Autoimmune encephalitis (AIE)

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The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field in order to standardize producers to assist the reasoning and decision-making of doctors.
The information provided through this project must be assessed and criticized by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical status of each patient.

INTRODUCTION

Autoimmune encephalitis is an inflammatory disease characterized by a subacute involvement of short-term memory and very diverse symptomatology (psychotic symptoms, atypical clinical manifestations, and epileptic seizures), which makes the differential diagnosis a real challenge. Paraneoplastic neurological syndromes (PNS) are rare and associated with the antibodies of the collapsin response mediator protein (CV2/CRMP5), with a bad prognosis. However, with the recent discovery of antibodies directed at the membrane surface, today it is recognized that a large proportion of cases have no underlying neoplasia (*non-paraneoplastic)*, thus presenting better prognosis. Paraneoplastic limbic encephalitis (PLE) is a type of autoimmune encephalitis that involves the hippocampus, amygdala, frontal basal, and insular regions and is linked to tumors and antibodies against intracellular neuronal antigens, manifesting typically through seizures and mental and behavioral changes. Although in some cases it appears to involve exclusively the limbic regions, there are several clinical characteristics that imply the involvement of other areas outside the limbic system. For this reason, authors prefer the term Autoimmune Encephalitis (AIE).

In the pathophysiology of AIE, the disease can be classified based on its location, the causal antigens, and the probable mechanisms of the disease. Generally, antibodies for intracellular antigens are associated with underlying malignancies, in contrast to membrane antigens, which generally do not reflect the presence of a tumor but can be associated with tumors in some cases. Thus, an extensive search for any underlying malignancies must always be considered in patients with suspected AIE.

The antibodies for intracellular antigens (neuron) are glutamic acid decarboxylase (Gaed), Hu, or Anna1 (Hu-Abs), Ma2, CV2, and amphiphysin. Autoimmune neuronal lesions triggered by the antibodies, which follow the deleterious action of cytotoxic T lymphocytes, are the most probable pathogenic mechanism. These damages appear to be irreversible and the prognosis is generally poor. An exception appears to exist in patients with Gaed antibodies: these patients may have AIE, epilepsy, or other neurological syndromes; its association with tumors is uncommon and recovery is possible, although patients are generally less responsive to immunotherapies.

Antibodies against cellular membrane surface antigens are the VGKC complex (LGI1, CASPR2), NMDA, Ampa, Gaba-B, and glycine receptors. This category has been increasingly recognized as much less associated with malignant diseases, and the disease is believed to be mediated by the very antibodies. These diseases tend to have a better response to immunotherapy. The first syndrome to be recognized in this category was the VGKC-complex antibody syndrome.

Due to the great variety of diseases that must be excluded during the differential diagnosis, the diagnosis of encephalitis is often difficult and delayed.

Clinical setting

Patients with a diagnosis of autoimmune encephalitis associated with neoplasia.

Clinical question

In autoimmune encephalitis, is the treatment with immunoglobulins better than the conventionally used corticosteroids or plasmapheresis?

Eligibility criteria

PATIENT

P - Patients with paraneoplastic autoimmune encephalitis

INTERVENTION

I - Treatment with immunoglobulin

COMPARISON

C - Treatment with corticosteroids or plasmapheresis

OUTCOME

O - Effectiveness or harm

Search strategy. Databases searched: Medline, PubMed. Randomized clinical trial (RCT). No time or language restrictions. Full text or summary of data. Clinical and non-intermediary outcomes.

