Review Article

Immunomediated Encephalitis: New Diagnoses on the Neurology–Psychiatry Interface

Encefalite imunomediada: novos diagnósticos na interface neurologia–psiquiatria

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Abstract

Immune-mediated encephalitis is a real diagnostic challenge. Initially, patients present with subacute behavioral alterations, evolving over months, being attributed to purely psychiatric mechanisms, as well as neurological symptoms that often go unnoticed by professionals who are not neurologists. The etiologies behind these diseases are represented by paraneoplastic syndromes (including occult tumors) as well as viral infections, in both cases constituting true immunological triggers with exposure of antigens that will lead to a cross-immunological response directed at healthy structures of the nervous system. In the current review, we present the different clinical scenarios which differ based on antibodies against membrane receptors described so far, emphasizing the relevance of an early diagnosis for a smaller impact on prognosis.

Keywords

- encephalitis
- autoimmune encephalitis
- antibody-mediated encephalitis
- limbic encephalitis

Resumo

As encefalites imunomediadas constituem-se em um verdadeiro desafio diagnóstico. Inicialmente, os pacientes apresentam alterações comportamentais de caráter subagudo, com meses de evolução, sendo atribuídos a mecanismos puramente psiquiátricos, bem como sintomas neurológicos que passam muitas vezes despercebidos por profissionais não neurologistas. As etiologias por trás destas doenças são representadas por síndromes paraneoplásicas (incluindo tumores ocultos) bem como por infecções virais, em ambos os casos constituindo verdadeiros gatilhos imunológicos com exposição de antígenos que desencadeará uma resposta imunológica cruzada direcionada a estruturas saudáveis do sistema nervoso. Nesta revisão, apresentamos os diversos cenários clínicos diferenciados pelos anticorpos contra receptores de membrana descritos até o momento, enfatizando a relevância de um diagnóstico precoce para um menor impacto nos prognósticos.

Palavras-chave

- encefalite
- encefalites autoimune
- encefalite mediada por anticorpos
- encefalite límbica

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Introduction

Immune-mediated encephalitis constitutes a group of acute/subacute diseases that present antibodies directed against neuronal structures, clinically translating into psychiatric alterations, such as behavioral alterations. These antibodies can be directed against the neuronal plasma membrane, membrane receptors, ion channels, synaptic proteins, and intracellular structures, the latter of which are onconeural antibodies.[1,2]

Immune-mediated encephalitis is considered the most common form of noninfectious encephalitis, with anti-N-methyl-D-aspartate (anti-NMDA) antibodies being the most studied. Theoretically, any age can be affected, with some antibodies being more frequent in children and young adults.

The clinical expression of these diseases may include behavioral changes, psychosis, seizures, cognitive impairment, amnesia, movement disorders, dysautonomia, and lowered level of consciousness. Unlike other autoimmune diseases, there are many cases with no systemic manifestations other than dysautonomia, thus revealing the disease's behavior is more directed against structures of the nervous system. Among the triggers for this encephalitis, we must consider paraneoplastic conditions (cancers), as well as viral infections, which expose antigens that trigger activation of the immune system.[2,3]

Objective

The objective of the present study is to present the current knowledge about the pathophysiology of immune-mediated encephalitis, with emphasis on its main clinical presentations, mechanisms, and the need for diagnosis and prompt therapeutic implementation.

Methods

The Latin American and Caribbean Literature in Health Sciences (LILACS) and National Library of Medicine (PubMed) databases were searched during November and December 2020, using the following descriptors: *encephalitis*, *antibody encephalitis*, *autoimmune encephalitis*, *antibody-mediated encephalitis*, and *limbic encephalitis*.

Development

The estimated annual incidence of all types of encephalitis is of around 5 to 8 cases per 100 thousand inhabitants, half of which are individuals younger than 30 years of age.[4] Diagnoses of immune-mediated encephalitis emerged in the 1980s, referring to patients with neurological manifestations in the presence of cancer, thus constituting paraneoplastic syndromes.[5]

In immune-mediated encephalitis, antibodies are directed against extracellular protein epitopes, present on the cell surface; another possible mechanism of aggression are antibodies directed against intracellular protein antigens (also called onconeural), activating a Th1 cell response mechanism (involving $CD8^+$ T cells, complement system, and *natural killer cells*), typically coursing with neuronal dysfunction, synaptic impairment, and even neuronal death. The presence of the antibody can result in receptor blockade (anti-gamma-aminobutyric acid receptor B [anti-$GABA_B$]), receptor internalization (anti-NMDA) or interference in synaptic protein interaction.[6–8]

