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Relationship between iron deficiency anemia and febrile seizures in children: A systematic review and meta-analysis

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ABSTRACT

Purpose: The association between iron deficiency anemia (IDA) and febrile seizures (FS) during childhood is inconclusive due to inconsistent results reported in different studies. We performed a systematic review and meta-analysis to determine an association between IDA and FS in children.
Methods: We searched PubMed, EMBASE, and Cochrane Library databases for studies published up to August 2015 using the following key words: ["iron deficiency" OR "iron status"] AND ["febrile seizure" OR "febrile convulsion"] AND ["pediatric" OR "infant" OR "child"]. Pooled odds ratios (OR) and 95% confidence intervals (CI) were calculated using standard meta-analysis techniques. Subgroup analysis also was performed.
Results: A total of 17 studies enrolling 2416 children with FS and 2387 controls were included in the meta-analysis. The results indicated that IDA was significantly associated with FS (OR, 1.98; 95% CI, 1.26–3.13; $P = 0.003$). Subgroup analyses evaluated the diagnostic indices for IDA including serum iron, plasma ferritin, and mean corpuscular volume (MCV). The results indicated that IDA diagnosed on the basis of plasma ferritin (OR, 3.78; 95% CI, 1.80–7.94; $P < 0.001$) or MCV (OR, 2.08; 95% CI, 1.36–3.17; $P = 0.001$) was modestly associated with FS, whereas IDA diagnosed on the basis of two serum iron studies was not associated with FS (OR, 0.57; 95% CI, 0.24–1.37; $P = 0.210$).
Conclusion: The results of this meta-analysis suggest that IDA is associated with an increased risk of FS in children.

1. Introduction

Febrile seizure (FS) is the most common seizure type in young children, which is not triggered by central nervous system infection or metabolic disorders [1]. It usually occurs in infants and children aged 6–60 months, and has 2–5% incidence of at least one episode in this population. Iron deficiency anemia (IDA) is a common nutritional deficiency in children with a prevalence of 1–15% in the USA depending on ethnicity and socioeconomic status [2,3], and a prevalence of 0.5–5% in South Korea [4]. Iron is essential for proper growth and development, and iron deficiency is reported to involve behavioural disorders, mental retardation, and impaired immune function [5].

The peak ages for FS and IDA coincide [6], and numerous studies have been performed to determine an associative relationship. However, individual studies have provided conflicting results with other studies. Some studies reported an association between IDA and FS [7–16], whereas other studies did not detect an association [17,18]. A few studies even suggested a protective effect of IDA on FS [19–21]. Systematic reviews and meta-analyses published in 2010 [22] and 2014 [23] examined the association between IDA and FS in children aged 3 months to 6 years. However, the earlier study included only a small number of published reports [22], and the later study conducted subgroup analysis using limited criteria for IDA (iron status, hemoglobin, and hematocrit) [23].

The primary aim of the present study was to determine whether IDA and FS are associated in children by conducting a systematic review and meta-analysis of all available literature. This study will serve to update a previous literature review and include additional data published since 2013. Our secondary aim was to provide a

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more precise estimate of the relationship between IDA and FS by performing subgroup analyses based on different diagnostic indices for IDA.

2. Methods

2.1. Search strategy

We performed a meta-analysis according to the guidelines in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [24–27]. We searched PubMed and EMBASE databases and the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library database using the following terms: ["iron deficiency" OR "iron status"] AND ["febrile seizure" OR "febrile convulsion"] AND ["pediatric" OR "infant" OR "child"]. The databases were searched up to 31 August, 2015, irrespective of language. A clinical librarian with expertise in systematically searching literature databases performed the searches. Titles and abstracts were initially screened to identify relevant articles. Subsequently, full-text articles were reviewed independently by two authors (BOK and RL) to determine inclusion in this meta-analysis. The reference lists in the retrieved papers were manually searched to identify all relevant studies. Unpublished materials or abstracts, and reports from scientific meetings were not included in this meta-analysis.

2.2. Eligibility criteria

The selected studies were subjected to the following inclusion criteria for this meta-analysis: (1) case-control or comparative study designs with clear case and control groups; (2) subjects included children aged 3 months to 6 years with febrile seizures; (3) febrile seizures were compared with febrile illness without seizure; (4) incidence of iron deficiency anemia was measured as risk ratio or odds ratio (OR) with 95% confidence intervals (CI), or provided sufficient data for these calculations.

