FULL-LENGTH ORIGINAL RESEARCH

Treatment of electrical status epilepticus in sleep: A pooled analysis of 575 cases

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Summary

Objective: Epileptic encephalopathy with electrical status epilepticus in sleep (ESES) is a pediatric epilepsy syndrome with sleep-induced epileptic discharges and acquired impairment of cognition or behavior. Treatment of ESES is assumed to improve cognitive outcome. The aim of this study is to create an overview of the current evidence for different treatment regimens in children with ESES syndrome.

Methods: A literature search using PubMed and Embase was performed. Articles were selected that contain original treatment data of patients with ESES syndrome. Authors were contacted for additional information. Individual patient data were collected, coded, and analyzed using logistic regression analysis. The three predefined main outcome measures were improvement in cognitive function, electroencephalography (EEG) pattern, and any improvement (cognition or EEG).

Results: The literature search yielded 1,766 articles. After applying inclusion and exclusion criteria, 112 articles and 950 treatments in 575 patients could be analyzed. Antiepileptic drugs (AEDs, n = 495) were associated with improvement (i.e., cognition or EEG) in 49% of patients, benzodiazepines (n = 171) in 68%, and steroids (n = 166) in 81%. Surgery (n = 62) resulted in improvement in 90% of patients. In a subgroup analysis of patients who were consecutively reported (585 treatments in 282 patients), we found improvement in a smaller proportion treated with AEDs (34%), benzodiazepines (59%), and steroids (75%), whereas the improvement percentage after surgery was preserved (93%). Possible predictors of improved outcome were treatment category, normal development before ESES onset, and the absence of structural abnormalities.

Significance: Although most included studies were small and retrospective and their heterogeneity allowed analysis of only qualitative outcome data, this pooled analysis suggests superior efficacy of steroids and surgery in encephalopathy with ESES.

KEY WORDS: Landau-Kleffner syndrome, Continuous spikes and waves during sleep, Epilepsy, Systematic review, Meta-analysis.

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Key Points

- Treatment of ESES syndrome is assumed to improve cognitive outcome
- This pooled analysis of 575 cases suggests that corticosteroids and surgery are most effective, whereas benzodiazepines may be an appropriate alternative
- Conventional antiepileptic drugs were reported less effective
- Evidence is limited to mostly retrospective case-series
- A randomized controlled trial is needed to provide definite answers for children with this often devastating epilepsy syndrome

Electrical status epilepticus in sleep (ESES) was first described in 1971 in six children with continuous spike-wave discharges persisting during whole night's non–rapid eye movement (NREM) sleep and subsiding on awakening. In the initial definition, epileptic activity had to be present during at least 85% of the NREM sleep electroencephalography (EEG), recorded on at least three occasions over a period of at least 1 month. More recently ESES cases with a spike-wave index of 50–85% were added to the spectrum.[1–4]

The clinical presentation of children with an ESES EEG pattern is variable. The most severe clinical syndrome can present with global cognitive regression in addition to clinical seizures. However, atypical cases have been described with developmental delay from birth or developmental arrest but no regression of cognitive functioning. The age at onset ranges from 1 to 14 years, with a peak between 4 and 8 years. Although seizures may be absent in up to 20% of cases, they are most often the presenting symptom, after which a developmental delay, a developmental arrest, or a regression in cognitive performance or behavior becomes evident. The Landau-Kleffner syndrome is closely related to ESES and is characterized by an acquired aphasia. In these patients, the cognitive symptoms focus mainly on the language domain. These clinical syndromes are referred to as "epileptic encephalopathy with ESES," ESES syndrome, or continuous spikes and waves during sleep (CSWS) syndrome. The EEG features of ESES frequently resolve spontaneously during puberty, whereas cognitive sequelae often remain.[5–7]

The concept of ESES was introduced describing patients with unknown etiology and has been expanded to patients with structural or genetic abnormalities. Recently, *GRIN2A* mutations were found to be present in up to 20%, mostly the familiar cases.[8–10] However, the etiology remains undetermined in the majority of patients.[11–13] An underlying inflammatory process has been suggested, mainly because steroids appear to be effective in the treatment of ESES syndrome. Inflammation may be either the cause of ESES or an epiphenomenon.[4,5,14,15] The mechanism of how continuous epileptic activity during sleep leads to cognitive decline is incompletely understood.

