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Association between epilepsy and systemic autoimmune diseases: A meta-analysis

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ABSTRACT

Purpose: To investigate the association between systemic autoimmune diseases (SAD) and epilepsy and to determine whether the strength of this association is increased in the young.
Methods: A meta-analysis was done, analyzing the association between epilepsy and SAD using the available data in Medline and Embase through February 2016. We followed the recommendations of the PRISMA (preferred reporting items for systematic reviews and meta-analyses) statement and the MOOSE (meta-analysis of observational studies in epidemiology) guidelines.
Results: A total of twenty-five studies met the inclusion criteria for this meta-analysis, which included 10,972 patients with epilepsy (PWE) and 2,618,637 patients with SAD. The PWE cohort was shown to have more than a 2.5-fold increased risk of SAD. The patients with SAD were also shown to have a more than 2.5-fold increased risk of epilepsy. The results indicated that patients <20 years of age had a 3-fold increased risk of SAD and epilepsy (OR = 3.04 [95% CI 1.27–7.27], $P = 0.01$; OR = 3.15 [95% CI 1.92–5.15], $P < 0.01$; respectively), and these risks were shown to be higher than patients >20 years of age. The PWE cohort had a 2.6-fold increased risk of celiac disease (OR = 2.65 [95% CI 1.41–4.97], $P < 0.01$). The patients with systemic lupus erythematosus had a 4.5-fold increased risk of epilepsy (OR = 4.57 [95% CI 2.40–8.67], $P < 0.01$).
Conclusions: There is an association between epilepsy and SAD, which was shown to be stronger at a young age.

1. Introduction

Systemic autoimmune diseases (SAD) have gained notoriety as being a risk factor for epilepsy. Conversely, recent studies have reported that epilepsy increases the risk of systemic autoimmune diseases [1,2]. Based on the emerging data, one may speculate that there is an underlying biological mechanism, such as pro-inflammatory conditions and antibodies, which links epilepsy and SAD [2,3]. Numerous studies have focused on clarifying this association, as it could help elucidate the different roles of auto-Abs and inflammation in epileptogenesis. Additionally, whether age is a risk factor for epilepsy in patients with SAD has also investigated, however, the results were inconsistent [4,5].

Considering that a meta-analysis of these results has yet to be done, the aim of this study was to synthesize all of the available data regarding the association between SAD and epilepsy in order to establish an association between the two. We also evaluated the role that young age plays in this association. This study highlights the need for neurologists to pay attention to the underlying SAD in cases of epilepsy.

2. Methods

2.1. Search strategy and selection criteria

The recommendations put forth by both PRISMA (preferred reporting items for systematic reviews and meta-analyses) [6] and MOOSE (meta-analysis of observational studies in epidemiology) [7] were followed. The protocol used in this study was based on the Cochrane Review Methods (www.cochrane-handbook.org). Two electronic databases (Medline and Embase) were searched using a combination of medical subject headings and text words, including autoimmune disease, type 1 diabetes mellitus, rheumatoid arthritis, Crohns disease, ulcerative colitis, inflammatory bowel disease, systemic lupus erythematosus (SLE), antiphospholipid

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syndrome, celiac disease, bullous pemphigoid (BP), Sjögren syndrome, myasthenia gravis, seizure, and epilepsy from 1980 to 2016 Feb 29 with an English language restriction. The references of each identified publication were also examined for any additional studies. The literature search was performed by two authors independently, in which the abstracts and full texts were screened and the relevant data was extracted. Studies were eligible for inclusion if they reported (1) the number of patients with epilepsy or SAD (2) the control groups or matched groups. Studies would be excluded if (1) they had no controls or only self-control (2) data were not available or full-text cannot be found (3) data were repeated (4) only acute symptomatic seizures, or only specific seizure patterns, or specific epileptic syndromes were included (5) they are reviews, editorials, single cases and case series, studies published only as abstracts, letters, and commentaries. Any disagreements regarding article were resolved through discussion by all authors.

2.2. Data extraction

The following information was recorded for both the study groups and the control groups for each of the included studies: first author, year of publication, country, study design, diagnostic criteria of patients, sample size, percentage of females, age, epilepsy occurrences and SAD. The risk of bias was determined using the Newcastle-Ottawa Scale (NOS) in domains of selection, comparability, and outcome [8]. The NOS score was categorized as 1–3, 4–6, or 7–9, and labeled as low, medium, or high quality of evidence.