Two of the potential triggers for immune-mediated encephalitis are cancer and viral infections. Tumors that express nervous tissue or neuronal proteins promote epitope exposure to antigen-presenting cells, thus initiating an autoimmune response.[1] Encephalitis caused by herpes simplex is also a potential trigger for the anti-NMDA type, as it exposes neuronal surface protein epitopes. Typically, encephalitis with antibodies directed against neuronal membranes has a better prognosis with a greater response to immunosuppression.[9]

There are four different laboratory techniques used for the detection of antibodies against cell surface antigens: cell-based assay (CBA) with HEK293 cells; tissue-based assay (TBA) through indirect immunohistochemistry or indirect immunofluorescence; and culture of rat hippocampal neurons. Tests for the detection of antibodies should be performed both in cerebrospinal fluid (CSF) and in serum. There are some reasons for this indication:

1. In some syndromes, such as anti-NMDA, the antibodies can only be found in the CSF, while in others, such as anti-leucine-rich glioma-inactivated protein 1 (anti-LGI1), only in the serum;
2. Some patients may have the presence of different antibody spectra in the CSF and in the serum (anti-NMDA in the CSF and in the serum associated with anti-gamma-aminobutyric acid receptor A [anti-$GABA_A$] only in the serum), in this case, the antibody present in the CSF will define the clinical syndrome gift;
3. The CSF antibody titers will have better clinical correlation with the syndrome in question; and
4. Serum-only tests may result in more false positives.

Recently, anti-NMDA immunoglobulin M (IgM) and immunoglobulin A (IgA) antibodies were found in schizophrenic patients, patients with Creutzfeldt-Jakob, parkinsonian, and depressive patients, in addition to normal individuals. However, they were absent in the cerebrospinal fluid of these individuals. It is important to emphasize that negative results for antibody dosage do not exclude the diagnostic possibility, the use of corticosteroids may interfere with the test results.[10]

Clinical Syndromes

In recent decades, several antibodies have been identified, explaining, at least in part, some clinical presentations initially attributed to purely behavioral (psychiatric) conditions, thus revealing their hitherto unknown immune-mediated substrate (►**Fig. 1**).

The anti-NMDA was first described in 2007 in a group of 12 patients, 11 of whom had ovarian teratoma.[11] Found in

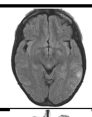
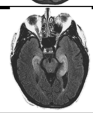
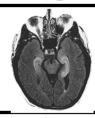
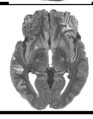
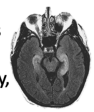
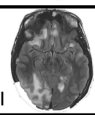
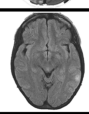
ANTIBODY	CLINICAL FEATURES / MRI		In Vitro MECHANISM	IMUNOGLOBULIN CLASS	NEOPLASM ASSOCIATION
Anti-NMDA	Seizures, choreoathetosis, psychiatric symptons; MRI: unspecific lesions		Receptor internalization; Excitatory synaptic dysfunction	IgG1	Ovarian Teratoma Testicular Teratoma Oat Cells
Anti-LGI1	Focal seizures with braquiofacial dystonia, hyponatremia e amnesia; MRI: temporal lobe hypersignal		Inhibition of LGI1 interaction with proteins ADAM22 and ADAM23; AMPA reduction	IgG4	Tymoma
Anti-$GABA_B$	Seizures, *Status Epilepticus*; Opsoclonus-Mioclonus; Amnesia, mental confusion; MRI: temporal lobe hypersignal		GABA receptor blockade	IgG1	Oat Cells
Anti-AMPA	Amnesia, mental confusion, psychiatric disorders; MRI: temporal lobe hypersignal		AMPA receptor internalization	IgG1	Oat Cells Tymoma Breast Cancer
Anti-$CASPR_2$	Amnesia, insonia, ataxia, disautonomic features, Morvan's syndrome, neurophatic pain, peripheral nerve hyperexcitability, MRI: temporal lobe hypersignal		Gefirina protein alterations (inhibitory synapses)	IgG4	Variable according clinical features Morvan's Syndrome: Tymoma
Anti-$GABA_A$	Seizures, *Status Epilepticus*, comportamental alterations; MRI: FLAIR cortical and subcortical (>2 areas) hypersignal		$GABA_A$ density reduction	IgG1	Tymoma
Anti-DPPX	Mental confusion, diarrhea, weight loss, hyperekplexia, *Stiff-Person Spectrum*; MRI: unspecific lesion		DPPX and Kv4.2 density reduction	IgG4	B Cell Neoplasm
Anti-$mGluR_5$	Ophelia's Syndrome MRI: normal / unspecific lesion		mGluR5 density reduction	IgG1	Hodgkin's Lymphoma