Although the importance of (early) treatment of convulsive status epilepticus has convincingly been demonstrated,[16] it remains to be established whether treatment of sleep-induced status epilepticus, the neurophysiologic hallmark of ESES syndrome, prevents permanent cognitive impairment. Treatment decisions are often based on expert opinion. Mainly small and retrospective studies have reported on the EEG effects or cognitive outcome of various conventional antiepileptic drugs, benzodiazepines, steroids, intravenous immunoglobulins, ketogenic diet, and epilepsy surgery. So far only one small randomized controlled trial has been performed that compares levetiracetam with placebo in patients with ESES.[17,18] The aim of this meta-analysis of individual patient data is to create an overview of all published treatments in children with epileptic encephalopathy with ESES and their effects on cognitive outcome or EEG pattern.

Methods

Search strategy

A literature search in PubMed and Embase was performed with various synonyms for ESES and treatment (Table S1). The initial search was performed in July 2012 yielding 1,663 articles. An update on the May 15, 2013, resulted in a total of 1,766 articles. The search strategy was defined by three investigators (VvD, BvdM, and FEJ). The search was performed by two authors (VvD and BvdM), and in rare cases of discordant judgment a third author was consulted (FEJ).

Study selection and data acquisition

Published studies were selected for possible inclusion if the effect of treatment on the EEG pattern or on cognitive functioning was described. All search results were reviewed based on title and abstract by applying the inclusion and exclusion criteria (Fig. 1). Of the selected articles, full texts were reviewed. A cross-reference check was performed to prevent missing relevant articles.

The corresponding authors of all selected studies were contacted for additional individual patient information including patient characteristics, qualitative and, if possible, quantitative EEG results, and information on cognitive functioning. Patients were included in the pooled analysis if sufficient data were reported in the article or provided by the author to allow analysis of individual treatment effect (i.e., if data on EEG or cognition were available before and after change in one treatment).

Quality assessment/reduction of bias

Case reports and small case series are likely to be influenced by publication and selection bias. To limit these