Search

Encephalitis AND (((((Immunoglobulin OR Immunoglobulins OR Globulins)) AND ((Autoimmune OR Autoimmune Diseases OR N-methyl-D-aspartate receptor OR NMDAR OR leucine-rich OR glioma-inactivated protein-1 OR LGI1 OR contactin-associated protein-2 OR Caspr2 OR α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor OR AMPAR OR γ-aminobutyric acid-A receptor OR GABAAR OR γ-aminobutyric acid-B receptor OR GABABR OR Glycine R) OR (N-methyl-D-aspartate receptor OR NMDAR OR leucine-rich OR glioma-inactivated protein-1 OR LGI1 OR contactin-associated protein-2 OR Caspr2 OR α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor OR AMPAR OR γ-aminobutyric acid-A receptor OR GABAAR OR γ-aminobutyric acid-B receptor OR GABABR OR Glycine R))) = 3036

Eligibility criteria for the studies

1. Patients with paraneoplastic autoimmune encephalitis.

2. Treat with immunoglobulin.

3. Study design: case series or observational cohorts or clinical trials.

4. No time restrictions.

5. Language: portuguese, english, spanish, and italian.

After assessing the studies based on title, design, and language, 450 were selected. After assessment of the abstracts and the final selection, 33 studies were left for full-text analysis, namely: 32228575 32123047 31782181 31874360 31796119 31473641 30449706 31286710 30979857 30182259 30177907 29166136 29759996 28585453 28935354 28959704 29399043 28154970 28150403 26940288 27632180 27242065 27776544 27056053 27428233 26694143 26889260 26770517 26277996 25465439 23290630 20159432 17397768.

Anexos: Table 1 - Inclusion and exclusion. Table 2 - Analysis of the full texts included. Table 3 - Results in patients with lung cancer.

Studies selected based on the search strategy – 3,036

Excluded for not answering to the PICO during the assessment of the title – 2,586.

Selection of 450 studies.

Selection by abstract: 417 excluded for being unrelated to the clinical question.

Selection of 33 studies.

Analysis of the full texts: 28 excluded – review – Non-paraneoplastic – case report – guidelines – No comparison. Table 1 in the annex.

A total of 5 studies were selected - included in the review.

RESULTS

Eleven patients with a mean age of 63 years were assessed at the Hospital of the Hebei Medical University, from February 2016 to October 2016, with encephalitis of unknown etiology and a positive test for receptor antibody (anti-GABA-B) in the blood and/or cerebrospinal fluid[13]. Five patients were diagnosed with small-cell lung tumors. The therapy established at first was neurological symptomatic medication and first-line immunotherapy (steroid and/or immunoglobulin). Patients with a diagnosis of lung cancer also received specific treatment (surgery and/or chemotherapy and/or radiotherapy). In the evaluation of outcomes, we used the modified Rankin Scale (mRS) for therapeutic effects (mRS <2: complete neurological setting, mRS 2: partial neurological improvement) and functional outcome (mRS 2: favorable prognosis, mRS> 2: poor prognosis). In cancer patients, the evolution of the mRS scale was 2 → 1 (complete response) in two patients, 3 → 2 (partial response) in one patient, 4 → 3 (partial response) in one patient, and 5 → 5 (no response) in another.[13] (Table 3 in annex).

In the Peking Union Medical College Hospital, between June 2011 and October 2014, 10 women with a mean age of 23 years diagnosed with ovarian teratoma associated with paraneoplastic encephalitis with positive antibodies against N-methyl-D-aspartate receptor (anti-Nmdar) were assessed.[24] After resection of the tumors, all patients received first-line immunotherapy with intravenous immunoglobulin (IVIG) associated or not to corticosteroids and plasmapheresis; in the event of failure, a second line of medication was instituted. Nine patients had significant relief of neurological symptoms during the mean follow-up time of 14.2 months, with 13.7±5.5 days for relief of symptoms after the surgery[24].

A multi-institutional observational study (2007-2012) evaluated 135 patients with positive NMDAR antibodies in serum or cerebrospinal fluid (CSF) who met the criteria previously described[31]. In the hospitals of the universities of Pennsylvania and Barcelona, all other patients were collected from 200 centers worldwide (32 countries), with a total of 577 patients. The treatment, which did not have a defined protocol, included first-line immunotherapy (steroids, immunoglobulin, plasmapheresis), second-line immunotherapy (rituximab, cyclophosphamide), and tumor resection. In the evaluation of outcomes, the antibodies were assessed at the onset of symptoms, and after 4, 8, 12, 18, and 24 months. Of out 501 patients (mean follow-up of 24 months): 472 (94%) were treated with first-line immunotherapy or tumor resection, with the improvement of 251 patients (53%) in 30 days. The first-line therapy failed in 221 patients; of these, 125 (57%) received second-line treatment with improvement in comparison to those who did not (OR 2.69, CI 1.24 to 5.80, p=0.012).