Fig. 1 Overview of some immune-mediated encephalitis, immune mechanism of injury, clinical and radiological presentation as well as possible correlations with neoplasms. Note: modified from Dalmau et al..[1]

patients with a mean age ranging from 12 to 45 years, this type of encephalitis is strongly related to the presence of ovarian teratoma ($\sim$ 94% of cases), extraovarian teratoma (2%), and other tumors. The herpes simplex virus type 1 also has a strong correlation with the disease, often revealing itself months or years after the presentation of herpetic encephalitis. In these cases, in younger individuals, it often appears as behavioral changes (insomnia, irritability, restlessness, and reduced verbal fluency) and movement disorders (dystonia, chorea, or choreoathetosis), while in older individuals it appears more commonly in the form of psychiatric symptoms (hallucinations, delusions, psychosis, agitation, and catatonia) and epileptic seizures.

Approximately 70% of patients may have nonspecific prodromal symptoms such as fever, headache, nausea, vomiting, diarrhea, and flu-like symptoms. In an earlier phase of encephalitis, the patient typically presents behavioral changes, psychosis, hallucinations, and memory deficit progressing to catatonia and mutism, accompanied by lowered level of consciousness and autonomic instability. Patients with anti-NMDA encephalitis are more sensitive to neuroleptics, so it is important to avoid the administration of these medications under the risk of neuroleptic malignant syndrome. Epileptic conditions may also be present, including the form of status epilepticus with electroencephalogram showing a characteristic extreme delta brush pattern, which can be found in up to 30% of cases.

Neuroimaging with magnetic resonance imaging (MRI) only reveals nonspecific alterations in approximately 35% of cases, in the form of hyperintense lesions affecting the gray and white matter of the cortical, subcortical, and cerebellar areas. The scans revealing changes in the basal ganglia and brainstem allow an important differential diagnosis: anti-D_2 encephalitis (parkinsonism, dystonia, and psychiatric symptoms), as shown in ►**Fig. 2A**. Hyperintensity of the claustrum can also be observed in the cases that course with refractory status epilepticus (new-onset refractory status epilepticus, NORSE), which may be associated with a recent history of fever (febrile infection-related epilepsy syndrome, FIRES) associated with anti-NMDA encephalitis, as shown in ►**Fig. 2B**. Some diagnostic criteria have been proposed for this type of encephalitis (►**Table 1**).[1]

Furthermore, anti-NMDA encephalitis may have an overlapping syndrome, such as multiple sclerosis, or neuromyelitis optica (NMO) represented by anti-aquaporin 4 antibody against myelin oligodendrocyte glycoprotein (anti-MOG), and antibody against the glial fibrillary acidic protein (anti-GFAP).[1,2]

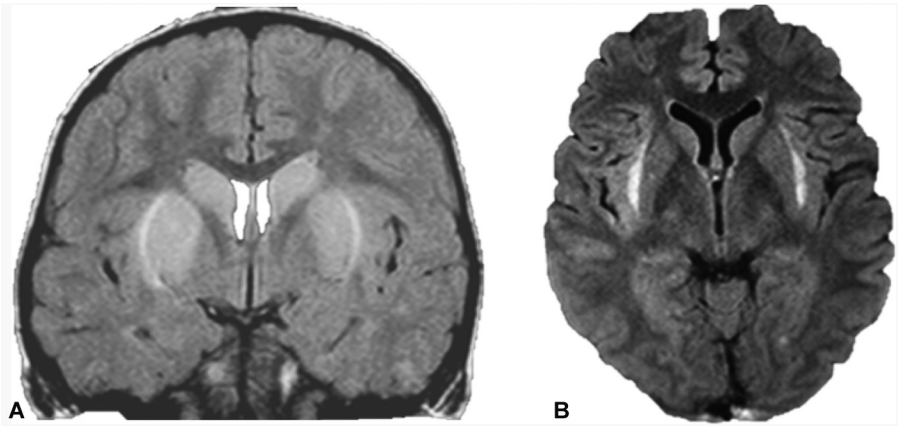


Fig. 2 (**A**) Neuroimaging of encephalitis mediated by anti-D_2 antibodies, with hypersignal in the subcortical structures of the basal ganglia (putamen, caudate, claustrum and globus pallidus) and brainstem, an important differential diagnosis of anti-N-methyl-D-aspartate (anti-NMDA) encephalitis. (**B**) Bilateral claustrum sign observed in new-onset refractory status epilepticus (NORSE).