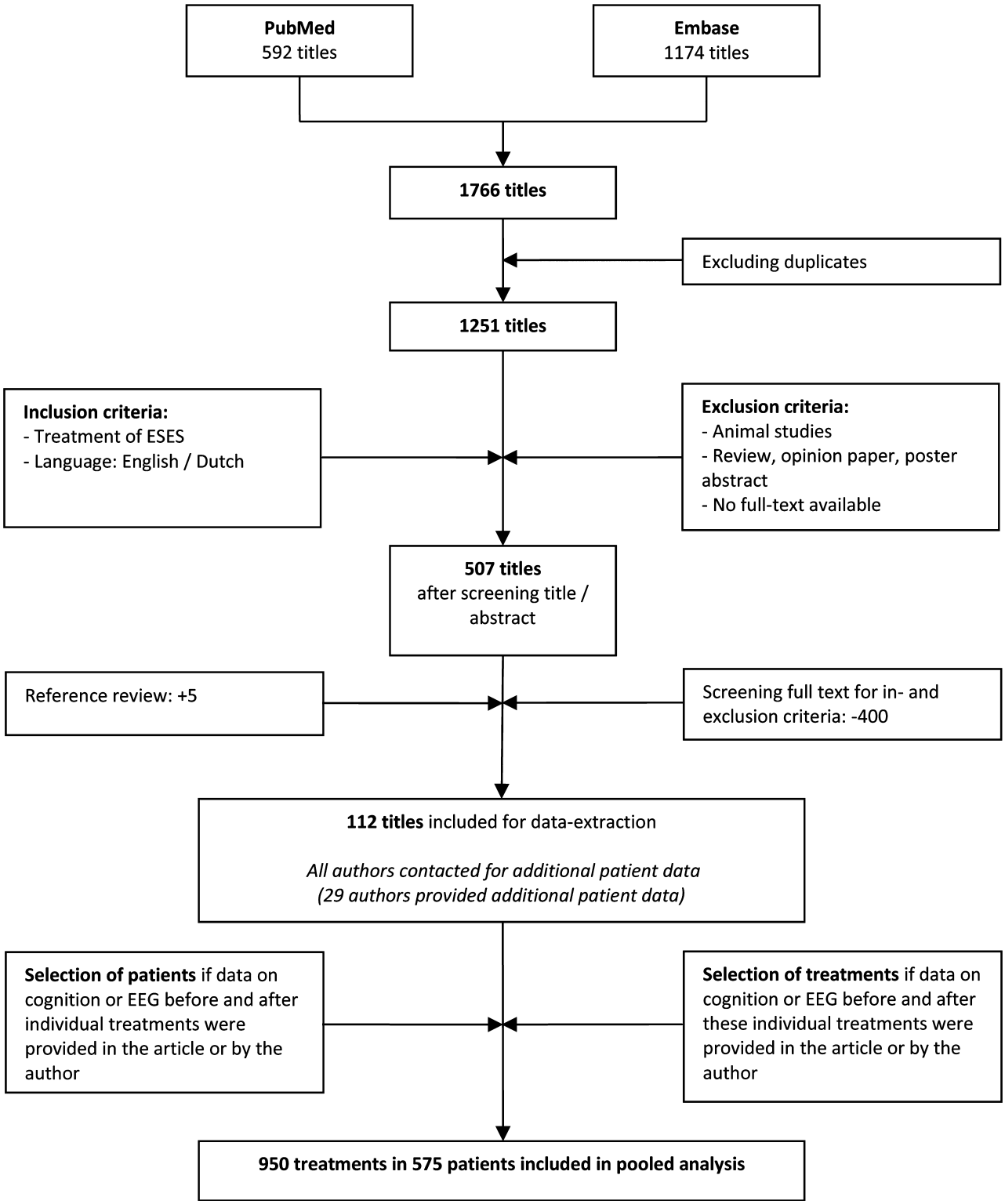

Figure 1.
Flow chart search and selection process.
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influences, a subgroup analysis was performed including only studies reporting all consecutive patients fulfilling the inclusion criteria in a given specific period. This approach has been recommended by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) study group.[19]

Data extraction and coding of data

A standardized data-extraction form, containing 44 variables, was created. Patient characteristics before and after onset of ESES, treatment regimen under analysis (dosage and duration), and effects on cognitive function and EEG characteristics were included. Extraction of raw data from all studies was performed by one author (VvD). A random selection of 10% of relevant articles was checked by a second author (BvdM). There were some small differences in judgment that were settled by consensus meeting. None of these differences concerned the primary outcome (cognitive or EEG improvement).

Primary outcome assessment

The three main outcome measures were improvement in cognitive function, EEG pattern, and any improvement (cognition or EEG). To allow a pooled analysis, all available data were coded according to the following criteria:

Cognition: improvement was defined primarily by the judgment of the author of the original article or as a gain of at least 10 IQ points after start of treatment (when both pre- and post-treatment IQs were available).

EEG: improvement was primarily defined as an improvement of the sleep-induced status epilepticus pattern, as subjectively indicated by the author, or as a reduction of at least 25% in Spike Wave Index (SWI, if pre- and posttreatment spike wave indices were given).

Any improvement: qualitative or quantitative improvement of either cognition, EEG, or both.

Coding of data was performed by two authors: BvdM and FEJ for seizure type and EEG data. The other variables were coded by VvD and BvdM. In case of discordant judgment by the two reviewers the individual patient data were evaluated by a third independent reviewer (VvD or FEJ).

