Official Journal of the European Paediatric Neurology Society

Original article

Treatment of electrical status epilepticus in sleep: Clinical and EEG characteristics and response to 147 treatments in 47 patients

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ARTICLE INFO

Article history:
Received 17 November 2016
Received in revised form
11 August 2017
Accepted 26 August 2017

Keywords:
Electrical status epilepticus in sleep
ESES
CSWS
Landau–Kleffner syndrome
LKS
EEG

ABSTRACT

Objective: Electrical status epilepticus in sleep (ESES) syndrome is characterized by near-continuous sleep-induced epileptiform activity and acquired cognitive deficits. Treatment is assumed mandatory to improve cognitive outcome. We aimed to compare EEG characteristics, subjective evaluation and objective neuropsychological assessment as measures to evaluate treatment efficacy, and to analyze possible predictors.

Methods: We retrospectively included patients with ESES syndrome treated in our center. Treatment effect was analyzed on sleep EEG spike wave index (SWI) and cognitive functioning.

Results: 47 patients had 147 (43 steroid and 104 non-steroid) treatments. Cognitive improvement was reported after 36% of treatments at first follow-up and 45% of treatments at last follow-up. The median SWI change for treatments resulting in subjective cognitive improvement was −44%, and 0% for those not resulting in subjective cognitive improvement at first follow-up ($p = 0.008$) and −50% vs. +5% at last follow-up ($p = 0.002$). No clear association between subjective cognitive improvement and IQ change, and between SWI and IQ change was found. By means of logistic regression we found that steroid treatment, as compared to non-steroid treatment, was associated with cognitive improvement at first follow-up (multivariate OR after multiple imputation 2.5, 95% CI 1.1–5.7), while at last follow-up, higher age at diagnosis was related to cognitive improvement only in univariate analysis (OR 1.02, 95% CI 1.01–1.04).

Conclusions: We found that in children with ESES, cognitive improvement after treatment was strongly associated with SWI decrease, while it was not reflected by a significant IQ increase. Steroid treatment was most successful in improving cognitive performance.

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https://doi.org/10.1016/j.ejpn.2017.08.006

1. Introduction

Encephalopathy with electrical status epilepticus in sleep (ESES), ESES syndrome and continuous spikes and waves during sleep (CSWS) have been used interchangeably to define patients with an EEG pattern of near-continuous spike and wave discharges during non-REM sleep and acquired neuropsychological deficits. Typical cases have a spike wave index (SWI) of at least 85% during non-REM sleep, while in recent years cases with a SWI of 50–85% were added to the spectrum.[1–5] This epilepsy syndrome is typically age related, presenting at an age between 2 and 14 years, with a peak at 4–8 years. Although seizures are present in the majority of patients and can form a serious burden, cognitive decline is the most frightening symptom of the disorder.[2,6,7] While the ESES EEG pattern resolves during puberty, cognitive deficits often remain.[2]

Structural brain abnormalities have been reported in 20–50% of patients with ESES and an important role of the thalamus has become evident from recent studies.[8–12] Also, etiological as well as treatment studies have linked inflammation to ESES.[13,14] How ESES leads to cognitive decline is incompletely understood. The epileptiform activity has been suggested to interfere with normal recuperative functions of sleep, thereby adversely affecting learning abilities, language, memory and other cognitive domains.[15,16]

Early and adequate treatment of ESES is assumed mandatory to prevent further cognitive decline and possibly recover skills that were lost. A recent study has shown that treatment strategies vary widely between clinicians.[17] No adequately powered randomized controlled trials are available and evidence is limited to mostly small and retrospective case series. A pooled analysis of 575 cases reported in literature revealed that conventional anti-epileptic drugs are often not successful in improving cognitive outcome, while benzodiazepines and steroids seem better alternatives. Surgery is highly successful in selected cases.[8] Although a causative relation is assumed, it is unclear whether resolution of the ESES EEG pattern is necessary for treatment efficacy or can serve as a predictive biomarker.[18] Cognitive improvement should be leading, but its assessment is often based on subjective measures (parents' opinion, clinician's judgment).

In a large, single center cohort study of patients with ESES syndrome we aimed to address the following questions: (1) What is the effect of treatment on cognitive functioning and EEG-abnormalities? (2) Is there an association between EEG response to treatment, measured as a change of the spike-wave index, subjective cognitive functioning and IQ test results?, and (3) what are predictors of cognitive outcome?