Limbic Encephalitis and Related Antibodies

The criteria that define limbic encephalitis include the presence of four conditions: 1) subacute presentation (rapid progression in the last 3 months) of working memory deficit, seizures, or psychiatric symptoms (behavioral changes); 2) bilateral mesial temporal lobe abnormalities observed on T2-weighted MRI scans and fluid-attenuated inversion recovery (FLAIR) sequences; 3) Temporal lobe epileptic changes on electroencephalograms (EEGs) or CSF pleocytosis; 4) exclusion of more likely diagnoses.

Anti-LGI1 encephalitis: it was formerly called anti-voltage-gated potassium channel (anti-VGKC) antibody-associated encephalitis, but anti-LGI1 is now recognized as a synaptic protein that participates in the interaction between two other synaptic interaction complexes called ADAM22 and ADAM23, involving potassium channels and the α-amino 3-hydroxy 5-methyl 4-isoxazole propionate (AMPA) receptor. The functional impairment of this LGI-1 protein promotes symptoms attributed to limbic encephalitis, temporal lobe epilepsy, and hyponatremia. About 50% of patients have epilepsy with faciobrachial dystonia, which may, in some cases, also involve the lower limbs. They are rarely correlated with paraneoplastic conditions.[12,13]

Anti-$GABA_B$ encephalitis is characterized by cognitive symptoms associated with status epilepticus. There are descriptions of saccadic intrusions without an intersaccadic interval, such as opsoclonus-myoclonus and ataxia. There is an important association between the presence of these antibodies and oat-cell lung cancers (small cells).[14]

Anti-AMPA encephalitis: AMPA is a glutamatergic receptor, and the presence of its antibodies is related to the presence of seizures, amnesia and psychosis. The literatures describes cases of movement disorders as well as sleep disorders.[15] In approximately 64% of the cases, there is a correlation with the paraneoplastic syndrome in the presence of thymomas, breast and lung cancers, and ovarian teratoma.[15]

Anti-contactin-associated protein-like 2 ($CASPR_2$) encephalitis: like anti-LGI1 encephalitis, it was initially considered to

Table 1 Diagnostic criteria for immune-mediated encephalitis caused by anti-NMDA antibodies

Probable anti-NMDA encephalitis (ALL 3 criteria are required)
Period of symptoms < 3 months associated with at least 4/6 of the following:
a) Psychiatric symptoms with cognitive dysfunction
b) Language dysfunction (verbal reduction, mutism, pressure to speak)
c) Seizures
d) Movement disorder (dystonia, dyskinesia, rigidity)
e) Lowering of the level of consciousness
f) Autonomic dysfunction with central hypoventilation
At least ONE laboratory alteration:
a) EEG extreme delta brush OR focal or diffuse slowing or disorganized activity OR epileptic activity
b) CSF with pleocytosis or presence of oligoclonal bands
Exclusion other diseases
a) Ovarian teratoma corroborates the diagnosis
b) Anti-NMDA antibody against the N1 fraction confirms the disease

Abbreviations: CSF, cerebrospinal fluid; EEG, electroencephalogram; NMDA, N-methyl-D-aspartate.

belong to the group of anti-VGKC encephalitides. Currently, it is identified as a juxtaparanodal adhesion molecule that interacts with contactin 2 and the cytoskeleton, interfering with the synaptic interaction of myelinated axons. The presence of these anti-$CASPR_2$ antibodies is associated with peripheral nerve hyperexcitability, clinically represented by myokymia, fasciculations, and cramps.[16] Dysautonomia and insomnia (*Agrypnia excitata*) are also described, in addition to Morvan's syndrome. The presence of paraneoplastic syndrome should be considered, as it is associated with thymomas, lung cancer, and endometrial carcinoma.[17]

Anti-$GABA_A$ encephalitis: GABA is the main inhibitory neurotransmitter in the nervous system. The presence of antibodies directed against this receptor was described in 2014.[18] Clinically, there is a description of rapidly progressive encephalopathy with cognitive alterations, refractory seizures, and multifocal lesions on MRI. The CSF exam reveals lymphocytic pleocytosis with or without the presence of oligoclonal bands. Paraneoplastic association is not common, however, thymomas should be investigated. There may be overlapping of autoimmune diseases, such as thyroiditis and myasthenia gravis.[19]

