Brazilian consensus recommendations on the diagnosis and treatment of autoimmune encephalitis in the adult and pediatric populations

Consenso brasileiro sobre o diagnóstico e o tratamento de encefalites autoimunes nas populações adulta e pediátrica

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Abstract

Background Autoimmune encephalitis (AIE) is a group of inflammatory diseases characterized by the presence of antibodies against neuronal and glial antigens, leading to subacute psychiatric symptoms, memory complaints, and movement disorders. The patients are predominantly young, and delays in treatment are associated with worse prognosis.

Objective With the support of the Brazilian Academy of Neurology (Academia Brasileira de Neurologia, ABN) and the Brazilian Society of Child Neurology (Sociedade Brasileira de Neurologia Infantil, SBNI), a consensus on the diagnosis and treatment of AIE in Brazil was developed using the Delphi method.

Methods A total of 25 panelists, including adult and child neurologists, participated in the study.

Results The panelists agreed that patients fulfilling criteria for possible AIE should be screened for antineuronal antibodies in the serum and cerebrospinal fluid (CSF) using the tissue-based assay (TBA) and cell-based assay (CBA) techniques. Children should also be screened for anti-myelin oligodendrocyte glucoprotein antibodies (anti-MOG). Treatment should be started within the first 4 weeks of symptoms. The first-line option is methylprednisolone plus intravenous immunoglobulin (IVIG) or plasmapheresis, the second-line includes rituximab and/or cyclophosphamide, while third-line treatment options are bortezomib and tocilizumab. Most seizures in AIE are symptomatic, and antiseizure medications may be weaned after the acute stage. In anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis, the panelists have agreed that oral immunosuppressant agents should not be used. Patients should be evaluated at the acute and postacute stages using functional and cognitive scales, such as the Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA), the Modified Rankin Scale (mRS), and the Clinical Assessment Scale in Autoimmune Encephalitis (CASE).

Conclusion The present study provides tangible evidence for the effective management of AIE patients within the Brazilian healthcare system.

Keywords

- Autoimmune Encephalitis
- Anti-N-Methyl-D-Aspartate Receptor Encephalitis
- Delphi Technique
- Rituximab
- Tocilizumab

Resumo

Antecedentes Encefalites autoimunes (EAIs) são um grupo de doenças inflamatórias caracterizadas pela presença de anticorpos contra antígenos neuronais e gliais, que ocasionam sintomas psiquiátricos subagudos, queixas de memória e distúrbios anormais do movimento. A maioria dos pacientes é jovem, e o atraso no tratamento está associado a pior prognóstico.

Objetivo Com o apoio da Academia Brasileira de Neurologia (ABN) e da Sociedade Brasileira de Neurologia Infantil (SBNI), desenvolvemos um consenso sobre o diagnóstico e o tratamento da EAIs no Brasil utilizando a metodologia Delphi.

Métodos Um total de 25 especialistas, incluindo neurologistas e neurologistas infantis, foram convidados a participar.

Resultados Os especialistas concordaram que os pacientes com critérios de possíveis EAIs devem ser submetidos ao rastreio de anticorpos antineuronais no soro e no líquido cefalorraquidiano (LCR) por meio das técnicas de ensaio baseado em tecidos (*tissue-based assay*, TBA, em inglês) e ensaio baseado em células (*cell-based assay*, CBA, em inglês). As crianças também devem ser submetidas ao rastreio de de anticorpo contra a glicoproteína da mielina de oligodendrócitos (*anti-myelin oligodendrocyte glycoprotein*, anti-MOG, em inglês). O tratamento deve ser iniciado dentro das primeiras 4 semanas dos sintomas, sendo as opções de primeira linha metilprednisolona combinada com imunoglobulina intravenosa (IGIV) ou plasmaférese. O tratamento de segunda linha

Palavras-chave
- Doenças Autoimunes do Sistema Nervoso
- Encefalite Antirreceptor de N-Metil-D-Aspartato
- Técnica Delphi
- Rituximab
- Tocilizumab

inclui rituximabe e ciclofosfamida. Bortezomib e tocilizumab são opções de tratamento de terceira linha. A maioria das crises epilépticas nas EAIs são sintomáticas, e os fármacos anticrise podem ser desmamadas após a fase aguda. Em relação à encefalite antirreceptor de N-metil-D-aspartato (*anti-N-methyl-D-aspartate receptor*, anti-NMDAR, em inglês), os especialistas concordaram que agentes imunossupressores orais não devem ser usados. Os pacientes devem ser avaliados na fase aguda e pós-aguda mediante escalas funcionais e cognitivas, como Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Modified Rankin Scale (mRS), e Clinical Assessment Scale in Autoimmune Encephalitis (CASE).

Conclusão Esta pesquisa oferece evidências tangíveis do manejo efetivo de pacientes com EAIs no sistema de saúde Brasileiro.

INTRODUCTION

Autoimmune encephalitis (AIE) comprises a group of inflammatory diseases characterized by the presence of antibodies (abs) against neuronal and glial antigens. The disease was first described in 2005,[1] but the first case series was published by Dalmau et al.[2] in 2008, who reported a group of female patients with a severe form of encephalitis associated with orofacial dyskinesia, psychosis, memory impairment, ovarian teratoma, and abs against the anti-N-methyl-D-aspartate receptor (anti-NMDAR). In the past 15 years, more than 12 other abs directed against cell-surface antigens have also been associated with AIE, most of them directed against neurotransmitter receptors, or proteins of the neuronal surface and glial antigens.[3] Additionally, epidemiological studies[4] conducted in developed countries have indicated that AIE predominantly affects children and young adults, with a prevalence rate of 7–13.5 cases per 100 thousand individuals. This rate is comparable to the estimated prevalence of neuromyelitis optica spectrum disorder in people of African descendant, of $\sim$ 10 cases per 100 thousand individuals,[5] suggesting that the prevalence rate of AIE might be similar to, or even higher than, that of other neuroimmunological diseases.

