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Neurodevelopmental outcome of infantile spasms: A systematic review and meta-analysis

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Infantile spasms;
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Summary
Background: The aims of this systematic review and meta-analysis were to assess (i) estimates of good neurodevelopmental outcome in infantile spasms (IS), (ii) if neurodevelopmental outcome has changed since the publication of the first guideline on medical treatment of IS in 2004 and (iii) effect of lead time to treatment (LTTT).
Methods: The Medline, Embase, Cochrane, PsycINFO, Web of Science and Scopus databases, and reference lists of retrieved articles were searched. Studies inclusion criteria were: (i) >5 patients with IS, (ii) mean/median follow-up of >6 months, (iii) neurodevelopmental outcome, and (iv) randomized and observational studies. The data extracted included proportion of good neurodevelopmental outcome, year of publication, cryptogenic or symptomatic IS and LTTT.
Results: Of the 1436 citations screened, 55 articles were included in final analysis, with a total of 2967 patients. The pooled estimate for good neurodevelopmental outcome was 0.236 (95% CI: 0.193—0.286). There was no difference between the proportions of good neurodevelopmental outcome for the 21 studies published after 2004 [0.264 (95% CI: 0.197—0.344)] compared to the 34 studies published before 2004 [0.220 (95% CI: 0.168—0.283)] (Q value = 0.862, $p = 0.353$). The pooled estimate of good neurodevelopmental outcome for cryptogenic IS [0.543 (95% CI: 0.458—0.625)] was higher than symptomatic IS [0.125 (95% CI: 0.09—0.171)] (Q value = 69.724, $p < 0.001$). Risk ratio of LTTT <4weeks relative to >4weeks for good neurodevelopmental outcome of 8 studies was 1.519 (95% CI: 1.064—2.169).

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Conclusion: Neurodevelopmental outcome was overall poor in patients with IS and has not changed since the publication of first guideline on IS. Although cryptogenic IS has better prognosis than symptomatic IS, the outcome for cryptogenic IS remained poor. There was heterogeneity in neurodevelopmental outcome ascertainment methods, highlighting the need for a more standardized and comprehensive assessment of cognitive, behavioural, emotional and functional outcomes.

Introduction

Infantile spasms (IS) constitutes a distinct and often catastrophic form of epilepsy of early infancy, characterized by epileptic spasms, often accompanied by neurodevelopmental regression and an EEG finding of hypsarrhythmia. When all three components are present, the term ''West syndrome'' is commonly used. The incidence of IS ranges from 2 to 3.5 per 10,000 live births (Luthvigsson et al., 1994; Riikonen, 2001). IS associated with an underlying disorder is known as symptomatic IS (Jellinger, 1987; Riikonen, 2001), and IS with no detectable underlying cause is known as cryptogenic IS. Those with cryptogenic IS were considered to have a better prognosis. The diagnosis and management of IS posed significant challenges to the treating physician. The first evidence-based guideline on the medical management of IS was published in 2004 (Mackay et al., 2004), and the two drugs that were determined most likely to be effective in the short-term management were ACTH and Vigabatrin. The authors also concluded that at the time of publication of the guideline, the effect of medical treatment on long-term neurodevelopmental outcome remains unknown.

The aims of this systematic review and meta-analysis were to determine (i) the neurodevelopmental outcome of IS, (ii) if neurodevelopmental outcome has changed since the publication of the guideline on medical treatment of IS in 2004 and (iii) the effect of lead time to treatment (LTTT) on neurodevelopmental outcome.

Materials and methods

Data sources

A comprehensive literature search of Medline, Embase, Cochrane, PsycINFO, Web of Science and Scopus databases was conducted on Oct 15, 2013 (see Supplementary Table 1). We also searched bibliographies of reviews and original articles for additional articles. Searches were restricted to full-length English articles. No restriction was placed on the time of publication. References were exported and managed using EndNoteX7.

Study selection

The titles and abstracts were screened to identify those reporting on original research that involved IS or West syndrome and neurodevelopmental outcome. The full-length articles of abstracts identified in the first screen were obtained and screened for inclusion into the systematic review and meta-analysis. The inclusion criteria were: (i) reports of >5 patients with IS or West syndrome, (ii) neurodevelopmental outcome reported, (iii) outcomes reported after a mean/median follow-up of >6 months, (iv) the number of patients with good or poor neurodevelopmental outcome was reported, and (v) randomized controlled trials and observational studies. The instrument used to measure neurodevelopmental outcome, and the criteria used to define good neurodevelopmental outcome is shown in Supplementary Table 2. Duplicate publications, that is, studies with any overlapping patient populations from the same centre were excluded. Conference abstracts, unpublished studies, and surgical treatment of IS were excluded. Disagreements of eligibility were resolved through discussion.

Data extraction

Two reviewers extracted data from the selected articles. The following data were extracted: study information (author, year), total number of participants, condition information (cryptogenic or symptomatic), estimates of good neurodevelopmental outcome, instrument for measuring development or cognition, and follow-up period. Additional data extracted included LTTT and number of patients with good neurodevelopmental outcome treated within or beyond a pre-defined LTTT.

Study quality

The quality of the retrieved articles was assessed using a modified version of the Quality Index (Downs and Black, 1998). For the purpose of this review, the original 27-item has been reduced to 15 items (Ferro and Speechley, 2009). Each item was scored 0 (no/unable to determine) or 1 (yes), with a maximum score of 15. The three subscales are reporting (7 items), external validity (3 items), internal validity (4 items) and study power (1 item) (Ferro and Speechley, 2009). Higher scores indicated studies of higher methodological quality.

Data analyses

Data analyses were conducted using the Comprehensive Meta-Analysis software (Englewood, USA). To assess for significance between study heterogeneity, the Q statistic was calculated and I^2 was used to quantify the magnitude of between-study heterogeneity. If statistically significant heterogeneity was present (Q statistic $p < 0.05$), the pooled estimate of the proportion of good neurodevelopmental outcome and 95% confidence intervals (CIs) would be calculated