Epilepsy & Behavior 85 (2018) 32–36

Contents lists available at ScienceDirect

Epilepsy & Behavior

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

Review

Causes of mortality in early infantile epileptic encephalopathy: A systematic review

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ARTICLE INFO

Article history:
Received 6 March 2018
Revised 25 April 2018
Accepted 5 May 2018
Available online xxxx

Keywords:
Ohtahara syndrome
Early infantile epileptic syndrome
Suppression burst
Epilepsy

ABSTRACT

Introduction: Early infantile epileptic encephalopathy syndrome (EIEE), also known as Ohtahara syndrome, is an age-dependent epileptic encephalopathy syndrome defined by clinical features and electroencephalographic findings. Epileptic disorders with refractory seizures beginning in the neonatal period and/or early infancy have a potential risk of premature mortality, including sudden death. We aimed to identify the causes of death in EIEE and conducted a literature survey of fatal outcomes.

Methods: We performed a literature search in MEDLINE, EMBASE, and Web of Science for data from inception until September 2017. The terms "death sudden," "unexplained death," "SUDEP," "lethal," and "fatal" and the medical subject heading terms "epileptic encephalopathy," "mortality," "death," "sudden infant death syndrome," and "human" were used in the search strategy. The EIEE case report studies reporting mortality were included.

Results: The search yielded 1360 articles. After screening for titles and abstracts and removing duplicate entries, full texts of 15 articles were reviewed. After reading full texts, 11 articles met the inclusion criteria (9 articles in English and 2 in Japanese, dated from 1976 to 2015). The review comprised 38 unique cases of EIEE, 17 of which had death as an outcome. In all cases, the suppression-burst pattern on electroencephalographies (EEGs) was common. Most cases (55%) involved male infants. The mean (standard deviation [SD]) age at onset of seizure was 19.6 ± 33 days. The mean (SD) age at death was 12.9 ± 14.1 months. Most infants (58.8%) survived less than one year. The cause of death was described only in eight (47%) patients; the cause was pneumonia/respiratory illness or sudden unexpected death in epilepsy (SUDEP).

Discussion: The results show EIEE as a severe disease associated with a premature mortality, evidenced by a very young age at death. Increasing interest in the detection of new molecular bases of EIEE is leading us to a better understanding of this severe disease, but well-reported data are lacking to clarify EIEE-related causes of death.

1. Introduction

Early infantile epileptic encephalopathy (EIEE) was first described by Ohtahara as a devastating condition in infants. Also named as Ohtahara syndrome, this rare clinical entity is characterized as frequent spasms in neonates/infants associated with a suppression-burst (S-B) pattern on electroencephalography (EEG) [1–3]. The EIEE is usually described as a part of the same epileptic, age-dependent continuum of West syndrome (WS) and Lennox–Gastaut syndrome (LGS) [3]. The major causes of EIEE include structural brain abnormalities, with genetic mutations frequently in STXBP1, KCNQ2, ARX, and CDKL5, among several others, also having a massive role in the syndrome [4–6]. This rare disease has a poor prognosis. Usually described as a progressive and untreatable disease, EIEE is also associated with severe physical and cognitive disabilities and unexplained death [3]. Among several causes of death in epilepsy, sudden unexplained death in epilepsy (SUDEP) is rising. It is defined as the "sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrawning death in patients with epilepsy with or without evidence of a seizure, and excluding documented status epilepticus, in which post-mortem examination does not reveal structural or toxicologic etiology of death" [7]. Although mortality has increased among children with epilepsy [8], so far, no clear data are available on the causes of death in EIEE. To better understand

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https://doi.org/10.1016/j.yebeh.2018.05.015
1525-5050/

this point, we propose a systematic and comprehensive literature review searching for EIEE outcomes.

2. Material and methods

A systematic review using the methodology outlined in the Cochrane Handbook for Systematic Reviewers was performed [9]. The data were reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [10]. The review protocol was registered in the International Register of Prospective Systematic Reviews under the registration number CRD42017058801.

2.1. Database search

A literature search was performed in the MEDLINE (through PubMed), EMBASE, and Web of Science for data from inception until September 2017. The following terms and medical subject headings (MeSH) were used in the search strategy: "epileptic encephalopathy" AND "death sudden" OR "SUDEP" OR "unexplained death" OR "mortality" OR "death" OR "sudden infant death syndrome" OR "lethal" OR "fatal" AND "case control" OR "cohort analysis" OR "retrospective study" OR "epidemiologic studies" OR "observational (study or studies)" OR "longitudinal" OR "retrospective" AND "human." The detailed strategies for PubMed are given in Appendix I. The strategies for other databases are available on request. Articles published in all languages were included. The bibliography of the included articles was manually searched. Two authors (G.R. and W.B.V.) independently evaluated the titles and abstracts of all studies identified in the search based on the abovementioned terms and MeSH. Disagreements were resolved by consensus or by a third reviewer (L.P.).