Statistical analysis

The baseline characteristics and effect of individual treatments were analyzed using IBM SPSS Statistics Software version 20. The baseline characteristics of the patients from consecutive cohorts were compared to those of the total study population, using the chi-square test for categorical variables (with Yates' Correction for Continuity for binomial variables) and the Mann-Whitney *U*-test for continuous variables (as these variables were not normally distributed). The same tests were applied to compare patients with known etiology to those with unknown etiology. The proportion of patients that showed improvement after the analyzed treatment is reported for all patients and for the subgroup of consecutive patients. The corresponding 95% confidence intervals were calculated using normal approximation methods.

To identify variables that influence treatment outcome, a predictor analysis was performed with univariate and multivariate logistic regression analysis. Univariate analysis was performed for treatment category, gender, age at diagnosis, interval from diagnosis to treatment under evaluation, history of febrile seizures, mental development before the onset of ESES, presence of computed tomography (CT) or magnetic resonance imaging (MRI) abnormalities and for the number of previous treatments. This analysis was first performed including only "complete cases" regarding included determinants, that is, cases for which complete predictor data were available. To account for missing data, a sensitivity analysis using multiple imputation methods was then performed, a procedure recommended for datasets with a significant proportion of missing data.[20] All analyzed possible predictors with missing data were included in the model to allow an analysis of all treatments. Ten imputed datasets were created and a pooled analysis was carried out. The same procedure was used to perform a multivariate logistic regression analysis including treatment category and other possible predictors. There was a substantial proportion of missing data for most possible predictors. Therefore, a multivariate analysis including only complete cases for all predictors would result in an analysis of only a small number of patients and is not reported.

Results

Study and patient selection

The search strategy and study and patient selection are shown in Figure 1. Descriptive information of the 112 included studies is available in Table S2. The included articles were published between 1977 and 2013. Some of these 112 articles showed overlap in patient population and were therefore included as 98 patient cohorts (grouping patients from the same center and integrating data of duplicate cases). From 94 (96%) of these 98 cohorts, cognitive outcome was reported, and from 88 (90%) EEG outcome. The treatment categories that were analyzed were conventional antiepileptic drugs in 48 cohorts, benzodiazepines in 23 cohorts, steroids in 41 cohorts, surgery in 18 cohorts, and other treatments in 11 cohorts. The consecutive subgroup consisted of patients reported in 23 articles, which could be included as 15 different patient cohorts. The number of patients per included cohort was substantially higher in the consecutive subgroup (mean 23, median 10) compared to the total included population (mean 6, median 2).

Additional individual patient data were provided by 29 authors for 413 patients, of whom 675 individual treatments could be included in this analysis. By combining the data of 112 original articles with additional information provided by the authors, data of 575 patients could be included in whom 950 individual treatments and their effect were reported. The subgroup of consecutive patients consisted of 282 patients with 585 individual treatments.

Patient characteristics

A large majority (94%) of patients had at least one seizure, and their first seizure occurred at a median age of three

Table 1. Patient characteristics

	All patients[a]	"Consecutive patients"[a,b]	p-Value for comparison[c]
Number of patients	575	282	
Male	333/550 (61%)	166/282 (59%)	0.69
Abnormal perinatal history	138/341 (40%)	118/256 (46%)	0.20
Positive family history for epilepsy	49/238 (21%)	41/196 (21%)	1.00
History of febrile seizures	32/497 (6%)	22/204 (11%)	0.07
Mean/median age at seizure onset	44/42 months (n = 384)	42/36 months (n = 212)	0.16
Mean/median age at developmental delay, arrest or regression	65/60 months (n = 306)	68/63 months (n = 205)	0.24
Mean/median age at ESES diagnosis	75/72 months (n = 416)	77/78 months (n = 240)	0.20
CT/MRI abnormalities	213/461 (46%)	147/273 (54%)	0.05
Presumed etiology			
Genetic	29/432 (7%)	26/266 (10%)	0.28
Structural	215/432 (50%)	136/266 (51%)	
Metabolic	2/432 (1%)	0/266 (0%)	
Unknown	186/432 (43%)	104/266 (39%)	
Abnormal development prior to ESES onset	167/362 (46%)	141/261 (54%)	0.06
Type of (previous) seizures			
None	26/464 (6%)	7/261 (3%)	0.00
Focal	208/464 (45%)	93/261 (36%)	
Generalized	98/464 (21%)	43/261 (17%)	
Both	132/464 (28%)	118/261 (45%)	
Frequency of seizures at inclusion			
None	43/261 (17%)	20/209 (10%)	0.16
Monthly	97/261 (37%)	88/209 (42%)	
Weekly	37/261 (14%)	34/209 (16%)	
Daily	84/261 (32%)	67/209 (32%)	
Mean/median follow up duration after start of treatment	36/24 months (n = 349)	36/24 months (n = 172)	0.15
Number of treatments	950	585	