In the first 24 months, 394 of 501 patients achieved a good result (mRS from 0 to 2 in an average of 6 months) and continued to improve for 18 months after the onset of symptoms, with the death of 30 patients. The predictors of good outcomes were early treatment (OR 0.62, CI 0.50 to 0.76, p<0.0001) and no admission to the ICU (OR 0.12, CI 0.06 to 0.22, p<0.0001)[31].

A retrospective analysis of 24 patients diagnosed with newly acquired encephalitis and neurxo-psychiatric deficit underwent an investigation for positive anti-NMDA receptor in a medical center in Taiwan[9]. All patients were medicated with corticosteroids and/or immunoglobulin and/or plasmapheresis with first-line therapy. With treatment failure in 14 patients, these received second-line medication, with immunoglobulin and rituximab and/or cyclophosphamide. There was no comparative arm for the therapy. Seventeen patients were admitted to an intensive care unit due to an altered level of consciousness, epileptic status, and impending respiratory failure. The average length of hospital stay was 60.38+/- 62.2 days. This may be due to a greater awareness of doctors regarding combined therapy. In the first six months, 20 patients (20/24), i.e., 83% achieved a good outcome, with mRS ≤2, and 15 patients (15/24), i.e., 62.5% recovered completely[9].

Thirty-three patients (21 women and 12 men) and with a mean age of 29.7 years and a diagnosis of encephalitis, neuropsychiatric abnormalities, and positive anti-NMDAR in the CSF, associated or not with other diagnoses, were treated in the Department of Neurology of the Beijing Xuan Wu Hospital between January 2011 to December 2013[28]. The treatment using corticosteroids, intravenous immunoglobulin, and plasma exchange alone or in combined therapy is the first line. Cyclophosphamide or azathioprine were used in isolation or in combination when the first line failed. In the evaluation of outcomes, the *modified Rankin Scale (mRS)* was used to estimate the neurological status: *mRS = 0 corresponds to complete restoration; mRS = 1-2 corresponds to significant improvement; mRS> 2 corresponds to a partial improvement*. The outcomes of treatment in 3 of 33 patients with teratoma were: a 29-year-old patient treated with immunoglobulin for nine days plus symptomatic medications presented a gradual recovery in two months of assessment and mRS=3. In another, a 34-year-old, the medication used were corticosteroids in association with immunoglobulin and symptomatic treatment; recovery was complete in the assessment after three months with mRS=0. The third patient, a 23-year-old, was medicated with corticosteroids, immunoglobulin, and plasmapheresis and presented a gradual improvement in the 12-month assessment and mRS=3 (Table 4, in annex)[28].

Synthesis of evidence

After a detailed search in the literature, we could not find any randomized clinical trials dealing specifically with the clinical question at hand. We obtained a list of observational cohorts, case reports, and reviews. They also did not respond to the comparison of drugs proposed in the PICO. In the analysis of selected cohort studies, there is no clear guideline of the therapeutic approach for paraneoplastic encephalitis. The therapies are not presented or tested in an isolated manner, but always associated in several ways, such as in the first line, i.e., with steroids, immunoglobulin, plasmapheresis, and, as the second line, i.e., as rituximab, cyclophosphamide, azathioprine. This is due to the severity of cases and, oftentimes, the ineffectiveness of the therapy initially chosen, something that leads physicians to opt for other therapies and their associations. This shows an apparent contradiction, as in the greater the treatment, the worse the outcome; but in truth, the relationship is the worse the patient, the more treatments are combined. Thus, therapies and associations seem to be similar in regard to efficacy, with low quality of evidence.