2. Methods

2.1. Patients

We retrospectively selected all children with epileptic encephalopathy with ESES, further called ESES syndrome, who consulted the pediatric neurology clinic of the UMC Utrecht, the Netherlands between January 2002 and December 2013. The study was approved by the medical ethics committee who judged that the Dutch Medical Research Involving Human Subjects Act did not apply.

Patients were selected according to predefined inclusion criteria: 1) a diagnosis of ESES syndrome before the age of 12 years, since improvement of the ESES EEG pattern afterward is expected in the natural course of the disorder,[19] 2) availability of a diagnostic EEG performed during sleep (either a whole night EEG or a nap EEG after sleep deprivation) with a SWI during sleep of at least 50% and 3) presence of acquired cognitive deficits or behavior disorders, including cases with a clear deterioration in the context of a pre-existing delay.

To analyze the effect of treatment on cognitive functioning and follow up EEG, the treatments were included if they fulfilled the following criteria: 1) follow-up duration of at least one month after start of treatment (without another concurrent treatment change), 2) availability of a sleep deprived or whole night EEG before and after this treatment and 3) availability of information on (subjectively or objectively assessed) cognitive functioning and behavior before and after the treatment. Treatments were excluded from the analysis if they were given before ESES was diagnosed, if more than one pharmacologic treatment was started at the same time or if the treatment was given at a subtherapeutic dose.

2.2. Clinical data collection and coding

Baseline data on gender, perinatal history, etiology (MRI, genetic and metabolic test results), neurodevelopment, behavior, history of febrile seizures, family history of epilepsy, the date of diagnosis of ESES, the age at diagnosis of ESES, presence of seizures, age at seizure onset, seizure semiology, the IQ at diagnosis of ESES and the total number of treatments for ESES was extracted from the medical charts.

In addition the following data was collected for individual treatments: date at start and stop of treatment, duration of treatment, treatment type and category (AED, benzodiazepines, steroids, surgery, IVIG or other), dosages, and number of previous treatments for ESES. If a patient was treated with steroids, the first follow-up after completing the intended schedule (in most cases 6 monthly methylprednisolone pulses) was considered first follow-up after treatment. If a patient was treated with daily oral steroids, any follow-up visit at least one month after treatment initiation was considered the first follow up. If multiple different steroid regimens were given in one patient, each was counted as a single treatment (e.g. 6 methylprednisolone pulses and a year later oral prednisolone treatment were included as two separate steroid treatments). For each treatment, information on cognitive functioning (based on neuropsychological assessment, when available, or based on the report of the treating doctor), behavioral problems (scored as mild, moderate or severe according to Massa et al.)[20] and seizure frequency before and after treatment were collected. The follow-up results after a treatment were collected for both first-follow up after reaching the intended dosage as well as last follow-up before the start of another treatment or the last follow-up before May 1, 2014. If only one follow-up visit was available, this was included as the first follow-up after treatment.

2.3. EEG data acquisition and quantification of epileptiform activity

All EEGs were recorded at 21 scalp electrodes according to the international 10–20 system. All EEG data was collected using the SystemPlus Evolution Micromed software package. SWIs of EEGs were calculated by an experienced EEG technician (SD) or other researchers (CA or BvdM) and 20% was checked by an experienced epileptologist (FEJ).

The SWI of each EEG was calculated in an epoch of 10 min (600 s) duration, starting 5 min after the alpha attenuation or after sleep clinically had commenced. The number of seconds containing epileptiform discharges was divided by the total number of seconds in the epoch (600) and multiplied by 100 to reflect the SWI as a percentage.

2.4. Outcome definition

Primary outcomes for this study were change in cognitive functioning and SWI change. Subjective improvement of cognitive functioning was defined as present or absent based on medical chart review (parents' and clinician's judgment). If a neuropsychological assessment was available before and after an individual treatment, total IQ data were also used for analysis of treatment efficacy. Secondary outcomes were change in behavior, seizure frequency and side-effects of treatment.

2.5. Statistical analysis

The SWI and IQ data were assessed for normality with Q–Q plots and with a Shapiro–Wilk test. Based on the distribution of the data, either a parametric (student's t-test) or non-parametric test (Mann–Whitney U-test) was used for comparison of two groups. The agreement between the SWIs calculated by two researchers was assessed with a Bland–Altman plot and a two dependent samples test. Two independent samples tests were used to investigate the possible association between change in subjectively assessed cognitive functioning, IQ change and SWI change.

A complete case logistic regression analysis was performed to investigate possible predictors of cognitive improvement after treatment. Baseline variables that were considered of potential relevance were included in a univariate analysis. We also performed multiple imputation in SPSS (regression method) to create 10 imputed datasets using these variables and the output variables to account for missing data. Based on the results of the univariate analysis after multiple imputation, the variables with a p-value below 0.2 were subsequently entered in a multivariate model.