[a]Patient characteristics are shown as number of patients with this characteristic/total number of patients for whom this characteristic is available and the corresponding percentage.
[b]"Consecutive patients" = patients included from studies reporting all consecutive patients fulfilling the inclusion and exclusion criteria in a specified period.
[c]p-Values are reported for the comparison of baseline characteristics of the patients from consecutive cohorts to those of the total study population. The two groups were compared using the chi-square test for categorical variables (with Yates' correction for continuity for binomial variables) and the Mann-Whitney *U*-test for continuous variables.

and a half years, two and a half years prior to ESES diagnosis. Seizures were focal in 45% and generalized in 21%, and in 28% of patients both focal and generalized seizures were reported. Abnormal development was already present before ESES onset in 46% of patients. In 46% of all included patients, structural abnormalities were seen on CT or MRI, whereas a genetic or metabolic abnormality was reported in only a small proportion of patients (7% and 1%, respectively). The available baseline characteristics of all patients, and of those reported consecutively, are displayed separately in Table 1. Except for a different distribution in seizure types, no significant differences between both groups were detected. A comparison between patients with known etiology and those with unknown etiology revealed a larger proportion with an abnormal perinatal history, abnormal development before ESES onset, and CT/MRI abnormalities in patients with known etiology. These patients also had more frequent seizures, and a smaller proportion of them had a positive family history for epilepsy (Table S3).

Treatment response

The overall treatment effect ("any improvement") is reported including 95% confidence intervals in Table 2. Any improvement was seen in 49% of patients treated with conventional antiepileptic drugs (AEDs) and in 68% of patients treated with benzodiazepines. Treatment with steroids was associated with any improvement in 81% of patients, surgery in 90%, and other treatments in 54% of patients. Surgical techniques applied in 62 patients included multiple subpial transection (n = 31), hemispheric surgery (n = 13), corpus callosotomy (n = 9), lobar resection (n = 5), multilobar resection or disconnection (n = 2) and in two patients underwent other surgical procedures (cystoperitoneal shunting and an unspecified procedure). Cognitive improvement was seen after treatment with AEDs in 40%, benzodiazepines in 50%, steroids in 78%, and after surgery in 80%. EEG improvement was seen after treatment with AED in 45%, benzodiazepines in 59%, steroids in 70%, and after surgery in 80% of the patients (Table 2).

Of 771 included treatments (81% of all included treatments), outcome data were separately reported for cognition and EEG (for the remainder only data on "any improvement" were available). In these cases any improvement was seen after 470 treatments (61%). Of the 470 treatments that were associated with any improvement, 77 treatments (16%) were associated with EEG improvement without

Table 2. Reported treatment effect (percentage improved) in patients with encephalopathy with ESES

