBA
Anti GAD	50	- stiff person syndrome - PERM - limbic encephalitis	MRI usually normal	25% thymoma, small cell lung	CSF or serum CBA or ELISA

Diagnosis

In the diagnostic evaluation of AIE, instances of both underdiagnosis and overdiagnosis are not uncommon. Therefore, it is important for healthcare professionals to have a comprehensive understanding of the diagnostic criteria and employ a rational stepwise approach to ensure accurate diagnosis.

A subacute onset of neuropsychiatric symptoms are suggestive of AIE. More specific symptoms, such as orofacial dyskinesia in anti-NMDAR or fascio-brachial-dystonic seizures in anti-LGI 1, can suggest a specific type of AIE. Systemic manifestations are rare in AIE, hence basic investigations are usually unremarkable. MRI findings may be abnormal in cases with limbic encephalitis where there may be a temporal lobe involvement. EEG results can also be abnormal,

but are mostly nonspecific. In some cases, the presence of an extreme delta brush on the EEG may indicate NMDAR encephalitis. CSF studies may show high levels of protein, oligoclonal bands, and lymphocytes (typically less than 100 cells), but these are nonspecific and should be interpreted alongside other diagnostic criteria. While serum testing for NMDAR antibodies may yield false-positive or false-negative results, CSF testing is more specific and has a higher diagnostic yield.

It is important to note that early treatment is crucial for AIE, even before confirmation through antibody testing. To facilitate this, a stepwise approach to diagnosis was proposed in 2016 by Graus F, et al.⁹ This approach allows for early treatment in cases that meet the criteria for probable AIE while awaiting

confirmation. For a definitive diagnosis, either definite antibody positivity or the fulfillment of specific diagnostic criteria for a particular type of AIE is necessary. It is essential to rule out other similar conditions during the diagnosis process, especially central nervous system infections.

If a patient presents with symptoms indicative of AIE, they should undergo CSF studies, EEG, and MRI

as first-line investigations. To minimize treatment delay while awaiting specific antibody testing, diagnostic criteria for possible AIE syndromes were introduced (Box 1).⁹ If these criteria are met, and other differential diagnoses have been reasonably excluded, first-line immune therapy can be initiated. Patients with characteristic features of a specific AIE syndrome, such as anti-NMDAR encephalitis, can be directly evaluated for probable anti NMDAR encephalitis (Box 2).⁹

Box 1. Diagnostic criteria for possible autoimmune encephalitis

Diagnosis can be made when all three of the following criteria have been met:

- 1) Subacute onset (rapid progression of <3 months) of working memory deficits (short term memory loss), altered mental status* or psychiatric symptoms
- 2) At least one of the following:
 - New focal CNS findings
 - Seizure not explained by a previously known seizure disorder
 - CSF pleocytosis (white blood cell count of more than five cells per mm³)
 - MRI features suggestive of encephalitis**
- 3) Reasonable exclusion of alternative causes

* Altered mental status defined as decreased or altered level of consciousness lethargy or personality change.

** brain MRI hyperintense signal on T2 FLAIR highly restricted to one or both medial temporal lobes (limbic encephalitis), or in multifocal areas involving gray matter, white matter or both compatible with demyelination or inflammation.

Box 2. Diagnostic criteria for anti NMDA receptor encephalitis

Probable anti NMDA receptor encephalitis*

Diagnosis can be made when all three of the following criteria have been made

- 1) Rapid onset (< 3 months) of at least 4/6 following major groups of symptoms:
 - Abnormal (psychiatric) behaviour or cognitive dysfunction
 - Speech dysfunction (pressured speech, verbal reduction, mutism)
 - Seizures
 - Movement disorder, dyskinesia or rigidity/abnormal postures
 - Decreased level of consciousness
 - Autonomic dysfunction or central hypoventilation
- 2) At least one of the following laboratory study results
 - Abnormal EEG (focal or diffuse slow or disorganized activity, epileptic activity, or extreme delta brush)
 - CSF with pleocytosis or oligoclonal bands
- 3) Reasonable exclusion of other disorders

Diagnosis can also be made in the presence of three of the above groups of symptoms accompanied by systemic teratoma.

Definite anti NMDA receptor encephalitis*

Diagnosis can be made in the presence of one or more of the six major groups of symptoms and IgG anti-GluN 1 antibodies,** after reasonable exclusion of other disorders

*Patients with a history of herpes simplex virus encephalitis in the previous weeks might have relapsing immune mediated neurological symptoms (post HSV encephalitis), **Antibody testing should include testing of CSF. If only serum is available, confirmatory tests should be included (eg. live neurons or tissue immunohistochemistry in addition to cell based assay).