The most common clinical symptoms in this novel group of diseases are psychiatric and cognitive impairment, seizures, abnormal movements, and autonomic symptoms.[3] Further clinical characterization shows that specific symptoms are associated with AIE subtypes, producing a phenotype-antibody correlation, as described in previous reports.[3,6] Anti-NMDAR encephalitis is the most common AIE subtype, primarily affecting children and young women.[7] Anti-leucine-rich glioma-inactivated 1 (anti-LGI1) antibody-associated encephalitis is the second most common type, mostly affecting older male patients and characterized by memory and behavioral changes, hyponatremia, and seizures, especially faciobrachial dystonic seizures.[6,8,9] Other abs associated with AIE include anti-contactin-associated protein-like 2 (anti-CASPR2), anti-alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (anti-AMPAR,) anti-gamma-aminobutyric acid type-A receptor (anti-$GABA_AR$), anti-gamma-aminobutyric acid type-B receptor (anti-$GABA_BR$), anti-immunoglobulin-like cell-adhesion molecule 5 (anti-IgLON5), and anti-glutamic acid decarboxylase (anti-GAD).[3]

Adult patients with AIE are diagnosed using the clinical criteria described by Graus et al.[10] in 2016 (►**Table 1**). In view of the specificities of the developing brain and the variability of symptoms among children, the criteria were modified in 2020 for the pediatric population.[11] The detection of anti-neuronal abs against cell-surface antigens is performed using two complementary laboratory techniques, tissue-based assay (TBA) and cell-based assay (CBA) in paired samples of the cerebrospinal fluid (CSF) and serum.[6,12–17] Currently, most available commercial diagnostic kits use the CBA technique. However, data have shown that the use of CBAs alone may yield rates of 4 to 14% of false negative results, especially in the detection of anti-LGI1, anti-$GABA_BR$ and anti-AMPAR abs.[13] A growing body of literature[18–21] indicates that misdiagnosis in AIE occurs, often because the disease is not readily recognized by specialists or due to misinterpretation of results.

Autoimmune encephalitis represents a high economic burden for the health care system, as patients often need intensive care units (ICU) beds, advanced complementary investigation, specific testing, and treatment with intravenous immunoglobulin (IVIG), plasmapheresis (PLX) and rituximab (RTX).[22] At present, treatment recommendations are based on expert opinions and retrospective series, since few randomized clinical trials involving AIE patients have been conducted.[3,6–8,11,23–29]

The Delphi method is a validated technique for scientific discussions among a panel of experts, intending to generate knowledge on topics with limited scientific information, such as AIE.[30] This method has four key characteristics: anonymity, iteration, controlled feedback, and statistical response from the group, to promote an equitable forum for discussion and the exchange of opinions.[31] Thus, a selected group of experts contribute to the creation of a scientifically-recognized consensus on the proposed topic. The method has been previously used in the international consensus for pediatric AIE.[27]

Table 1 Diagnostic criteria for autoimmune encephalitis (AIE)

Diagnostic criteria for possible autoimmune encephalitis in adults (all three of following criteria met):
1. Subacute onset (rapid progression in fewer than than three months) of working memory deficits (short-term memory loss), altered mental status (decreased level of consciousness, lethargy or personality changes), or psychiatric symptoms 2. At least one of the following: New focal CNS findings Seizures not explained by a previously-known seizure disorder CSF pleocytosis MRI suggestive of encephalitis 3. Reasonable exclusion of alternative causes.
Diagnostic criteria for possible autoimmune encephalitis in the pediatric population (all three of following criteria met):
1. Onset of neurologic and/or psychiatric symptoms over $\leq$ 3 months in a previously-healthy child. 2. Two of the following: Altered mental status/level of consciousness, or EEG with slowing or epileptiform activity (focal or generalized) Focal neurologic deficits Cognitive difficulties Acute developmental regression Movement disorder (except tics) Psychiatric symptoms Seizures not explained by a previously-known seizure disorder or other condition 3. Reasonable exclusion of alternative causes, including other causes of CNS inflammation.

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; EEG, electroencephalogram; MRI, magnetic resonance imaging.
Note: Adapted from Graus et al.[10] (2016) and Cellucci et al.[11] (2020).

Two recent papers[32,33] have highlighted several barriers to the treatment and diagnosis of AIE in Brazil. The challenges faced by patients and the healthcare system encompass limited test availability, restricted access to treatment, and insufficient staff knowledge about the disease. A median delay of 6 months for AIE diagnosis has been reported in a Brazilian series.[33] In collaboration with the Brazilian Academy of Neurology (Academia Brasileira de Neurologia, ABN) and the Brazilian Society of Child Neurology (Sociedade Brasileira de Neurologia Infantil, SBNI), the objective of the present study was to formulate evidence-based guidelines for the diagnosis and treatment of AIE in Brazil, employing the Delphi method. Given the distinct pathophysiology of neurological immune-mediated diseases, the present study specifically focuses on seropositive AIE associated with cell-surface abs. It is important to note that the current study does not encompass immune-mediated conditions linked to high-risk abs that target intracellular antigens (such as anti-Hu, anti-Yo, and anti-Ma2) or synaptic antigens (such as anti-GAD and anti-amphiphysin). Consequently, the recommendations herein presented are not applicable to high-risk syndromes or other forms of immune-mediated encephalitis.

METHODS

Study design

A cross-sectional study was conducted in which invited experts participated in the development of a consensus on the diagnosis and treatment of AIE using the Delphi method.

A steering committee (ST) was established comprising 4 principal investigators, 7 members of the neuroimmunology scientific section of the ABN, and 1 member of the SBNI. The ST played a key role in overseeing the planning and implementation of the study but was not involved in the voting process.

The present study was overseen by an external consultant with expertise in the Delphi method, who ensured its methodological rigor. The process included meticulous participant selection, an exhaustive literature review, and implementation of two Delphi rounds, complemented by a pivotal online meeting (►**Figure 1**).