2.2. Eligibility criteria

The inclusion criteria were the following: (1) case reports or case–control or cohort studies reporting mortality and (2) criteria for the diagnosis of EIEE as (a) age up to four months; (b) S-B pattern on EEGs; (c) tonic spasms, generalized seizures, hemiconvulsions, or focal motor seizures [11,12]; and (d) death as outcome with the diagnosis of EIEE.

Exclusion criteria were studies of systematic reviews, letters, and experimental studies. In addition, the studies with incomplete EIEE diagnosis criteria were excluded. Fig. 1 shows a flowchart of study selection and inclusion.

2.3. Data extraction

The databases were searched and duplicate entries were removed. Abstracts that did not provide sufficient information regarding the inclusion and exclusion criteria were selected for full-text evaluation. In the second phase, the same reviewers independently evaluated the full text of these articles and made their selection in accordance with the eligibility criteria. Data on the following were collected: the number of cases, age (days) at seizure onset, underlying pathology, outcome, and cause of death categorized as SUDEP, infective, other, or unknown. The SUDEP cases were classified as definite, probable, or possible [7].

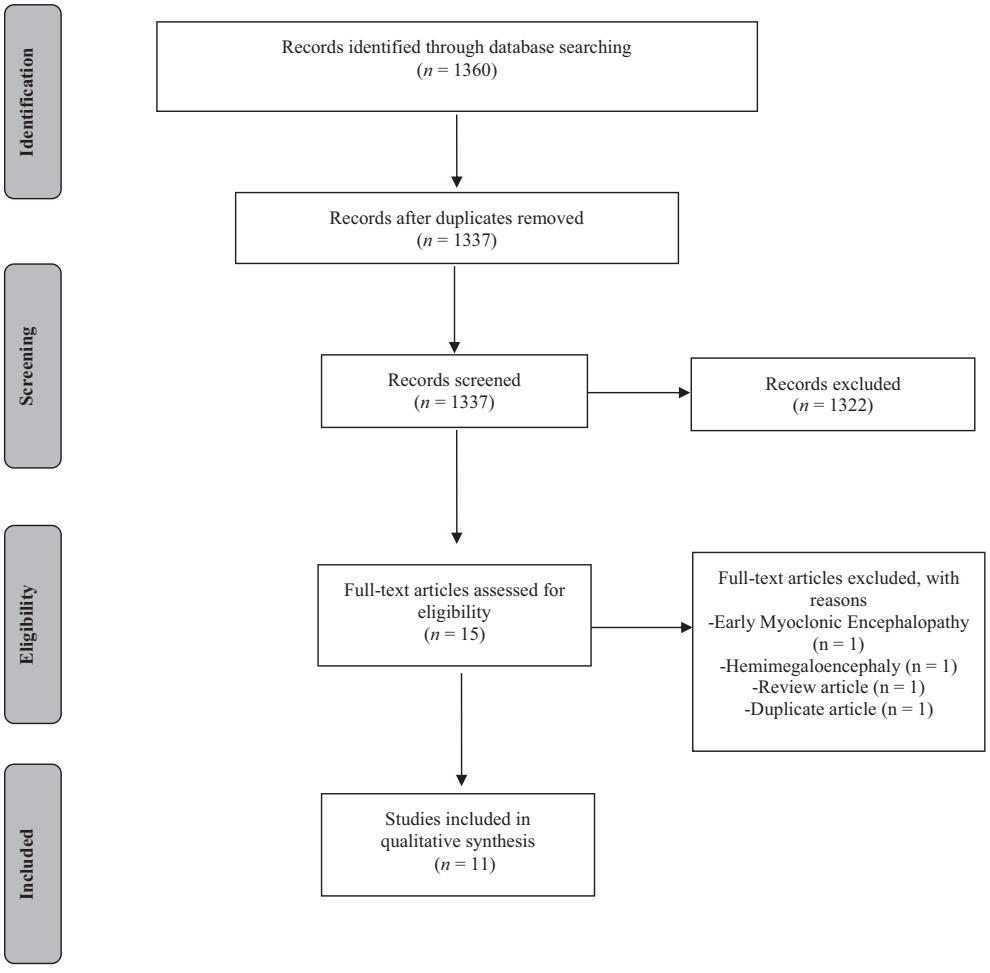

Fig. 1. Summary of evidence search and study selection.