The next step is to confirm the diagnosis based on specific diagnostic criteria, eg: criteria for definite anti NMDAR encephalitis (Box 2), for definite autoimmune limbic encephalitis (Box 3).⁹

Box 3: Diagnostic criteria for definite autoimmune limbic encephalitis

Diagnosis can be made when all four* of the following criteria have been met

- 1) Subacute onset (rapid progression of < 3 months) of working memory deficits, seizures, or psychiatric symptoms suggesting involvement of the limbic system
- 2) Bilateral brain abnormalities on T2/ FLAIR MRI highly restricted to the medial temporal lobes**
- 3) At least one of the following:
 - CSF pleocytosis (white blood cell count of more than five cells per mm³)
 - EEG with epileptic or slow wave activity involving the temporal lobes
- 4) Reasonable exclusion of alternative courses

* If one of the first three criteria is not met, a diagnosis of definite limbic and capabilities can be made only with the detection of antibodies against cell surface, synaptic, or onconeural proteins. ** F-FDG PET can be used to fulfill this criterion. Results from studies from the past five years suggest that F-FDG-PET imaging might be more sensitive than MRI to show an increase in FDG uptake in normal appearing medial temporal lobes.

In some cases, patients may meet the criteria for possible or probable AIE, but all antibody tests are negative, and they do not fit into any definite AIE category or alternative diagnosis. In these cases, criteria for seronegative AIE have been introduced (Box 4).⁹

In addition, separate diagnostic criteria have also been introduced for other immune-driven conditions with encephalitis presentation, such as ADEM, Bickerstaff's encephalitis, and Hashimoto's encephalitis.⁹

Antibodies can be tested in serum and CSF.

When detecting cell surface antibodies, cell-based assays are more sensitive than ELISA. In contrast, intracellular GAD antibodies can be effectively detected by either method. The gold standard to detect GluN-1 subunit of NMDAR antibodies is CSF, as it is more specific and sensitive than serum. LGI 1 antibodies could individually be present either in CSF, serum or both. Hence, testing in both serum and CSF is recommended for LGI 1. Generally, serum assays are adequate to detect the rest of the antibodies. Immunohistochemistry of biopsied tissues is another reliable method to confirm the presence of antibodies.

Box 4. Criteria for autoantibody-negative but probable autoimmune encephalitis

Diagnosis can be made when all four of the following criteria have been met:

- 1) Rapid progression (< 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 (e.g. typical limbic encephalitis, Bickerstaff brainstem encephalitis, ADEM)
- 3) Absence of well characterised autoantibodies in serum and CSF, and at least two of the following criteria:
 - MRI abnormalities suggestive of autoimmune and capabilities*
 - 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 courses

*Some inherited mitochondrial and metabolic disorders can present with symmetric or asymmetric MRI abnormalities and CSF inflammatory changes resembling and acquired autoimmune disorder.

Management

The primary treatment for AIE is immunotherapy (Figure 1), and it is crucial to start it as early as possible for better outcomes. The first-line immune therapies include corticosteroids (IV methylprednisolone 1g for 3-5 days), intravenous immunoglobulin (0.4g/kg/day for five days), or 5 cycles of plasmapheresis.¹⁰ Patients who respond well to first-line treatment can continue with steroids for several weeks to months, and taper off gradually over 3 to 6 months. However, there is a higher chance of recurrence during this steroid tapering phase.

Patients who do not respond adequately to first-line therapy or experience relapses should be considered for second-line immune therapy, such as rituximab (375 mg/m² for 4 weeks or two doses of 500mg - 1g, 2 weeks apart) or cyclophosphamide (750 mg/m² every 4 weeks for 3-6 months). In cases where patients poorly respond to rituximab, tocilizumab (a monoclonal antibody to IL-6) has been shown to be significantly beneficial in the acute phase.¹¹ Bortezomib, a protease inhibitor, has also shown some positive results in a few case reports but needs further evidence to use in AIE.

Following the acute phase, maintenance therapy should be started for patients who need long-term immune therapy. The overall relapse rate of AIE has been reported as 10-35%. However, the decision of when to start long term treatment should be made individually, balancing the risks and benefits. Clear criteria for starting long-term preventive medication have not been formed yet.¹²

The long term treatment options include IVIg (0.4 - 1g/kg every 2 to 4 weeks), rituximab (every 6 months), mycophenolate mofetil (MMF) (500 to 3,000 mg/day), azathioprine (1 to 3 mg/kg/day), or cyclophosphamide (1 to 2 mg/kg/day orally).¹⁰ The duration of long-term treatment varies depending on individual response, tolerability and relapse rate of the disease, ranging from 6 months to years, mostly used duration in the literature is 3 years.¹²

Additionally, supportive therapy, such as anti-seizure medications, anti-psychotics, mood stabilizers, and pain management, may be necessary to alleviate symptoms in some cases. It is essential to screen for malignancy at the time of diagnosis and regular screening every 6 months to one year for up to 4 years is practiced.