Participant selection

All members of the ABN and SBNI were invited to participate through the respective societies via the local mailing systems. Additional information was collected from the 87 individuals who expressed an interest in taking part, including details on:

- specialty and subspecialty;
- Brazilian region of medical residency;
- number of years dedicated to the specialty after residency; and
- number of seropositive patients treated in the last 2 years.

After receiving the initial data, the ST selected participants to provide representation for all Brazilian regions, using the following criteria:

- three or more years in the specialty after residency;
- experience in treating at least 5 patients with confirmed seropositive autoimmune encephalitis in the past 2 years; and
- availability to participate in the project.

Participants undergoing training (residency or fellowship) and those employed by the pharmaceutical industry or a diagnostics laboratory were excluded. Each institution included one expert for every five confirmed cases. In cases in which an institution had more than one expert, senior level professionals were selected.

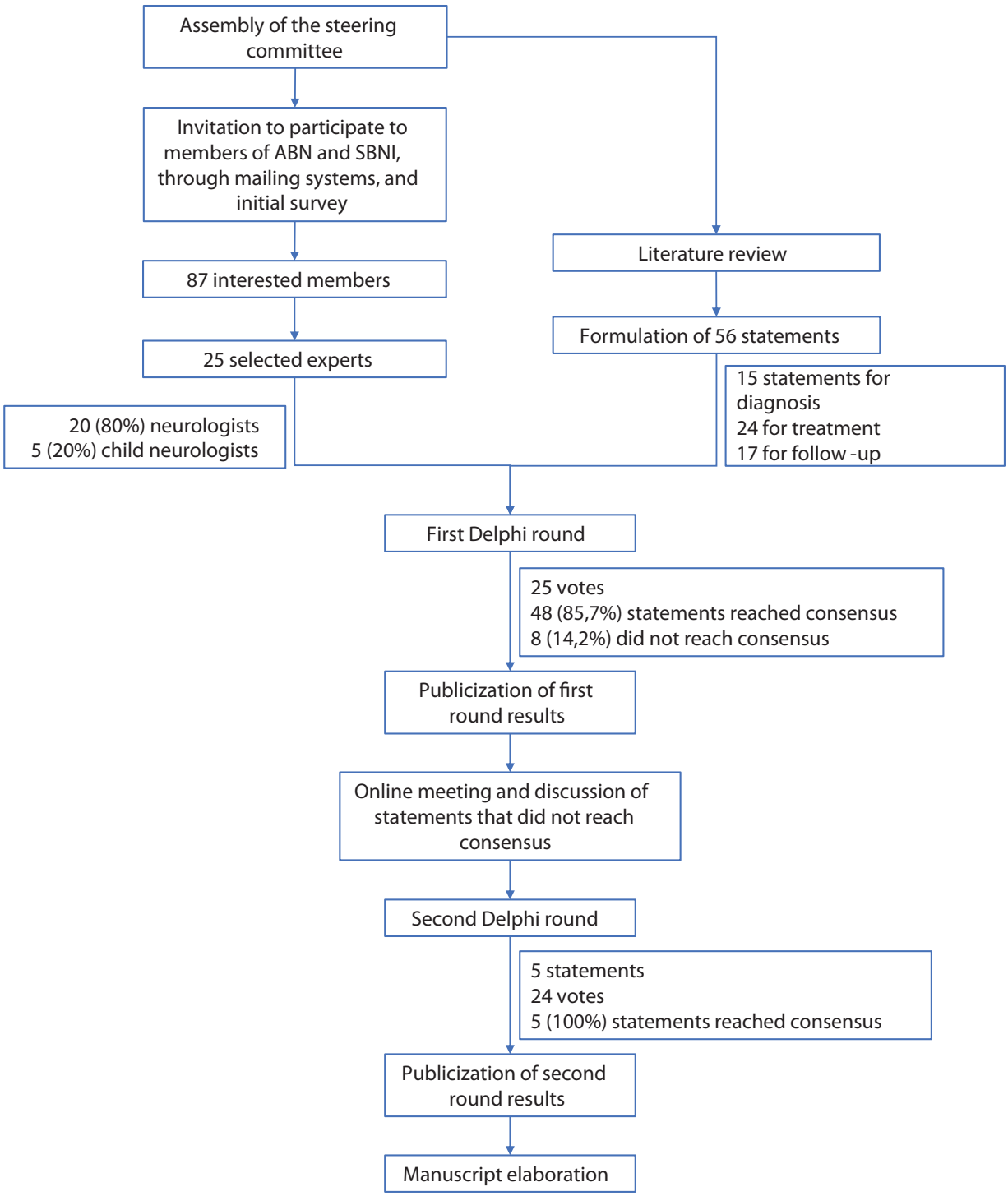


Figure 1 Brazilian consensus on AIE, study design.

A convenience sample of 25 experts comprised the expert panel, and they were invited to participate by email in the ensuing Delphi rounds. In total, 20 (80%) panelists were adult neurologists, and 5 (20%) were pediatric neurologists. All participants had experience working in both the public and private health systems. Regarding region, 12 participants (48%) were from Brazil's Southeastern region, 3 (12%), from the Northeastern region, 2 (8%), from the Midwestern region (8%), and 8 (32%), from the Southern region. All panelists provided informed consent, and the study was approved by the local Ethics Committee, under permit registration no. 63315922.1.0000.0071.

Literature review and Delphi rounds

The ST conducted a comprehensive systematic review focusing on the diagnosis and treatment of AIE. The team elected key themes derived from the literature for discussion during the Delphi rounds. The literature search was based on main

topics of the Medical Subject Headings (MeSH) controlled vocabulary thesaurus, including *autoimmune diseases* and *autoimmune diseases of the nervous system*. The inclusion criteria covered all available studies published in English or Portuguese between 2007 and 2023, excluding case reports. A total of 278 articles were initially identified on the PubMed/MEDLINE and EMBASE databases, 188 of which underwent a thorough review.