	All/consecutive subgroup	Any improvement, % (95% CI)	Cognitive improvement, %[a] (95% CI)	EEG improvement, %[b] (95% CI)
AED	All (n = 495)	49 (44–53)	40 (23–31)	45 (41–50)
	Cons. (n = 310)	34 (29–39)	32 (26–37)	33 (28–38)
Benzodiazepines	All (n = 171)	68 (61–75)	50 (42–59)	59 (52–67)
	Cons. (n = 107)	59 (50–68)	45 (35–54)	46 (37–56)
Steroids	All (n = 166)	81 (75–87)	78 (72–85)	70 (62–77)
	Cons. (n = 100)	75 (67–83)	70 (60–79)	68 (58–77)
Surgery	All (n = 62)	90 (83–98)	80 (70–90)	80 (68–91)
	Cons. (n = 30)	93[c]	83 (70–97)	74 (58–91)
Other	All (n = 56)	54 (41–67)	67 (51–82)	29 (15–43)
	Cons. (n = 38)	58 (42–74)	71 (53–89)	26 (8–44)
Total	All (n = 950)	61 (58–64)	53 (49–56)	54 (50–56)
	Cons. (n = 585)	50 (46–54)	44 (40–49)	43 (39–47)

N, number of treatments analyzed; any improvement, improvement of cognition or EEG; missing n, missing number of treatments for this outcome; 95% CI, 95% confidence interval; AED, conventional antiepileptic drugs.
[a]For 126 (all patients)/40 (consecutive subgroup) treatments cognitive outcome was missing.
[b]For 68 (all patients)/25 (consecutive subgroup) treatments EEG outcome was missing.
[c]No 95% confidence interval mentioned due to small sample size and large proportion.

Table 3. Odds of treatment response (any improvement)

Treatment	OR (95% CI) Univariate (complete case)	OR (95% CI) Univariate (MI)	OR (95% CI) Multivariate (MI)
AED	Reference	Reference	Reference
Benzodiazepines	**2.2 *(1.5–3.2)*** *	**2.2 *(2.0–2.5)*** *	**2.1 *(1.4–3.1)*** *
Steroids	**4.4 *(2.9–6.7)*** *	**4.4 *(3.9–5.0)*** *	**4.2 *(2.7–6.5)*** *
Surgery	**9.8 *(4.1–23.1)*** *	**9.8 *(7.5–12.6)*** *	**8.6 *(3.5–21.4)*** *
Other	1.2 *(0.69–2.1)*	**1.2 *(1.0–1.4)*** *	1.1 *(0.6–2.0)*
Patient characteristics			
Male gender	1.2 *(0.9–1.6)*	1.2 *(0.9–1.5)*	**1.4 *(1.0–1.8)*** *
Age at diagnosis	1.0 *(1.0–1.0)*	1.0 *(1.0–1.0)*	1.0 *(1.0–1.0)*
Interval diagnosis—treatment	1.0 *(1.0–1.0)*	1.0 *(1.0–1.0)*	1.0 *(1.0–1.0)*
Febrile seizures	1.2 *(0.7–2.1)*	1.3 *(0.7–2.3)*	1.4 *(0.8–2.6)*
Abnormal development before ESES onset	**0.6 *(0.5–0.9)*** *	**0.6 *(0.5–0.8)*** *	0.6 *(0.4–0.8)**
CT/MRI abnormalities	0.8 *(0.6–1.1)*	0.8 *(0.6–1.1)*	1.0 *(0.7–1.4)*
CT/MRI abnormalities in nonsurgically treated patients	0.7 *(0.5–1.0)**	0.7 *(0.5–1.0)*	1.0 *(0.7–1.4)*
Number of previous treatments	1.2 *(1.1–1.4)**	1.1 *(0.9–1.3)*	1.1 *(0.9–1.0)*

OR, odds ratio; AED, conventional antiepileptic drugs; complete case, complete case analysis; 95% CI, 95% confidence interval; MI, pooled analysis after using multiple imputation methods. Confidence intervals are indicated by italic type.
Multivariate analysis was performed using patient characteristics and treatment category as covariates.
*$p < 0.05$.

cognitive improvement and 69 treatments (15%) were associated with cognitive improvement without EEG improvement. After 324 treatments (69%), both cognitive performance and EEG were reported to have improved. A subgroup analysis was performed on the 282 patients who were treated consecutively in reporting centers, with 585 individual treatments. In this subgroup improvement percentages were lower for AEDs (34%), benzodiazepines (59%), and steroids (75%). The percentage of patients who improved after surgery was similar in this subgroup (93%).