Then, the selected studies were subjected to the following exclusion criteria: (1) reports designed as case studies, single-arm cohort studies, commentaries, letters, or editorials; (2) studies enrolling cases and controls with non-febrile seizures, central nervous system infections, neurological or hematological disorders, or chronic multisystem diseases; (3) studies lacking specified criteria for defining iron deficiency.

2.3. Data extraction

The following data were extracted from each study: first author, publication year, study design, country, study period, age, gender, criteria used to diagnose iron deficiency, sample size (cases and controls), and incidence of iron deficiency in each group. Two authors (BOK and RL) independently reviewed the full-text articles of all selected studies and extracted data using a standard extraction form. Any discrepancy in data interpretation was resolved by discussion and consensus among the authors.

2.4. Quality assessment

The quality of each study was assessed for three categories using the Newcastle-Ottawa scale (NOS) [28]: selection (0–4), comparability (0–2), and exposure (case-control studies) or outcome (cohort studies) (0–3). The following nine-star scoring system was used to reflect the study quality: total score 0–4, low-quality study; 5–7, moderate-quality study; and 8–9, high-quality study. Two authors (BOK and RL) independently evaluated study quality, and any disagreement was resolved by discussion and consultation with the third author (SNK).

2.5. Data synthesis and analysis

In this meta-analysis, the overall OR and 95% CI were calculated to generate pooled estimates for the relationship between IDA and FS in children. Statistical heterogeneity was assessed using Cochran's Q test and the I^2 statistic [29]. If substantial heterogeneity was detected using the Q test ($P < 0.1$) or I^2 statistic (>50%), a random-effects model (DerSimonian-Laird method) was used to estimate the combined OR. Otherwise, a fixed-effects model (Mantel-Haenszel method) was used for the meta-analysis. Subgroup analysis was performed according to the definition of IDA because the diagnostic criteria used in each study were different. Subgroup analysis was planned *a priori* before data collection and analysis. Sensitivity analysis was conducted by sequentially eliminating each study from the meta-analysis to determine the effect on the pooled OR and the robustness of the conclusion. Cumulative analysis was conducted by sequentially adding each study according to publication year to detect temporal trends. Publication bias was evaluated using the Begg- Mazumdar rank correlation test, Egger's regression test, and fail-safe N test [30–32]. A funnel plot was constructed to evaluate publication bias

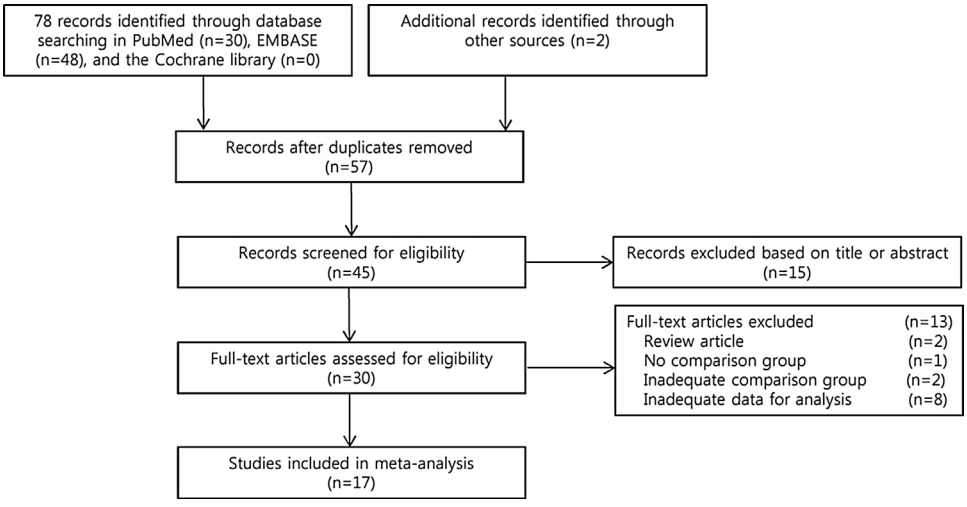

Fig. 1. Flow diagram of literature search and study selection procedure.