The first Delphi round consisted of an online questionnaire (see ►**Supplementary Materials**; https://www.arquivosdeneuropsiquiatria.org/wp-content/uploads/2024/05/ANP-2023.0302-Supplementary-Material-1-to-4.zip) containing 56 statements on the diagnosis, treatment, and follow-up of AIE patients. The questionnaire was delivered using the SurveyMonkey app (SurveyMonkey Inc., San Mateo, CA, United States). All statements had a 5-point Likert scale voting option, ranging from "strongly disagree" to "strongly agree."

In the initial Delphi survey, all 25 participants received the questions and provided their responses after an introductory kickstart meeting designed to explain the study methodology and objectives. The statements presented encompassed evidence-based recommendations and drew on the personal clinical experiences of the ST members. Consensus was defined when 75% or more of the votes fell within the Likert scale range of 4 or 5. The Answers were collected anonymously within a 14-day period and shared exclusively with the third-party consultant, ensuring the ST remained blinded to individual responses. The results of this survey were then summarized and distributed to all participants.

Twenty days after the online voting, the expert panel took part in an online meeting, at which the ST presented the results for each statement. Statements for which no consensus was reached were discussed by the panel. All participants had an equal opportunity to express their opinions, and the suggestions made by the panel were compiled. This online meeting lasted 2 hours and had a rate of 96% of attendance (24/25 experts), with 1 participant excluded from subsequent rounds for failing to participate in this meeting. Following additional refinements in wording, statements that initially failed to achieve consensus underwent a subsequent round of voting. The voting outcomes were then summarized and expressed as numbers and percentages.

RESULTS

The percentage agreement on statements related to the diagnosis of AIE are presented in ►**Table 2**. A summary of the percentage agreement for treatment is provided in ►**Table 3**, while details regarding the consensus on statements about the follow-up of AIE patients are shown in ►**Table 5**. Delphi voting results are available in the ►**Supplementary Material S1** to **S4** (online only; https://www.arquivosdeneuropsiquiatria.org/wp-content/uploads/2024/05/ANP-2023.0302-Supplementary-Material-1-to-4.zip). No consensus was reached for statements 14, 32, 50, and 52 during the first round of voting. These statements were adjusted after the online meeting, and consensus was reached on them after a second round of voting.

Diagnosis of AIE patients

Autoimmune encephalitis should be suspected in patients presenting with acute or subacute (< 3 months) psychiatric symptoms, memory complaints, seizures and/or movement disorders. Adult patients fulfilling the Graus criteria for possible AIE,[10] or the pediatric Cellucci criteria,[11] should be tested for antineuronal abs (►**Table 1**). All patients should be investigated using brain MRI, EEG, and CSF analysis, including the immunoglobulin G (IgG) index and oligoclonal bands (OCBs).

Antineuronal abs should be investigated in paired serum and CSF samples using TBAs and CBAs.[3,6,10,34] The panelists recommended adding anti-MOG testing for all pediatric patients with possible AIE, regardless of the MRI findings.[11] Moreover, the panelists recommended against testing for anti-voltage-gated potassium channel (anti-VGKC) abs.

Treatment of AIE patients

All patients fulfilling the criteria for possible or definite AIE should receive treatment within 4 weeks of symptom onset. Sample collection (of the CSF and serum) for abs testing should preferably be performed before immunotherapy, but its initiation should not be delayed while waiting for the results.

The first-line treatment should be methylprednisolone (MP) plus IVIG, or MP plus PLX. The choice of regimen should be based on local availability and the expertise of the attending physician. No consensus was reached on the clinical features indicating first-line treatment with MP plus PLX.

The experts agreed that satisfactory clinical response is defined as clinical and/or functional improvement within 10 to 14 days after starting the treatment. Treatment response should be monitored using clinical parameters such as reduced seizure frequency, partial improvement in cognitive and psychiatric symptoms, restored level of consciousness, or improvements in abnormal movements, ataxia, and in signs of brainstem dysfunction.[35] Patients failing to partially improve within 14 days should receive the second-line treatment, which includes RTX or/and cyclophosphamide (0.75 mg/m^2). The use of RTX (1,000 mg and repeat after 14 days) has been associated with better prognosis and lower relapse rate, and RTX can be prescribed alone or in association with cyclophosphamide in patients aged > 16 years.[36]

The panelists agreed that the third-line treatment options include tocilizumab and bortezomib. Other treatment options should be discussed with an AIE expert team. Oral immunosuppression with azathioprine or mycophenolate should not be routinely prescribed, especially for patients with anti-NMDAR encephalitis, according to data from a meta-analysis.[29] The panelists strongly agreed (92%) that, if required, RTX should be the choice for maintenance immunosuppression.

Antiseizure medications (ASMs) should be prescribed only if the patient presents with seizures. Neurologists should consider weaning of ASMs in the months after the acute stage of the disease if the patient is stable. Further treatment recommendations are presented in ►**Table 3** and ►**Figure 2**. Proposed doses and regimens are summarized in ►**Table 4**.