2.3. Statistical analysis

The discontinuous variables were compared using the Mantel–Haenszel test, the odds ratio (OR) and the 95% confidence interval (CI). The data were analyzed using a random-effect model, taking into consideration the heterogeneity of the study, for example, different areas of study, different races included in the study, and variations in the design and controls used. The occurrences of epilepsy or presence of SAD in patients were used as outcome measures. Subgroup-analysis was also done for patients with a mean age of <20 years and of >20 years as well as patients with different SAD. Considering the lack of studies with paired patients with a mean age of <20 years against patients >20 years, we were unable to use weighted methods in order to find ORs. Instead, an indirect comparison was made in order to compare the odds risk of epilepsy or SAD in different age groups using a common reference (controls)-based indirect comparison meta-analysis. For example, if we tried to indirectly pair A against B, direct evidence was provided by studies that compare A vs C and B vs C, respectively. However, indirect evidence was provided from studies compared A vs C and B vs C and were analyzed jointly. The ITC software (www.cadth.ca) and the Bucher approach were applied for indirect comparisons [9]. The sensitivity analysis was performed in order to test the reliability of the results of the significant findings using a cycle in which a single study was removed and the analysis of 5 or more studies was repeated. If the result of the study did not change significantly upon the removal of a study, the result of the study was thought to have high stability. Publication bias was qualitatively assessed by a visual inspection of the funnel plots.

3. Results

3.1. Identification and description of studies

A total of 6482 unique articles were identified, of which, 83 were potentially relevant to this study. Twenty-five studies met our inclusion criteria for this meta-analysis (Fig. 1) [10–34]. The features of the included studies are presented in Table 1. A total of 10,972 patients with epilepsy and 2,618,637 patients with SAD were included. The majority of the studies came from Europe. The diagnosis of epilepsy in most of the studies, 18 of 25, was based on the International League Against Epilepsy (ILAE) [35–37] or the International Classification of Diseases, 9th Revision (ICD-9). The diagnosis of SAD in most studies, 19 of 25, was based on a biopsy, positive antibodies and/or ICD-9. Eight of the twenty-five included studies reported the prevalence of celiac disease in patients with epilepsy [10–17]. Three of the twenty-five studies reported the prevalence of systemic lupus erythematosus [18], type 1 diabetes mellitus [19], and rheumatoid arthritis [18,20] in patients with epilepsy. One study reported the prevalence of epilepsy in multiple SAD [22]. With the exception of one study [22], two of the twenty-five studies reported the prevalence of epilepsy in patients with systemic lupus erythematosus [21,23]. Three of the twenty-five studies reported the prevalence of epilepsy in patients with celiac disease [24–26]. Four of the twenty-five studies reported the prevalence of epilepsy in patients with BP [27–30]. Four of the twenty-five studies reported the prevalence of epilepsy in patients with inflammatory bowel disease [31,32], type 1 diabetes mellitus [33], and rheumatoid arthritis [34]. Each of the included studies had a NOS score of 4 or more.

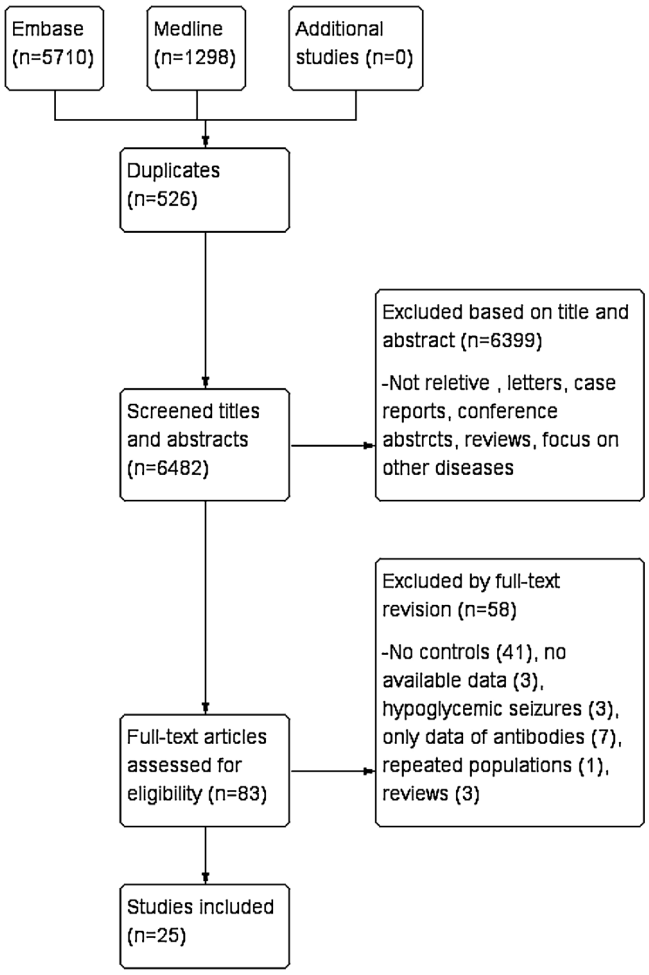

Fig. 1. Flowchart.

3.2. The risk of epilepsy and SAD

Overall, PWE were shown to have a 2.6-fold increased risk of SAD (OR = 2.58 [95% CI 1.48–4.50], $P < 0.01$) (Fig. 2). Patients with