Recommendation

The evidence available comparing corticosteroids with immunoglobulin in the treatment of patients with clinical symptoms of paraneoplastic encephalitis is limited and of poor quality, with few patients studied through case reports and observational cohorts. Therefore, there is no consistent evidence currently available that allows us to estimate the benefits and/or the risks from the use of immunoglobulin in comparison to the current use of corticosteroids in these patients.

This work was developed with the participation of members of the Comitê Estadual de Medicina Baseada em Evidência Científica das Unimeds do Estado de São Paulo, through of (virtual) meetings.

ANNEXES

TABLE 1. INCLUSION AND EXCLUSION (WITH REASONS)

STUDY	DESIGN	REASON FOR EXCLUSION
Li TR (2020)	REVIEW	EXCLUDED - review
Munõz LA (2020)	RETROSPECTIVE COHORT	EXCLUDED - non-paraneoplastic
Zhang L (2020)	RETROSPECTIVE COHORT	EXCLUDED - no comparison
Dubey D (2019)	RCT	EXCLUDED - non-paraneoplastic
Mason G (2019)	COHORT	EXCLUDED - immunotherapy alone
Liu H (2019)	CASE REPORT	EXCLUDED - case report
Zhang X (2019)	RETROSPECTIVE COHORT	EXCLUDED - no comparison
de Bruijn MAAM (2019)	OBSERVATIONAL COHORT	EXCLUDED - non-paraneoplastic
Kong SS (2019)[9]	RETRO OBS COHORT	INCLUDED
Melamud LI (2018)	MEDICAL CHART REVIEW	EXCLUDED - non-paraneoplastic
Chen Z (2018)	COHORT	EXCLUDED - non-paraneoplastic
Chiang S (2018)	CASE REPORT	EXCLUDED - non-paraneoplastic
Cui J (2018)[13]	CASE REPORT	INCLUDED
Iizuka T (2017)	SÉRIE DE CASOS	EXCLUDED - no immunoglobulin
Wang Y (2017)	RETRO COHORT	EXCLUDED - children
Shin YW (2017)	COHORT observational	EXCLUDED - review
Mackeon G (2017)	SYSTEMATIC REVIEW	EXCLUDED - review
Bartolini L (2017)	Electronic search	EXCLUDED - decision of treatment
Hattori Y (2017)	CASE REPORT	EXCLUDED - case report
Abdul-Rahman (2016)	COHORT	EXCLUDED - case report
Huang Q (2016)	OBSERVATIONAL COHORT	EXCLUDED - non-paraneoplastic
Li Z (2016)	COHORT	EXCLUDED - non-paraneoplastic
Nosadini M (2016)	RETROSPECTIVE COHORT	EXCLUDED - study in children
Bai Y (2016)[24]	COHORT	INCLUDED
Von Rhein B (2017)	RETROSPECTIVE COHORT	EXCLUDED - non-paraneoplastic
Yu J (2016)	RETRO COHORT	EXCLUDED - no comparison
LIU.J (2016)	CASE REPORT	EXCLUDED - no immunoglobulin
Huang X (2015)[28]	COHORT observational	INCLUDED
Liu J (2015)	REVIEW	EXCLUDED - case report
Dubey D (2014)	Case report review	EXCLUDED - non-paraneoplastic
Titulaer MJ (2013)[31]	COHORT observational	INCLUDED
Breese EH (2010)	CASE REPORT	EXCLUDED– case report
Feasby T (2007)	REVIEW	EXCLUDED - guidelines