Table 2 Brazilian consensus on AIE – diagnosis statements

Statement		% Agree (n)
1. AIE should be suspected in patients with acute or subacute (< 3 months) onset of focal or diffuse neurological symptoms, psychiatric symptoms, epileptic seizures, movement disorders, or dysautonomia.		100% (25)
2. In adults, the definition of possible AIE follows the criteria proposed by Graus et al., 2016.[10]		100% (25)
3. In adults, the definition of probable seronegative AIE follows the criteria proposed by Graus et al.[10].		96% (25)
4. In children, the definition of possible AIE follows the criteria review proposed by Cellucci et al., 2020.[11]		100% (25)
5. The definition of definite AIE follows the criteria proposed by Graus et al.[10]		100% (25)
6. The definition of autoimmune limbic encephalitis follows the criteria proposed by Graus et al.[10]		96% (25)
7. All patients meeting the criteria for possible AIE should be tested for autoantibodies in paired serum and CSF samples.		84% (25)
8. In cases of suspected AIE, patients should be investigated with:	Brain MRI	100% (25)
	EEG	96% (25)
	OCBs (in the CSF)	88% (25)
	IgG Index (in the CSF)	84% (25)
	PCR for herpesvirus (in the CSF)	92% (25)
9. The following findings on brain MRI are suggestive of AIE: hyperintensities on T2 and FLAIR sequences restricted to the medial temporal lobe, either unilateral or bilateral; multifocal involvement of white and/or gray matter that is suggestive of demyelination or inflammation.		92% (25)
10. The search for antineuronal antibodies should be performed using the TBA and CBA methodologies.		96% (25)
11. For the detection of anti-MOG and anti-glycine antibodies, the CBA technique should be used.		96% (25)
12. Laboratory findings that should be interpreted with caution	Low titers of anti-GAD anti-GAD antibodies in the serum.	100% (24)
	Anti-TPO antibodies at any titer.	96% (25)
	Low titers of antibodies detected by other methodologies (such as radioimmunoassay).	96% (25)
	Exclusive presence of anti-NMDAR antibodies in the serum.	100% (25)
	Low titers of anti-CASPR-2 antibodies.	87% (23)
13. The detection of antibodies solely in the serum should be interpreted with caution. The determination of pathogenicity should consider the specific antibody detected, the clinical presentation, and discussion with experts in AIE.		100% (25)
14. Antibodies against the VGKC complex should not be requested.		65% (23)
14a. Antibodies against the VGKC complex should not be requested in the investigation of AIE		92% (24)
15. Anti-MOG testing should be requested in children with suspected autoimmune encephalitis, regardless of the findings on brain MRI.		84% (25)

Abbreviations: AIE, autoimmune encephalitis; anti-CASPR-2, contactin-associated protein-like 2; CBA, cell-based assay; CSF, cerebrospinal fluid; EEG, electroencephalogram; FLAIR, fluid-attenuated inversion recovery; GAD65, glutamic acid decarboxylase 65-kilodalton isoform; IgG, immunoglobulin G; MOG, myelin oligodendrocyte glycoprotein; MRI, magnetic resonance imaging; NMDAR, N-methyl-D-aspartate receptor; OCBs, oligoclonal bands; PCR, polymerase chain reaction; TBA, tissue-based assay; TPO, thyroid peroxidase; VGKC, voltage-gated potassium channel.

Follow-up of AIE patients

The experts agreed that patients should be screened for neoplasia at the time of clinical presentation. Screening options should be individualized according to the specific ab identified and its association with neoplasms. Screening in patients that exhibit abs commonly associated with neoplasm should be performed annually for 4 years. The initial screening should be performed though chest, abdominal and pelvic computed tomography (CT) scans with whole-body fluorodeoxyglucose-positron emission tomography (FDG-PET) ordered if initial CT scans prove inconclusive or negative. In addition, women should also be investigated using transvaginal ultrasonography and mammography to exclude ovarian and breast cancers respectively, while men should undergo scrotal ultrasonography to exclude testicular cancer.[6]

Table 3 Brazilian consensus on AIE – treatment statements

Statement	% agree (n)
1. Treatment should be initiated for patients with criteria for possible or definite AIE.	96% (25)
2. The collection of paired serum and CSF samples for diagnosis should be performed before initiating treatment.	96% (25)
3. Treatment should be considered for patients who meet the criteria for possible AIE following HSV (types 1 and 2) encephalitis.	92% (24)
4. The first-line treatment should preferably be the combination of MP and IVIG or MP and PLX.	100% (25)
5. MP can be administered concomitantly with PLX.	100% (25)
6. IVIG can be prescribed concomitantly with MP.	100% (25)
7. The choice between the combination of MP and PLX or IGIV should be made based on the availability and experience of the attending medical team.	96% (25)
8. In my practice, PLX would be considered the first therapeutic option in the following clinical manifestations: need for ICU admission; autonomic dysfunction; status epilepticus; and rapid progression to severe disease nadir.	 52% (25) 52% (25) 68% (25) 72% (25)
9. The second-line treatment should be initiated after 10 to 14 days of the start of the initial treatment if there is no satisfactory clinical response.	88% (25)
10. Satisfactory clinical response is defined as clinical and/or functional improvement within a period of 10 to 14 days after initiating treatment.	96% (25)
11. Treatment response should be monitored using parameters such as seizure control, cognitive symptoms, psychiatric symptoms, level of consciousness, movement disorders, gait and coordination, signs of brainstem dysfunction, and muscle weakness. Currently, there is no structured tool to quantify treatment response.	100% (25)
12. In my clinical practice, if maintenance treatment with immunosuppressive drugs is prescribed, it can be performed with: monthly IVIG infusions; oral corticosteroids; azathioprine; mycophenolate mofetil; and rituximab.	 72% (25) 60% (25) 68% (25) 63% (24) 92% (24)
13. The options for second-line treatment are rituximab alone or in combination with cyclophosphamide.	80% (25)
14. The use of rituximab in AIE is associated with improved functional outcomes and lower recurrence rates.	92% (25)
15. The use of cyclophosphamide is indicated for patients older than 16 years of age in cases of refractory AIE, contraindication to or unavailability of rituximab.	96% (25)
16. The options for third-line treatment include tocilizumab and bortezomib.	88% (24)
17. Patients with AIE should not receive long-term immunosuppression (> 6 months) with azathioprine, corticosteroids, methotrexate, or mycophenolate.	36% (25)
32a. As a routine practice, patients with AIE should not receive immunosuppression with azathioprine or mycophenolate, especially in cases of anti-NMDAR encephalitis.	100% (24)
18. AEDs should only be prescribed if the patient presents with epileptic seizures.	92% (25)
19. AEDs should be withdrawn after the treatment of the acute stage, considering the low risk of developing autoimmune epilepsy.	52% (25)
34a. In general, patients with AIE may present with symptomatic epileptic seizures, but most of them do not develop epilepsy in the long term.	100% (23)
20. The drugs of choice for hyperkinetic movements are: benzodiazepines; anticholinergics; valproate; and neuroleptics.	 92% (25) 32% (25) 68% (25) 56% (25)

Table 3 (*Continued*)