3. Results

3.1. Patient characteristics

Of 57 patients who were diagnosed with ESES syndrome, 47 (82.5%) met the inclusion criteria. Nine patients were excluded because SWIs did not exceed 50%, one patient never received treatment. The mean age at diagnosis of the included patients was 6.8 years and a male preponderance was seen (61.7%). Twenty-two patients had MRI abnormalities: 13 patients had vascular abnormalities, 7 patients had developmental malformations and 2 patients had hippocampal sclerosis. Genetic abnormalities included a KCNB1 mutation and copy number variants on chromosome 5, 9, 7, 15 and 16. In the 47 included patients 148 treatments were given. One treatment was excluded because insufficient clinical data was available. The patient and treatment selection process is shown in Fig. 1. Baseline characteristics of the included patients are shown in Table 1.

3.2. Effect of treatment on cognitive performance and EEG abnormalities

The effect of treatment on cognitive performance was assessable for 119 (81%) treatments at first follow-up (mean follow-up 4.7 months) and 94 (63.9%) at last follow-up (mean follow-up 13.1 months). Cognitive improvement was reported after 36% of treatments at first follow-up and 45% of treatments at last follow-up. For those treatments for which an IQ before and after this individual treatment was available, the mean change in IQ was −1.7 points (median −0.5, n = 40) at first follow-up and −1.5 points (median −2.0, n = 11) at last follow-up.

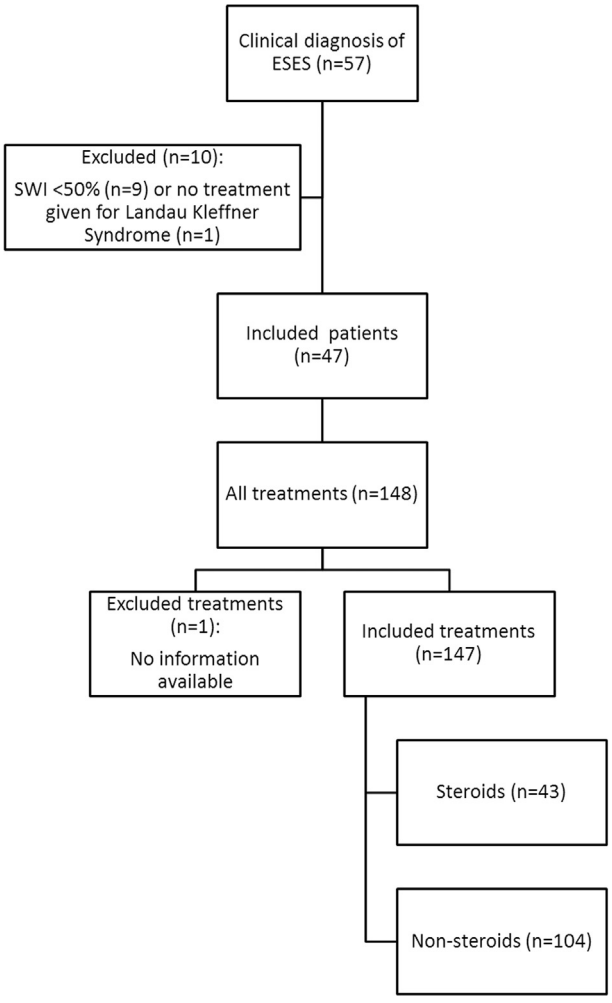

Fig. 1 – Flow chart patient and treatment selection.

Table 1 – Baseline patient characteristics (n = 47).

Mean/median age at ESES diagnosis (years, SD)	6.8/6.8 (2.3) n = 47
Male gender	29 (62%)
Complicated pregnancy	11/47 (23%)
Complicated delivery	17/47 (36%)
Abnormal MRI	22/45 (49%)
Abnormal genetic testing	9/28 (32%)
History of febrile seizure	9/45 (20%)
Family history positive for epilepsy/seizures	8/47 (17%)
Abnormal development before ESES diagnosis	18/45 (40%)
Mean/median total IQ at diagnosis (SD)	76/76 (22) n = 44
Abnormal motor development	14/47 (30%)
Abnormal language development	16/47 (34%)
Behavioral deficit[a]	36/46 (78%)
Any seizures	42/45 (93%)

Notes:
For categorical variables the number of patients with this finding and the total number of patients for whom this variable is available are shown. Percentages shown represent the proportion of the patients for which this variable is available.
[a] Behavioral deficit as reported at time of ESES diagnosis.

