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Efficacy of antiepileptic drugs in autoimmune epilepsy: A systematic review

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ABSTRACT

Objective: Review the evidence of the efficacy of AEDs (antiepileptic drugs) in autoimmune epilepsy.
Material and methods: Literature research on Medline and Embase was carried out through January 2018. We included MeSH terms, free text and terms related to "autoimmune epilepsy", "autoimmune encephalitis", "limbic encephalitis", "autoimmune seizures", "antiepileptic drug", "seizure treatment", and "epilepsy treatment". The research was carried out by two reviewers who independently examined titles, abstracts and selection criteria. The main outcome was AED efficacy. Results regarding types of AEDs and autoantibody presence and type in responding patients were considered secondary endpoints. Quality of evidence was analysed by reading the whole text and following Scottish Intercollegiate Guidelines Network (SIGN) guidelines.
Results: After an initial selection of 1656 articles, only six retrospective observational studies with a level of evidence between 2+ and 3 and a SIGN B recommendation degree remained. The total number of patients examined was 139. The estimated efficacy of AEDs with AE was 10.7%. There was response to AEDs in 18% of seronegative patients, 11% in VGKC positives and in 8% with GAD65. Seventy-three percent of responders to AEDs were in treatment with Na+ channel blockers in monotherapy or in combination.
Conclusions: The efficacy of AEDs in AE was low, although this may be in part due to a selection bias. Nevertheless, patients could benefit from these drugs even after immunotherapy failure. Seronegative patients seemed to have a better response to AEDs.

Introduction

Epileptic seizures are a frequent symptom in limbic encephalitis of autoimmune origin or in paraneoplastic syndromes. However, there is growing evidence of patients suffering from autoimmune-based epilepsy in isolation from other syndromic manifestations of encephalitis [1]. In one recent series of 127 patients with epilepsy of unknown origin, 20.5% of patients presented antibodies that strongly implied an autoimmune origin of this disease [2]. As a matter of fact, epilepsy of autoimmune origin is included in the new 2017 International League Against Epilepsy (ILAE) classification [3].

Autoimmune epilepsy has been linked to neural antibodies that target both intracellular proteins (glutamic acid decarboxylase [GAD65], Type 1 anti-neuronal nuclear antibody [ANNA-1], Ma, Purkinje cell cytoplasmic antibody [PCA-2], collapsin-response mediator protein-5 [CRMP-5]) and surface antigens (voltage-gated potassium channel complex [VGKC] specifically directed to leucine-rich glioma inactivated 1 [anti-IgL1] and contactin-associated protein-like 2 [Caspr2], N-methyl-D-aspartate receptor [NMDAR], alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor [AMPAR], B1 subunit of the gamma-amino-butyric acid [GABA-B], amphiphysin, thyroid peroxidase [TPO]) [2], although on occasion it happens without antibody detection [4].

One of the characteristics of this kind of epilepsy is that it is frequently resistant to AEDs (antiepileptic drugs)[4–12]. For this reason, it is essential to make a correct diagnosis, because patients can benefit from immunotherapy (IMT) [5,13–15]. On the other hand, although an ideal therapeutic regime has not been determined, it has been observed that early IMT onset leads to a better outcome [16]. Nevertheless, some patients may respond adequately to treatment with only AEDs from the beginning or after the residual phase of the inflammatory disease. For this reason, these drugs play an important role in autoimmune epilepsy [4]. Currently, the real efficacy of these drugs, both at general and

Abbreviations: AE, autoimmune epilepsy; AED, antiepileptic drug; IMT, immunotherapy; CBZ, carbamazepine; LCM, lacosamide; LTG, lamotrigine; LEV, levetiracetam; OXZ, oxcarbazepine; PHT, phenytoin.

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individual levels (e.g., type of AED), is unknown. Likewise, it is not known whether there are differences in efficacy for any particular anti-neural antibodies. It could be hypothesised that the response to a given AED group could be linked to a certain antibody. In our clinical practice, we observed response from only one patient with limbic encephalitis due to VGKC antibodies after starting treatment with Retigabine, a K+ channel opener [17].

The objective of this systematic review is to determine the efficacy of AEDs for epilepsy of autoimmune origin by means of the data provided in literature.

2. Methods

A systematic review was carried out on the studies that could answer the research question.

2.1. Identification and selection of studies

A comprehensive literature search was carried out in Medline and Embase, covering the period from January 1946 to January 2018. The research was not narrowed down by any language. The research strategy included MeSH terms and free text and terms related to "autoimmune epilepsy" OR "autoimmune encephalitis" OR "limbic encephalitis" OR "autoimmune seizures" AND "antiepileptic drug" OR "seizure treatment" OR "epilepsy treatment". Moreover, a secondary free search was carried out in Medline with the terms "autoimmune epilepsy" AND "treatment". These search strategies were carried out by two reviewers who independently examined titles, abstracts of articles and selection criteria.