Statement	% agree (n)
21. The use of neuroleptics should be rationalized due to the potential risk of developing neuroleptic malignant syndrome.	100% (25)
22. Refractory cases of movement disorders that pose a risk to patient care can be managed with propofol, midazolam, or tetrabenazine. After the acute stage, medications should be tapered and discontinued.	88% (25)
23. For symptomatic treatment of Morvan syndrome (peripheral hyperexcitability) the following drugs can be used: carbamazepine; and phenytoin.	 96% (23) 75% (24)
24. The principles of the treatment for relapses should be similar to those used for the initial manifestation of AIE.	92% (25)

Abbreviations: AEDs, antiepileptic drugs; AIE, autoimmune encephalitis; CSF, cerebrospinal fluid; HSV, herpes simplex virus; ICU, Intensive Care Unit; IVIG, intravenous immunoglobulin; MP, methylprednisolone; NMDAR, N-methyl-D-aspartate receptor; PLX, plasmapheresis.

Table 4 Proposed treatment regiments for AIE

First-line options	Dose/mode of administration
IVIG	2 g/kg for 2–5 days.
IV methylprednisolone	Children: 20–30 mg/kg/day (maximum: 1 g/day) for 3–5 days. Adults: 1,000 mg for 3–5 days.
Plasmapheresis	5–7 sessions over 7–14 days.
Second-line options	**Dose/mode of administration**
IV rituximab	The following doses are acceptable: 500–1,000 mg (500 mg for $<$ 40 kg, 1,000 mg for $>$ 40 kg) given twice and separated by 2 weeks, or 750 mg/m^2 (maximum: 1 g), given twice and separated by 2 weeks, or 375 mg/m^2 (maximum: 1 g) weekly for 4 weeks.
IV cyclophosphamide	500–1,000 mg/m^2 (maximum: 1,500 mg) monthly pulses.
Third-line options	**Dose/mode of administration**
IV tocilizumab	Children: 12 mg/kg/dose for $<$ 30 kg, 8 mg/kg/dose for $>$ 30 kg (maximum: 800 mg). Adults: 8 mg/kg/dose (maximum: 800 mg), given monthly.
SC bortezomib	Three cycles of 21 days, each one composed of 1.3 mg/m^2 on days 1, 4, 8 and 11.

Abbreviations: AIE, autoimmune encephalitis; IV, intravenous; IVIG, intravenous immunoglobulin; SC, subcutaneous.

Regular assessment of cognitive outcomes is recommended, utilizing the Modified Rankin Scale (mRS), the Montreal Cognitive Assessment (MoCA), and the Mini-Mental State Examination (MMSE) tools, despite their inherent limitations. The Clinical Assessment Scale in Autoimmune Encephalitis (CASE) constitutes a robust tool to predict outcomes during the acute stage of the disease in both the adult and pediatric populations.[35] While not formally validated for use in the Brazilian population, the panelists suggest drawing on its items to monitor symptom improvement.

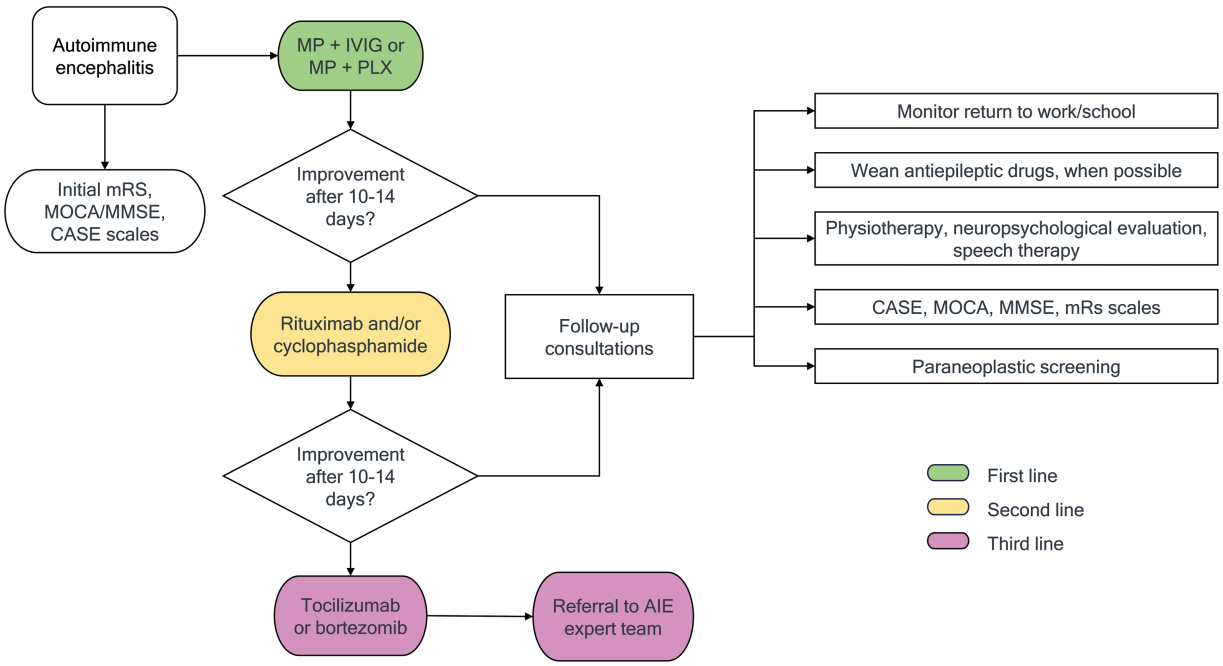
The experts do not recommend follow-up of ab titers as a routine practice, except in cases of anti-MOG encephalitis, in which monitoring can be useful, although there is no clearly-defined clinical relevance.[37] Other follow-up recommendations are presented in ►**Table 5**.