The calculation of spike-wave indices showed good agreement between researchers (p for Wilcoxon signed ranks test 0.655). The median SWI change (compared to before treatment) was −5% (mean −21%) at first follow-up and −24% (mean −31%) at last follow-up.

A subgroup analysis was performed, including only the first treatments after the diagnosis of ESES (n = 44). At first follow-up after first treatments, subjective cognitive improvement was reported in 46% (17 of 37), and the median change in spike-wave index was −23% (mean −32%, n = 30). At last follow-up after first treatments cognitive improvement was reported in 57% (16 of 28) and the median change in spike-wave index was −21% (mean −26%, n = 15). For those patients for whom an IQ test was available both before and after this first treatment, not interfered by another treatment change, the median IQ change was 0 (mean −1, n = 21). If any IQ measurement after treatment (regardless of other treatments) is considered, the median IQ change was −1 (mean −1, n = 28).

3.3. *Association of subjectively reported cognitive improvement and measured IQ change*

For all treatments (n = 33) where IQ scores were available both before and after therapy, we correlated the subjective evaluation by parents with the objectively measured change in IQ scores (Table 2). At first follow up, treatments that – according to parents – led to improvement were associated with a median IQ change of only +2.0 points (mean −0.4). Those without subjective improvement were associated with a median IQ change of −7 (mean −4.5, p = 0.32). At last follow-up, IQ scores and subjective data both before and after therapy were available for only 8 treatments (after 7 of these treatments cognitive improvement was reported) and no significant association was found.

3.4. *Association of subjectively reported cognitive improvement and SWI change*

For all treatments where sleep EEGs were available both before and after therapy, we correlated the evaluation by parents with the change in SWI (Table 2). At first follow up (n = 62), treatments that – according to parents – led to improvement were associated with a median SWI change of −44% (mean −40%). Despite this decrease in SWI, 48% had EEGs that still fulfilled the criteria of ESES (SWI > 50%). Those without subjective improvement were associated with a median SWI change of 0% (mean −8%). The SWI change was significantly different in the patients with subjective cognitive improvement, compared to those without subjective improvement (p = 0.008). At last follow-up, treatments (n = 28) that – according to parents – led to cognitive improvement were associated with a median SWI change of −50% (mean −45%), although 53% still fulfilled the criteria of ESES. Those without subjective cognitive improvement were associated with a median SWI change of +5% (mean +4%). Again, this difference is clearly significant (p = 0.002).

Table 2 – Comparison of IQ change and SWI change between patients who showed subjective cognitive improvement at first follow-up and patients who did not.

		First follow-up		Last follow-up	
		IQ change (mean/median)	SWI change (mean/median)	IQ change[a] (mean/median)	SWI change (mean/median)
Cognitive improvement	*Yes*	−0.4/+2.0	−40%/−44%	−4.2/−2.0	−45%/−50%
	n	18/43	25/43	7/42	21/42
	No	−4.5/−7.0	−8%/0.0%	+2.0/+2.0	+4%/+5%
	n	15/76	37/76	1/52	7/52
$P_{between\ groups}$		0.32	**0.008**	0.42	**0.002**

$P_{between\ groups}$: p-value for comparison between the patients who showed cognitive improvement and the patients who did not show cognitive improvement. Significant p-values (p < 0.05) are shown bold.
n: number of treatments for which both subjective cognitive data and objective data (IQ/SWI) are available/total number of treatments. EEG data were more widely available than IQ data, resulting in higher numbers that could be analyzed.
[a] Due to the limited availability of IQ data at last follow-up the comparison was based on only 8 patients (7 with subjectively reported improvement, 1 without subjectively reported improvement).

3.5. Correlation between IQ (change) and SWI (change)

In a comparison of baseline IQ and baseline SWI (before the first treatment was started) no significant correlation was found (Spearman's Rho 0.155, p = 0.397). The treatments for which IQ and SWI were available both before and after treatment, were analyzed for possible correlations between SWI change and IQ change after treatment. No significant correlation was found at first follow-up (Spearman's Rho 0.251, p = 0.166, n = 32). At last follow-up a significant positive correlation was found between SWI change and IQ change (Spearman's Rho 0.857, p = 0.014, n = 7).