Studies included according to their type were as follows: meta-analyses, systematic reviews, clinical trials, and observational studies (cross-sectionals, cohorts, case-control study, and case series). According to the participant profile, studies with patients diagnosed with autoimmune epilepsy were included in accordance with clinical-analytical and neuroimaging criteria. Patients suffering from any kind of epilepsy not of autoimmune origin were excluded. According to the type of intervention, studies assessing the treatment efficacy in patients who were only treated with AEDs from the beginning or after IMT failure were selected.

The main outcome studied was the efficacy of AEDs, that is, the percentage of seizure-free patients or those with a $\geq$ 50% reduction in seizure frequency at the end of the follow-up period in the study. The following were included as secondary endpoints: the type and average number of AEDs in patients in whom AEDs were effective; presence and type of autoantibodies in patients in whom AEDs were effective.

2.2. Data mining and bias assessment

Articles whose titles or abstracts were in line with the inclusion criteria were read in full. If any of the eligibility criteria failed, this proved to be sufficient reason for exclusion. Any disagreement on a study inclusion was resolved by consensus among the two reviewers with the help of a third reviewer. Two reviewers independently carried out the data mining of the documents in the form of a report.

Following the Scottish Intercollegiate Guidelines Network (SIGN) recommendations, the quality of evidence was analysed by reading the whole text.

3. Outcomes

3.1. Description of the studies

A total of 1656 studies published between 1946 and 2017 were selected through the main search. The following articles were eliminated: 421 duplicate documents, a total of 1203 documents after title reading; 24 after abstract reading; and four documents after full reading. Only four articles meeting established criteria remained. We included another two articles by a secondary free search. These six documents are the focus of this systematic review (see Fig. 1). They are retrospective observational studies (cohort or case series) with a level of evidence between 2+ and 3 and a grade of recommendation SIGN B.

Excluded studies and reasons for the exclusion are shown in Table 2 in Supplementary material. The total number of patients suffering from autoimmune epilepsy and treated with AEDs in monotherapy from the beginning or after IMT failure was 31, ranging from 1 to 11 patients, depending on the article. The length of the follow-up period of all cohorts observed in the studies was variable and ranged from 53 days to 84 months.

3.2. Efficacy of AEDs with autoimmune epilepsy

Out of a total of 139 patients with AE analysed in the six studies, 31 patients were treated with only AEDs either from the beginning (n = 17) or after IMT failure (n = 14). Out of these 31 patients, 15 (48.3%) responded to treatment with AEDs, but these patients accounted for only 18% of the total of patients responding to any therapy (n = 83, 59.7% of the total patients) and for 10.7% of analysed patients.

Outcomes of the analysed studies, which are summarised in Table 1, are detailed below.

In the cohort with the highest number of patients suffering from autoimmune epilepsy that were included in this review (n = 50), from Feyissa et al. [4], 11 patients (22%) were treated with only AEDs from the beginning or after IMT failure. This is a retrospective study, and criteria used to select a specific treatment were not indicated. Twenty-seven patients from the cohort became seizure-free at the end of the follow-up period. Out of these 27 patients, nine patients (33%) were treated with only AEDs from the start (n = 5) or after IMT failure (n = 4), which implies an efficacy of AEDs of 18% seizure-free patients compared to the total of the cohort at the end of the follow-up period (7–68 months).

In the von Podewils et al. study [18], with a cohort of 66 patients suffering from epileptic seizures, four patients were diagnosed with autoimmune epilepsy, and just one of them was treated with only AEDs and became seizure-free after a 14-month follow-up. This patient did not receive IMT due to his/her own decision. The

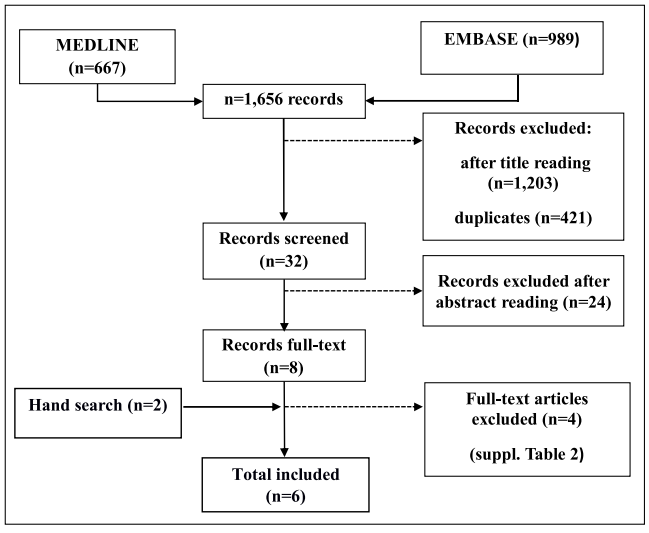

Fig. 1. Record selection.