DISCUSSION

In the present study, using the Delphi method, detailed information on the diagnosis, treatment, and follow-up of AIE patients is reported, to establish a framework for the clinical management of these patients. The study findings are in line with those of previously reported results, showing that neurologists should use the clinical criteria available to select patients for antineuronal abs detection, and that the clinical picture is of vital importance when AIE is suspected.[38–40]

The panelists agreed that a preliminary investigation using brain MRI, electroencephalography (EEG) and CSF analysis with OCBs is important to exclude alternative diagnoses, which include Creutzfeldt-Jakob disease, systemic lupus erythematosus, Alzheimer disease, and other degenerative conditions.[10,21,33] Herpesvirus encephalitis should be ruled out with CSF polymerase chain reactions (PCRs). The use of the clinical criteria helps prevent misdiagnosis, as previously described,[18–21] while data show that the laboratory yield in patients not fulfilling clinical criteria is low.[18,33] Morever, AIE can be triggered by herpes viral infections,[6] such as herpesvirus 1, varicella-zoster, and Epstein-Barr, and patients with herpetic encephalitis that present with relapse should be screened for AIE.[41–43]

Although a few reported cases[39,40] indicate that some AIE types (anti-LGI1, anti-IgLON5, anti-dipeptidyl-peptidase-



Abbreviations: mRs, modified Rankin scale; MoCA, Montreal Cognitive Assessment; MMSE, Mini-Mental State Examination; CASE, Clinical Assessment in Autoimmune Encephalitis; MP, methylprednisolone; IVIG, intravenous immunoglobulin; PLX, phasmapheresis.
Figure 2 Proposed algorithm for AIE management.

Table 5 Brazilian consensus on AIE – follow-up statements

Statement	% agree (N)
1. Screening for neoplasia should be performed in all patients with AIE at the time of clinical presentation.	100% (25)
2. Paraneoplastic screening should be individualized according to the specific antibody identified and its association with neoplasms.	80% (25)
3. In cases of AIE with antibodies frequently associated with neoplasms, screening should be performed every 12 months for 4 years.	76% (25)
4. The initial screening for neoplasms should include contrast-enhanced CT scans of the chest, abdomen, and pelvis. If CT is contraindicated, consider using MRI as an alternative.	92% (25)
5. Children and adults with a typical clinical syndrome of anti-NMDAR antibody encephalitis should be specifically investigated for teratoma using ovarian/testicular ultrasound or abdominal and pelvic MRI.	100% (25)
6. Whole-body FDG-PET can be requested when the initial CT scan is negative or inconclusive.	84% (25)
7. The prognosis is associated with treatment within the first 4 weeks of symptom onset.	92% (25)
8. During follow-up consultations for patients with AIE, it is important to evaluate cognition, psychiatric/behavioral symptoms, frequency of epileptic seizures, presence of abnormal movements, gait and coordination abnormalities, muscle weakness, presence of dysautonomia, and symptoms suggestive of brainstem dysfunction (such as ophthalmoparesis and dysphagia).	100% (25)
9. The performance cognitive screening tests at least semi-annually for ongoing monitoring and assessment of cognitive function is recommended.	92% (25)
10. Cognitive monitoring can be performed using the MoCA scale in adults.	78% (23)
11. Cognitive monitoring can be performed using the MMSE scale in adults.	61% (23)
50a. Cognitive monitoring can be performed using the MMSE scale in adults, considering the limitations of this assessment in cognitive domains such as memory and executive function.	79% (23)
12. Serial measurement of antibody titers is not indicated as a prognostic factor or as an indicator for second-line treatment or maintenance therapy.	92% (25)
13. In cases of anti-MOG-associated encephalitis, antibody titers should be monitored.	52% (25)
52a. In cases of encephalitis associated with anti-MOG antibodies, monitoring of anti-MOG titers can be useful, although there is no clearly-defined clinical relevance.	95.8% (24)

Abbreviations: AIE, autoimmune encephalitis; CT, computed tomography; FDG-PET, fluorodeoxyglucose-positron emission tomography; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; MOG, myelin oligodendrocyte glycoprotein; MRI, magnetic resonance imaging; NMDAR, N-methyl-D-aspartate receptor.

like protein 6 [anti-DPPX], and anti-NMDAR) may sometimes have a progressive initial presentation and might not fulfill the criteria for AIE, the data available remain scarce, and the present consensus recommends discussing these specific cases with the AIE expert team.

In the present study, the experts recommended testing for antineuronal abs using the TBA and CBA techniques in the serum and CSF. This is paramount, and clinicians should be aware of the different techniques available when ordering laboratory tests.[13] The optimal balance between sensitivity and specificity can be achieved with cross-validation of the combined methods in the serum and CSF samples.[12,15,16,44,45] The TBA is an immunohistochemistry assay conducted in the rat brain, providing supplementary information on novel or noncommercially-tested abs. This includes abs not routinely assessed by commercial CBAs, such as anti-metabotropic glutamate receptor (anti-mGluR) 1 and 5, and anti-GABA-$_A$R. It is important to test both the serum and CSF, as the sensitivity of commercial kits may differ for these two sample types.[12,46]

The panelists emphasized that anti-VGKC abs should not be ordered.[38,47,48] While preliminary reports[49,50] have linked AIE to these abs, subsequent studies[51,52] have clarified that LGI1 and CASPR-2 are the specific epitopes associated with AIE, rather than the VGKC complex. Moreover, a study[53] evaluating 1,455 patients showed that anti-VGKC positivity in the absence of abs to LGI1 and CASPR-2 is not a clear marker for autoimmune inflammation and does not appear to contribute to the clinical practice.

An interesting outcome of the present study was the recommendation of anti-MOG testing for children with AIE, based on results from Brazilian, Spanish,[54] Danish, and Chinese[56] pediatric cohorts, which identified anti-MOG as the second most common ab associated with AIE among children.[11,54–57] Although the literature[37,58–60] shows that anti-MOG titers may predict recurrent myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), its clinical significance in MOGAD encephalitis is not fully understood.