Treatment options for probable or definite AIE

Acute 1st line	• IV Methylprednisolone 1g daily for 3-5 days • IV immunoglobulin 0.4g/kg/day for 5 days • Plasma exchange 5 cycles
Acute 2nd line	• Rituximab - 375 mg/m² for 4 weeks or 2 X doses of 500 mg - 1g, 2 weeks apart • Cyclophosphamide 750 mg/m² for 3-6 months • Tocilizumab 8mg/kg once a month for 6 months (when there is poor response to one of the above two)
Maintenance	• IVIg (0.4 g/kg every 2 to 4 weeks) • Rituximab (every 6 months) • Mycophenolate Mofetil (MMF) (500 to 3,000 mg/day), Azathioprine (1 to 3 mg/kg/day) • Cyclophosphamide (1 to 2 mg/kg/day orally)

Figure 1. Acute and maintenance treatment options for probable or definite AIE in general

Concluding remarks

Prompt treatment of AIE is crucial for expediting recovery, avoiding permanent neurological harm, and minimizing the risk of recurrence. Awareness of the distinct characteristics of each AIE syndrome can aid early detection and prevent misdiagnosis to reduce delay in treatment.

It is essential to identify potential cases of AIE even prior to antibody confirmation to begin treatment as soon as possible. A systematic approach utilizing diagnostic criteria can facilitate timely management. It is also important to rule out other mimics of AIE, particularly CNS infections during the diagnostic process.

Key points

- A spectrum of AIE syndromes based on antibodies have been identified over the years of which anti-NMDA R encephalitis remains the most prevalent.
- Autoimmune encephalitis due to antibodies against cell surface or synaptic antigens respond well to immune therapy.
- The clinical suspicion of AIE should be considered when a patient presents with acute or subacute onset of psychiatric symptoms, cognitive decline, movement disorders, seizures, or sleep disorders.
- It is essential to identify potential cases of AIE even prior to antibody confirmation to begin treatment as soon as possible so as to reduce the chances of morbidity and mortality.

Author declaration

There are no conflict of interests.

List of abbreviations

NMDAR – N-Methyl D-aspartate receptor
 LGI 1 – leucine-rich, glioma-inactivated 1
 AMPA – α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
 GABA – γ -aminobutyric acid
 CSPR 2 – Contactin-associated protein-like 2
 DPPX – dipeptidyl-peptidase-like protein 6
 mGluR5 – Metabotropic glutamate R 5
 gly R – glycine receptor
 GAD65 – glutamic acid decarboxylase 65
 IGLON 5 – immunoglobulin-like cell adhesion molecule 5
 MOGAD – Myelin oligodendrocyte glycoprotein antibody disease
 ADEM – Acute disseminated encephalomyelitis
 CBA – cell based assay

References

- 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**(7): 899-904. DOI: 10.1093/cid/cir1038
- Dubey D, Pittock SJ, Kelly CR, et al. Autoimmune encephalitis epidemiology and a comparison to infectious encephalitis: autoimmune encephalitis. *Ann Neurol*. 2018; **83**(1): 166-77. DOI: 10.1002/ana.25131
- Kim TJ, Lee ST, Moon J, et al. Anti-LGI1 encephalitis is associated with unique HLA subtypes. *Ann Neurol*. 2017; **81**: 183-92. DOI: 10.1002/ana.24860
- Dalmau J, Graus F. Antibody-mediated encephalitis. *N Engl J Med*. 2018; **378**(9): 840-51. DOI: 10.1056/NEJMr1708712
- Amaia Muñoz-Lopetegui, et al. Neurologic syndromes related to anti-GAD65. Clinical and serologic response to treatment. *Neurology*. 2020; **7**(3). DOI: 10.1212/NXI.0000000000000696
- Meinck HM, Faber L, Morgenthaler N, et al. Antibodies against glutamic acid decarboxylase: prevalence in neurological diseases. *J Neurol Neurosurg Psychiatry*. 2001; **71**: 100-03. DOI: 10.1136/jnnp.71.1.100
- Wang D, Hao Q, He L, He L, Wang Q. LGI1 antibody encephalitis - detailed clinical, laboratory and radiological description of 13 cases in China. *Compr Psychiatry*. 2018; **81**: 18-21. DOI: 10.1016/j.comppsy.2017.11.002
- Hutchinson M, Waters P, McHugh J, et al. Progressive encephalomyelitis, rigidity, and myoclonus: a novel glycine receptor antibody. *Neurology*. 2008; **71**: 1291-2. DOI: 10.1212/01.wnl.0000327606.50322.f0
- Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol*. 2016; **15**(4): 391-404. DOI: 10.1016/S1474-4422(15)00401-9
- Justin R. Abbatemarco, MD, Chen Yan, Alexander Rae-Grant. Antibody-mediated autoimmune encephalitis: A practical approach. *Cleveland Clinic Journal of Medicine* 2021; **88** (8): 459-47. DOI: 10.3949/ccjm.88a.20122
- Lee WJ, Lee ST, Moon J, et al. Tocilizumab in autoimmune encephalitis refractory to rituximab: An Institutional Cohort Study. *Neurotherapeutics* 2016; **13**: 824-32. DOI: 10.1007/s13311-016-0442-6
- Abboud H, Probasco JC, Irani S. Autoimmune Encephalitis Alliance Clinicians Network, et al. Autoimmune encephalitis: proposed best practice recommendations for diagnosis and acute management. *J Neurol Neurosurg Psychiatry*. 2021; **92**: 757-68. DOI: 10.1136/jnnp-2020-325300