Predictors of treatment response

Subsequently, we analyzed possible predictors of treatment effect, including treatment category and patient characteristics (Table 3). "Any improvement" was associated with benzodiazepines, steroids, and surgery when compared to treatment with AEDs. An abnormal development of patients prior to ESES onset was associated with no improvement after treatment. The presence of CT/MRI abnormalities in nonsurgically treated patients and a lower number of previous treatments were significant predictors of poor treatment response in univariate analysis. However, this correlation did not sustain in multivariate analysis. These variables showed substantial differences among the treatment categories (Table S4). Male gender predicted better treatment response only in multivariate analysis of pooled data after multiple imputation. Separate analyses of possible predictors of EEG

and cognitive outcome provided comparable results (Table S5).

Discussion

The results of this individual patient data meta-analysis suggest that treatment with steroids and surgery (in suitable candidates) are most effective in the treatment of ESES syndrome. Treatment success percentages (for EEG or cognitive improvement) were reported between 80% and 90% for steroids and surgery, and these results are relatively preserved in the consecutive subgroup analysis. Benzodiazepines may be considered an appropriate alternative, with 69% and 59% overall treatment success in all and consecutive patients, respectively. Conventional AEDs were reported less effective in the included studies, with improvement seen in 49% and 34% of all patients and consecutive patients, respectively. Improvement most frequently reflected both EEG and cognitive outcomes. The strong influence of the treatment category chosen on treatment effect persists in a multivariate analysis with possible predictors. Among patient characteristics, developmental level before the onset of ESES was the only predictor with sustained significance in all analyses.

Normal development before the onset of ESES was found to be a significant predictor of treatment success, and this association was significant in all analyses. This confirms earlier observations that IQ, presence of cognitive impairment, and duration of cognitive impairment before the start of a treatment predict treatment response in patients with ESES.[13,21,22] However, in many patients it is unclear if "preexistent" abnormal development was unrelated to, or a first sign of "late recognized" ESES. Diagnostic delay is an important issue in children with epilepsy (especially in syndromes with nonconvulsive seizures or status epilepticus) and is associated with more severe cognitive impairment.[23] In our multivariate analysis the number of previous treatments was not associated with treatment efficacy. This contrasts to the results of a large study of AEDs for epilepsy in general, where a strong decrease in efficacy is seen after failure of a previous AED.[24] A possible explanation is that our approach focuses on cognition and EEG abnormalities and not on seizure freedom. Some treatments may have been prescribed primarily to control seizures, although they were reported in the context of an ESES diagnosis. In general, we hypothesize that there is a tendency to initially prescribe a conventional AED (especially in patients presenting with frequent seizures) or benzodiazepine and to consider corticosteroids and surgery (often more successful) only in refractory cases. This hypothesis is supported by the observation that the mean number of previous treatments is higher for treatment with steroids and surgery than with AEDs in our dataset (Table S4). These differences could potentially result in higher success rates for the drugs prescribed later in the course of ESES syndrome. Overall, better outcomes have been reported in cases with unknown etiology, as compared to cases with structural lesions, except for surgically treated patients.[11,13] We found that a structural lesion predicts unsuccessful treatment in univariate analysis for nonsurgical treatments. However, this association could not be confirmed in multivariate analysis.