In Brazil, the panelists suggested that the first-line treatment should be the combination MP plus IVIG or MP plus PLX. Given that the most common AIE subtype is anti-NMDAR, and that a meta-analysis[29] has shown better functional outcomes in patients initially treated with IVIG plus MP, with borderline results for IVIG plus PLX, combined with the fact that treatment within 4 weeks of the initial presentation is associated with better prognosis,[24,29,61,62] the panel agreed that combined initial therapy should be offered to all patients. This treatment regimen has been ratified by a recent Canadian consensus on AIE.[63] Debate remains over whether other AIE subtypes, especially anti-LGI1, respond to treatment with steroids alone. Nevertheless, in most anti-LGI1 reports,[8,64–66] more than 50% of the patients received additional immunotherapy (mostly IVIG) besides corticosteroids, while other studies suggest IVIG may also be beneficial for this AIE subtype.

The preferred option as the second-line treatment, RTX should be started early in the course of the disease. This approach is in line with growing evidence supporting RTX use in AIE. The GENERATE group[36] enrolled 358 patients with anti-NMDAR, anti-GAD65, anti-LGI1, and anti-CASPR2 for a mean follow-up of 41 months, and they showed that patients treated with RTX presented better clinical outcomes and lower relapse rates, especially in cases of anti-NMDAR. Other reports also support the use of RTX in adults and children.[6,7,24,27–29,62,63,67–81] The third-line options are bortezomib and tocilizumab, and they should be offered to refractory patients.[67,72,73,78–80,82–90]

Regarding maintenance therapy, the consensus among the panelists was that the existing evidence does not support the use of oral immunosuppressants, such as azathioprine (AZA) or mycophenolate mofetil (MMF), in the treatment of AIE. The total contingent of patients treated with oral immunosuppressants represents less than 10% of the reported cases, and the benefits remain unclear.[2,7,29,68,71,82,91,92] Furthermore, the available evidence supports the use of RTX, tocilizumab and bortezomib to treat refractory AIE (including real-world data and an ongoing randomized clinical trial),[36,85,86] particularly in cases of anti-NMDAR encephalitis.

Seizures are considered acute symptomatic events in AIE, resulting from cortical injury or dysfunction caused by the autoimmune process.[93–95] Therefore, the occurrence of seizures in AIE does not meet the diagnostic criteria for epilepsy, which specify a sustained predisposition to recurrent seizures.[96] Sodium channel blockers (phenytoin, carbamazepine, oxcarbazepine, lamotrigine, and lacosamide) are the first-line ASMs. However, caution is advised regarding the potential adverse effects of ASMs, which may resemble encephalitis symptoms, such as cognitive impairment (topiramate, phenobarbital, benzodiazepines), behavioral changes (levetiracetam, perampanel), and hyponatremia (carbamazepine, oxcarbazepine).[97]

When used for seizure management, ASMs should be continued for a defined period and then reassessed for further need. There is no routine recommendation for chronic use, even in cases evolving with residual brain lesions. Numerous studies have shown that most patients with AIE are seizure-free after one year.[65,93,98–104] Treatment following acute symptomatic seizures is typically recommended for 12 weeks, although the autoimmune process associated with encephalitis may remain active for an extended period.[105]

During follow-up, AIE patients should be evaluated though cognitive and functional assessments. Actively investigating symptoms such as fatigue, psychiatric and behavioral alterations, and assessing milestones such as returning to work or school and neurodevelopmental progress, is important.[106–108] Cognitive dysfunction is common after AIE, in which severity can range from mild and selective impairment to more generalized involvement of cognitive domains.[109] Episodic memory deficits are the most frequently reported, which is consistent with the limbic involvement in many AIE types.[107,110–112] Cognitive deficits may persist for several years and are a major cause of functional decline and difficulty in resuming previous activities.[107,113] Notably, disease severity and delayed immunotherapy have been reported as predictors of long-term cognitive outcomes, highlighting the importance of early diagnosis and adequate

treatment.[8,61,113] A cognitive-psychiatric syndrome that resembles schizophrenia spectrum disorders has been described in the postacute stage of anti-NMDAR,[108] and both sleep disorders and mood symptoms have been frequently reported.[111]

Patients should be screened using the MoCA, MMSE and mRS upon diagnosis and again at subsequent follow-up consultations. Nonetheless, clinicians must consider the inherent limitations of the aforementioned scores. The MMSE, for instance, provides limited information on memory and executive function, whereas the mRS can underestimate cognitive and functional outcomes.[114–117] The CASE scores demonstrate consistency in measuring the main AIE dysfunctions, serving as a useful instrument for the clinical practice, even for pediatric patients.[35,110,118–120]

The present study has certain limitations. The treatment of patients with probable seronegative AIE was not evaluated by the panelists. This was mainly due to the fact that the data available was controversial, as many studies have not classified patients according to the Graus criteria for probable seronegative AIE and did not perform the appropriate diagnostic workup with the TBA and CBA techniques.[21,38] At the moment, if a patient fulfills the criteria for probable seronegative AIE, treatment should follow the recommendations for AIE seropositive cases.[10]

In conclusion, the present study reports the results of the Delphi consensus on the diagnosis and management of AIE in Brazil, with the support of the ABN SBNI, as a guide for the general neurologist. Given the continental dimensions of Brazil and the shortage of trained specialists, further discussions on optimal strategies to deliver care to AIE patients within the Brazilian healthcare system should be explored. Considering that AIE is an acute condition with a chronic course, predominantly affecting young patients with viable treatment options, systematizing patient care through evidence-based practices is imperative.

Authors' Contributions

LAD, PVCS: conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, validation, writing of the original draft, and writing – review and editing. JHFF, ACM, FFT, CCFV, DGB, SLAP, TA, LJAR, LPBS, NACS, FVG: conceptualization, methodology, supervision, and writing – review and editing. ADP, BKDC, CCDD, CP, DADV, DSD, FFA, FRS, FTM, GJM, GDS, KL, LFP, MLSFS, MVMG, MBK, MEJH, OGPD, OJMN, PRN, PMP, RMPC, VD: writing – review and editing. All authors approved the final version of the manuscript and agree to be responsible for all aspects of the work.

Conflict of Interest

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