Epilepsy Research 136 (2017) 12–17

Contents lists available at ScienceDirect

Epilepsy Research

journal homepage: www.elsevier.com/locate/epilepsyres

Status epilepticus-related etiology, incidence and mortality: A meta-analysis

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ARTICLE INFO

Keywords:
Status epilepticus
Case fatality rate
Crude annual incidence rate
Etiology
Meta-analysis

ABSTRACT

Status epilepticus (SE) is a severe medical condition. To determine its epidemiology and outcome of SE, we performed a meta-analysis to investigate the etiology, incidence and mortality of SE. We searched PubMed and Embase between Jan 1, 2000, and Oct 31, 2016, with no regional restrictions, for observational studies of the etiology, incidence and mortality of SE. Forty-three studies were included in the meta-analysis. The pooled crude annual incidence rate, the pooled case fatality rate and the pooled crude annual mortality rate of SE were 12.6/100,000 (95% CI: 10.0–15.3), 14.9% (95% CI: 11.7–118.7) and 0.98/100,000 (95% CI: 0.74–1.22), respectively. Elderly subjects with SE had a higher case fatality rate (28.4% (95% CI: 17.7–42.3)) and crude annual incidence rate (27.1% (95% CI: 15.8–38.2)). The most important etiology-specific attributable fraction of patients with SE was acute symptomatic etiology (OR 0.411, 95% CI: 0.315–0.507). Age and economic income contributed to differences in SE incidence and short-term case fatality rate.

1. Introduction

Status epilepticus (SE) is a severe medical and common neurological emergency condition defined as an epileptic seizure that shows no clinical signs of arresting after a duration encompassing the great majority of seizures (generally 5 min) or recurrent seizures without interictal resumption of baseline central nervous system function (Blume et al., 2001). It is characterized by high mortality and morbidity (Jallon et al., 1999; Logroscino et al., 2005; Vignatelli et al., 2005; Vignatelli et al., 2003).

SE is not a syndrome or disorder per se but rather a state that results from underlying neurologic disorders, including epilepsy syndromes. The causal factor is thus far the most important determinant regarding SE outcomes and prognosis. Neurologic sequelae that may follow SE include secondary epilepsy, cognitive deterioration, behavioral problems, and focal neurologic deficits. Neurologic syndromes include diplegia, extrapyramidal syndromes, cerebellar syndromes, and decorticate rigidity (Ostrowsky and Arzimanoglou, 2010).

The estimates of etiology, incidence and mortality of SE worldwide vary considerably, likely reflecting differences in measurement and reporting, along with clinical characteristics such as etiology and SE type. There have been very few systematic reviews of SE etiology, incidence and mortality, and prior reviews on these topics did not use meta-analyses to explore the associated factors (Logroscino et al., 2005; Neligan and Shorvon, 2011).

Our aim was to estimate the etiology, incidence and mortality of SE from international studies and to determine the epidemiology and outcomes of SE using meta-analytic techniques.

2. Materials and methods

2.1. Search strategy

We systematically searched PubMed and Embase for relevant articles on the etiology, incidence and mortality of SE between Jan 1, 2000, and Oct 31, 2016. The following key words were employed: ‘fatality’; ‘incidence’; ‘mortality; “etiology” and combined with ‘status epilepticus’. The search results were limited to English- language publications.

2.2. Criteria for inclusion

Studies included in the current meta-analysis were required to meet the following eligibility criteria: (1) the paper should report prospective or retrospective studies of the etiology, incidence or mortality of SE; (2) studies that evaluated long-term mortality among people with SE were

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http://dx.doi.org/10.1016/j.eplepsyres.2017.07.006
Received 19 April 2017; Received in revised form 11 June 2017; Accepted 2 July 2017
Available online 15 July 2017
0920-1211/

excluded; (3) case reports, case series, reviews, articles in the meta-analysis, commentaries, treatment protocols and animal studies were excluded; and (4) the paper should define the SE.

2.3. Quality assessment and data extraction

The quality of included studies was evaluated according to "Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)" (Vandenbroucke et al., 2014) and included the study design, specific objection, sample representativeness, diagnostic criteria of SE, and assessment of outcome. Two independent reviewers assessed the quality of the included articles and extract the data. Each study was given a quality score of 0–5 based on the fulfillment of the quality criteria (≥4 scores as high-quality criteria).

The following data were extracted independently by two reviewers from each article: the first author's last name, year of publication, country and age of the study population, numbers of SE and mortality, definition of SE and short-time outcomes of SE, etiology of SE. When the article included data from different years, we extracted data from the most recent years.

2.4. Definitions

For SE, refractory status epilepticus (RSE) and short-term outcomes of SE, we used the definitions provided by the investigators. Short-term mortality was defined as death during hospital admission or 30 days. RSE is the persistence of seizure activity despite appropriate medical and anti-epileptic drug (AED) therapy. The elderly are defined as individuals aged ≥60 years. Developed countries were classified as high-income Asia Pacific, high-income North America, Western Europe, Australia and New Zealand. The remaining countries were classified as developing countries.