The results have to be interpreted in the setting of data acquisition. Many of the included studies are small and retrospective. These case reports and small case series may have been published because of an exceptionally good or bad treatment effect, causing selection and publication bias. This is consistent with the observed differences in treatment effect among all patients and in the subgroup of consecutive patients. The only randomized controlled trial compared levetiracetam treatment with placebo and found a significant reduction in spike-wave activity. No significant influence on cognitive performance was observed. The broad inclusion criteria of this trial (SWI >30%, many patients with only behavioral disturbances) and small sample size (n = 18 after exclusion of dropouts) limit the clinical relevance of these findings. This study could not be included in this meta-analysis as insufficient individual patient data were available.[17,18] In addition, the large heterogeneity of the included studies allowed analysis of qualitative outcome data only. Most authors clearly reported whether cognitive or EEG improvement was seen after treatment. We preferred to use quantitative data; however, this was not possible due to missing quantitative data for a majority of patients. Furthermore, due to the limited size of the included studies it was not possible to account for heterogeneity between studies in the analysis. The analysis was limited to a fixed-effect analysis of the individual patient data, and data were treated as a single study dataset. Moreover, specific treatments that may differ in efficacy had to be clustered in our analysis, because the quality and quantity of data were insufficient for valid treatment-specific analysis. Furthermore, adverse effects and relapse rates are not included in the analysis because of missing data. Finally, we could not include treatment duration and dosage in the analysis as these were not reported in the majority of studies. Because follow-up periods are heterogeneous in different studies, we were not able to evaluate outcomes at comparable points in time. This point is particularly relevant in a disorder where natural fluctuations in severity occur over time. In this context, a positive or negative effect may be incorrectly attributed to a drug effect when it may have represented just a natural fluctuation in the course of the disease. Only prospective controlled trials with long follow-up will be able to distinguish natural fluctuations in the disease from treatment effects.

The effect of treatment on seizure frequency was not included in this study, as we believe that cognitive disturbances and EEG abnormalities are the hallmarks of the syndrome and we considered these the most important outcomes of specific treatment for ESES syndrome.

Despite these challenges, this study provides valuable information. To our knowledge, it is the first pooled analysis of individual patient data evaluating the effect of different treatment regimens in patients with epileptic encephalopathy with ESES. The individual patient data meta-analysis approach allowed us to investigate the effect of a large number of individual treatments by combining the information from original articles with additional data provided by many authors. The adoption of an individual patient data analysis design has several advantages as compared to an aggregate analysis of literature reports only. Consistent inclusion and exclusion criteria can be used across studies and individual patients. In addition, missing data of individual patients can be observed and accounted for in the analysis at the individual level. Furthermore, studies that contain overlapping sets of patients can be identified and excluded from analyses, and the use of individual patient data enhances the possibilities of statistical testing.[25] We performed a subgroup analysis of consecutive patients, reducing the effects of publication bias. In addition, a predictor analysis was reported. By using multivariate logistic regression analysis we limited the influence of many possible confounders.

Our data suggest that surgery may be the most effective treatment for children with ESES syndrome. However, many of these surgically treated patients had a structural lesion and it is unlikely that surgery is equally effective in patients with ESES syndrome of unknown etiology, and it is unclear which technique can be applied in these patients. Multiple subpial transection (MST) has been suggested as a treatment option in Landau-Kleffner syndrome, but evidence is limited and it is unclear whether MST can also be beneficial in ESES patients with cognitive deficits outside the language domain.[26] Furthermore, adverse effects were not included in this analysis and reported qualitative improvement may not be sufficient to justify the risk of surgery. However, it is likely that surgery is underutilized and that surgery should be considered sooner in the treatment of ESES patients with regression of cognitive functioning and a structural lesion that is accessible for resection or disconnection.

In summary, this study provides new insights by combining the available evidence from mostly small and retrospective studies. Despite the large number of patients and treatments evaluated in the pooled analysis, no definite conclusions can be drawn on treatment effects. A very recent study showed that clinicians' approaches to the treatment of ESES syndrome differ a lot and although the current study is a step forward, no general recommendations can be made.[27] Further research is urgently needed to provide definite answers regarding treatment of children with this, often devastating, epilepsy syndrome. A randomized controlled European multicenter trial was recently initiated and may provide further directions (RESCUE ESES, Randomized European trial of Steroids versus Clobazam Usage for Encephalopathy with Electrical Status Epilepticus in Sleep).

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Search strategy in PubMed and Embase (subsequent rows were linked by "OR").

Table S2. Included studies.

Table S3. Distribution of patient characteristics among patients with known versus unknown etiology.

Table S4. Distribution of significant predictors in univariate analysis, not in multivariate analysis among treatment categories.

Table S5. Predictors of treatment response (cognition, EEG).