TABLE 2. CHARACTERISTICS OF THERAPEUTIC STUDIES

STUDY	POPULATION	INTERVENTION	COMPARISON	OUTCOME	FOL-LOW-UP TIME
Cui J 2018[13]	N=11 patients with suspected encephalitis with anti-GAB-AB receptor antibodies of unknown etiology. 5 patients with small cell tumor	First-line immunotherapy + standard treatment for lung cancer (surgery and/or CT and/or RT)	Corticosteroids vs IVI vs corticosteroids + IVI	Complete neurological and functional response; partial response and no response	11 months
Bai Y 2016 [24]	N=10, 10 women and mean age of 23 years with ovarian teratoma associated with anti-NMDAR encephalitis. Treated with TU resection AND immunotherapy, combined or not.	N=3 patients received only first-line immunotherapy with intravenous immunoglobulin therapy (IVIG).	N=7 patients received intravenous immuno-globulin and glucocor-ticoids. N=4 patients received intravenous immunoglobulin, glucocorticoids, and plasmapheresis	Improvement of mental and neurological symptoms	14.2 months
Titulaer MJ 2013 31	N=577 patients included for demographic analysis and treatment. 501 followed-up for at least 4 months. There was no predefined treatment protocol.	N=251 The first-line immu-notherapy was defined as the use of steroids, IVIG, or plasma exchange alone or combined.	N=125 The second line of immunotherapy included rituximab or cyclophosphamide alone or combined.	Good outcomes included - mRS improvement without ICU admission, ear-ly treatment, low severity	Average of 24 months
Kong SS 2019 [5]	N=24 Patients with positive anti-NMDA receptor AB, 16 women, and 71% younger than 18 years. 3 had neo-plasias.	N=24 All patients were treated with corticosteroids and/ or immunoglobulin and/ or plasmapheresis with 1st line (14 received 2nd line with immune. and rituximab and/ or cyclophosphamide) No patients were treated with IVIG alone.	Non-Comparative study	4 patients (16.7%) had a recurrence of the disease or relapse; 10 patients with 1st line therapy, 4 with respira-tory failure; and 6 admitted to the ICU; 14 patients with 2nd line treatment, 9 with re-spiratory failure, 4 relapsed	6 months
Huang X 2015 [28]	N=33 Patients with autoim-mune encephalitis, average age of 29.7 years. With anti-NMDAR encephalitis + N=3 cases with ovarian tera-toma and 01 cervical TU.	Of the 33 patients, 20 received antiretroviral drugs; N=331 1st line with immune steroid and plasmapheresis; None of the patients received IVIG alone	Non-comparative study	Average hospitalization = 36 days; Full recovery (asymptomatic) = 24, with 9 patients partially recovered (mild not detailed residual symptoms), among these, two with associated teratoma.	7.8 months

TABLE 3. RESULTS IN PATIENTS WITH LUNG CANCER[13].

Patients	Tumor	Immunotherapy	Tumor treat-ment	Anti-epileptic treatment	Response to treat-ment	Initial à follow-up mRS	Follow-up months
1	SCLC	cort	Surgery	yes	Complete	2à1	11
5	SCLC	IVIg + cort	CT + rad	yes	Complete	2à1	14
8	SCLC	IVIg	Surgery/CT	yes	Partial	4à3	12.5
9	SCLC	IVIg	Surgery/CT	yes	No response	5à5	7
11	SCLC	IVIg + cort	CT	yes	Partial	3à2	7

Reference: Table 3. Tumor association, treatment, and outcome.[13] SCLC = small cell lung cancer. IVIg = immunoglobulin IV. Cort = corticosteroids. CT = chemotherapy. Rad = radiotherapy. mRS = modified Rankin Scale score.

TABLE 4. RESULTS FROM PATIENTS WITH TERATOME[28].

Age years	Therapy dura-tion (days)	Corticosteroids	Immunoglobulin	Plasmapheresis	Other drugs	Follow-up (months)	Clinical course	mRS
29	9	yes	no	no	yes	2	G	3
34	20	yes	yes	no	yes	3	F	0
23	10	Yes	yes	yes	yes	12	G	3

Reference: Table 3. Treatments and follow-up[28]. Other drugs: acyclovir, anticonvulsant, antiepileptics. Clinical course - G = gradual improvement, F = total improvement.

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