2.5. Statistical analysis

Chi-square-based Q test and I^2 test were carried out to assess the heterogeneity between studies ($p < 0.10$ for the Q test and $I^2 > 50\%$ was considered statistically significant). A random effects model was used when the effects are assumed to be heterogeneous. Otherwise, a fixed model was used. Publication bias was investigated visually using funnel plots and statistically using Begg's (Begg and Mazumdar, 1994) and Egger's (Egger et al., 1997) tests. The Comprehensive Meta-Analysis 2.0 software was used for the meta-analysis.

3. Results

3.1. Study characteristics

We identified 7376 citations from 2 electronic data-bases (Fig. 1) in English. Of those, after removing duplications by reviewing the title, abstract and full text and screening for relevance, a total of 47 studies involving 80,307 SE cases were included in this systematic review and meta-analysis (Supple 2). Thirty-eight studies provided case fatality rates or calculated case fatality rates. Eleven studies provided crude annual incidence rates or calculated crude annual incidence rates. Nine studies provided crude annual mortality rates or calculated crude annual mortality rates. Twenty-five studies provided an etiology of SE.

3.2. Etiology

A total of 25 unique studies that provided etiology of SE met our inclusion criteria. An etiological classification is shown in Table 1. Acute symptomatic etiology (OR 0.411, 95% CI: 0.315–0.507) was the leading etiology-specific attributable fraction of patients with SE. The specific causes of SE are summarized in Table 2. Epilepsy history (OR 0.237, 95% CI: 0.138–0.335), central nervous system (CNS) infection (OR 0.177, 95% CI: 0.129–0.225) and cerebrovascular disease (OR 0.126, 95% CI: 0.094–0.157) were the important specific causes of SE. CNS infection (OR 0.233, 95% CI: 0.172–0.293), epilepsy history (OR 0.125, 95% CI: 0. 055–0.195) and cerebrovascular disease (OR 0.104, 95% CI: 0.070–0.138) were the important specific causes of SE in developing countries. However, epilepsy history (OR 0.351, 95% CI: 0.306–0.397) and cerebrovascular disease (OR 0.186, 95% CI: 0.102–0.269) were the important specific causes of SE in developed countries.

3.3. Crude annual incidence rate

A total of 11 unique studies that reported on the crude incidence rate of SE met our inclusion criteria. The pooled crude annual incidence rate was 12.6 per 100,000 person-years (95% CI: 10.0–15.3). There was heterogeneity between estimates ($I^2 = 99.9\%$, Q p-value < 0.000). The pooled crude annual incidence rate in developing countries was 13.8 per 100,000 person-years (95% CI: 9.0–18.7), whereas the pooled crude annual incidence rate in developed countries was 11.7 per 100,000 person-years (95% CI: 8.7–14.6). The pooled crude annual incidence rate was similar between females, with 11.1 per 100,000 person-years (95% CI: 7.0–15.3) and male, with 11.3 per 100,000 person-years (95% CI: 6.6–15.9). Elderly subjects with SE had the highest crude annual incidence rate, which was 27.1 per 100,000 person-years (95% CI: 15.8–38.3) (Table 3).

3.4. Case fatality rate

A total of 38 unique studies that reported on the case fatality rate of SE were included in thismeta-analysis. The pooled case fatality rate was 14.9% (95% CI: 11.7–18.7). The case fatality rate was elevated in developing countries with 15.6 (95% CI: 13.0–18.6). Elderly subjects with SE had a higher case fatality rate of 24.9% (95% CI: 15.5–37.5). The RSE group had the highest case fatality rate (33.3%) (95% CI: 23.9–44.2) (Table 4). Acute symptomatic etiology (OR 0.232, 95% CI: 0.157–0.307) was the first etiology attributable to mortality in patients with SE (Table 5).

3.5. Crude annual mortality rate

A total of 9 unique studies included the data that could be converted to a crude annual mortality rate. The pooled crude annual mortality rate was 0.98 per 100,000 person-years (95% CI: 0.74–1.22). The pooled crude annual mortality rate in developing countries was 2.92 per 100,000 person-years (95% CI: −1.7 to 7.53), whereas the pooled crude annual mortality rate in developed countries was 1.19 per 100,000 person-years (95% CI: 0.70–1.68) (Table 6).

3.6. Publication bias

Funnel plots and Begg's or Egger's tests were performed to assess the publication bias of the studies. There was no evidence of publication bias for any incidences of fatality or mortality (all $p > 0.05$).

3.7. Study quality

Meta-regression was performed to effect of study quality on the incidence fatality and mortality. There was no effect of study quality on the incidences of fatality or mortality (all $p > 0.05$).

4. Discussion

SE is a common cause of neurological emergency and is associated with high mortality (Logroscino et al., 2005; Vignatelli et al., 2005; Vignatelli et al., 2003). Over the past few decades, a large number of studies have addressed important aspects of SE etiology, incidence and