Anti-dipeptidyl-peptidase-like protein 6 (anti-DPPX) encephalitis: DPPX is a subunit of potassium channels (Kv4.2) expressed in the hippocampus, cerebellum, striatum, and myenteric plexuses. Patients who develop antibodies directed to DPPX may present with neuropsychiatric symptoms, such as mental agitation, confusion, myoclonus, tremors, startles (*startle*), convulsions, diarrhea, and presentation patterns compatible with stiff-person syndrome. Other symptoms are described, including dysautonomia, thermodysregulation, diaphoresis, sleep disturbances, and urinary symptoms. Classically, the CSF will show hyperproteinorrachia associated with pleocytosis; however, a normal evaluation as well as MRI do not rule out the presence of anti-DPPX encephalitis.[20,21]

Anti-glycine and anti-glutamic acid decarboxylase (anti-GAD) encephalitis: glycine receptors are chloride channels responsible for inhibitory neurotransmissions through the hyperpolarization of nerve cells. The presence of antiglycine antibodies has been described in patients with progressive encephalomyelitis with rigidity and myoclonus (PERM), within the spectrum of stiff-person syndrome. Also associated with cerebellar ataxias are anti-GAD encephalitis and demyelinating diseases, such as multiple sclerosis and optic neuromyelitis spectrum disorders. Despite the little correlation with paraneoplastic syndromes, there are descriptions of thymomas, small cell lung cancer, and chronic lymphocytic leukemias.[22,23] Glutamic acid decarboxylase is an enzyme responsible for catalyzing the conversion of glutamic acid to GABA. Some autoimmune diseases, such as diabetes mellitus, have the presence of antibodies directed to GAD. The main neurological diseases associated with the presence of anti-GAD are stiff-person syndrome, cerebellar ataxias (slow progression associated with downbeat-type nystagmus and eye movement disorders), epilepsy (temporal lobe and status epilepticus), and limbic encephalitis. Anti-GAD is rarely associated with paraneoplastic syndromes, but its presence concomitantly with limbic encephalitis increases the risk of paraneoplastic syndrome by 10 times.[24]

Anti-IgLON5 encephalitis: the fifth member of the neuronal cell adhesion molecule family (IgLON) belongs to the immunoglobulin superfamily. The presence of antibodies directed to IgLON5 manifests itself clinically with changes in rapid eye movement (REM) and non-REM sleep, central hypoventilation, obstructive sleep apnea, stridor, chorea, gait instability, dementia, dysarthria, dysphagia, dysautonomia, and supranuclear gaze palsy resembling the classic tauopathies. Post-mortem studies reveal neuronal deposits of hyperphosphorylated Tau protein involving the brainstem tegmentum and hypothalamus.[25,26]

Anti-glutamate encephalitis: type-1 and type-5 metabotropic glutamate receptors (mGluR1 and mGluR5) are G protein-coupled and very similar, structurally. These receptors are involved with excitatory synapses in the nervous system. Patients with antibodies directed at mGluR1 receptors develop subacute cerebellar ataxia, dysgeusia, paranoia, diplopia, and cognitive deficits. Prostate adenocarcinomas as well as hematological cancer seem to have an important correlation with anti-mGluR1.[27] The presence of anti-mGluR5, on the other hand, appears in the form of encephalitis attributed to Ophelia's syndrome, consisting of amnesia, psychosis, and Hodgkin's lymphoma.[28]

Clinical Management and Perspectives

The current recommendation for the management of immune-mediated encephalitis is based on expert opinion and case series. Immunotherapy associated with removal of the immune trigger (diagnosis and treatment of cancers) is advocated. The early approach correlates directly with the prognosis. Most encephalitis occurs within the blood-brain barrier, which largely limits the success of plasmapheresis, as well as immunoglobulins. Even so, in practice, those are the two main options for treatment, along with corticosteroids. In the absence of response, we still have rituximab and cyclophosphamide as alternatives. Spontaneous recovery is very unlikely, and once the diagnostic hypothesis has been established, treatment should be initiated. There are some cases of recurrence, after immunosuppression is completed.[29]

It is also worth noting that, for those antibodies with a strong correlation with neoplasms, a complete screening is recommended (including tumor markers, mammography, testicular ultrasonography, imaging tests of the chest and abdomen, and scintigraphy). Patients must follow neoplastic screening protocols for at least 5 years.[30]

The discovery of antibodies that cause encephalitis has broken paradigms between neurology and psychiatry over the last 10 to 15 years. Patterns of behavioral changes that are poorly explained by isolated psychiatric illnesses or even refractory to their approaches could have an immune-mediated neurological substrate. In the near future, we should seek better diagnostic tools, including more sensitive and specific biomarkers, as well as functional neuroimaging techniques.

Conflict of Interests
The authors have no conflict of interests to declare.

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