3.6. Reported effect of different treatment categories

The first treatment prescribed after the diagnosis of ESES was a conventional anti-epileptic drug (AED) in 10 patients, a benzodiazepine in 21 children, a corticosteroid in 14 and another treatment in one child. Subjective cognitive improvement at first follow-up was reported in 43% of the children first treated with AED, in 37% of those first treated with a benzodiazepine, and 64% of patients first treated with a corticosteroid. At last follow-up (prior to subsequent treatments) this was 50%, 50% and 83% of patients respectively (Supplementary Table 1). IQ before and after the first treatment, without another interfering treatment, was available for only a limited number of patients. Therefore, we also included the difference in IQ (delta IQ) before and after the first treatment regardless of other treatments (i.e. the first IQ after the first treatment and the last available IQ compared to the baseline IQ before the first treatment) in Supplementary Table 1. EEG showed a median spike-wave index change of +3% (AED), −9% (benzodiazepines) and −56% (corticosteroids) at first follow-up and +6% (AED), −4% (benzodiazepines) and −58% (corticosteroids) at last follow-up (Supplementary Table 2).

If all subsequent treatments are also included in the analysis, 35 AED treatments (most often levetiracetam) were associated with subjective cognitive improvement in 23% at first follow up (46% at last follow-up), 39 benzodiazepine treatments (most often clobazam) with 32% at first follow-up (36% at last follow-up), and 43 corticosteroid (methylprednisolone, prednisolone or dexamethasone) treatments with cognitive improvement in 53% at first follow-up (58% at last follow-up). Surgery was associated with reported cognitive improvement in 1 of 2 cases (50%) at first follow-up (100% at last follow-up) and intravenous immunoglobulins in 4 of 12 treatments (33%) at first follow-up (36% at last follow-up). A detailed overview of cognitive performance and SWI change after all treatments (n = 147) at first and at last follow-up can be found in Supplementary Table 3.

3.7. Predictors of subjectively assessed cognitive improvement after treatment

With univariate analysis we found that at first follow-up after a specific treatment, the number of previous treatments (OR 0.78; 95% CI 0.64–0.95) and the use of corticosteroids compared to AED (OR 3.7; 95% CI 1.2–11.4) were significantly associated with cognitive improvement and this finding was confirmed in the univariate analysis after multiple imputation (Table 3). In a subsequent multivariate analysis after multiple imputation, only the use of corticosteroids (compared to any other treatment category) was significantly associated with cognitive improvement at first follow-up (OR 2.5; 95% CI 1.1–5.7). The influence of the number of previous treatments on cognitive improvement at first follow-up of treatment is displayed in Fig. 2. A decreasing trend in proportion of subjective cognitive improvement was seen with an increasing number of previous treatments, although cognitive improvement was reported still relatively often after the fourth treatment.

At last follow-up, higher age at diagnosis of ESES (OR 1.02; 95% CI 1.01–1.04) showed an association with cognitive improvement, however this association was not significant in the multiple imputation dataset (Table 4).

Table 3 – Possible predictors of cognitive improvement at first follow-up.

Treatment category	OR (95% CI) Univariate CC	OR (95% CI) Univariate MI	OR (95% CI) Multivariate MI
AED	reference	reference	reference
Benzodiazepines	1.6 (0.5–5.2)	1.4 (0.3–5.5)	reference
Steroids	**3.7 (1.2–11.4)**	**3.3 (1.1–10.4)**	**2.5 (1.1–5.7)**
Surgery	3.3 (0.2–61.7)	2.8 (0.1–54.5)	Reference
IVIG	1.7 (0.4–7.5)	1.4 (0.3–7.0)	Reference
Other	1.1 (0.2–7.5)	1.3 (0.2–6.5)	Reference
Patient/treatment characteristics			
Male gender	0.9 (0.4–2.0)	0.9 (0.4–2.0)	[a]
Age at diagnosis	1.01 (0.99–1.02)	1.01 (0.99–1.02)	[a]
Interval diagnosis – treatment	0.98 (0.95–1.00)	0.98 (0.95–1.01)	0.99 (0.96–1.02)
Abnormal development before ESES onset	0.6 (0.3–1.3)	0.6 (0.3–1.2)	0.6 (0.3–1.4)
MRI abnormalities	1.4 (0.6–3.0)	1.3 (0.6–2.9)	[a]
Number of previous treatments	**0.78 (0.64–0.95)**	**0.77 (0.63–0.95)**	0.81 (0.63–1.03)

95% CI = 95% confidence interval, CC = complete case analysis, MI = analysis of multiple imputation dataset. N = 119 for complete case analysis, n = 147 for analysis after multiple imputation.
Statistically significant findings (p < 0.05) are shown bold.
[a] Not included in multivariate model, because p > 0.20 in univariate analysis.

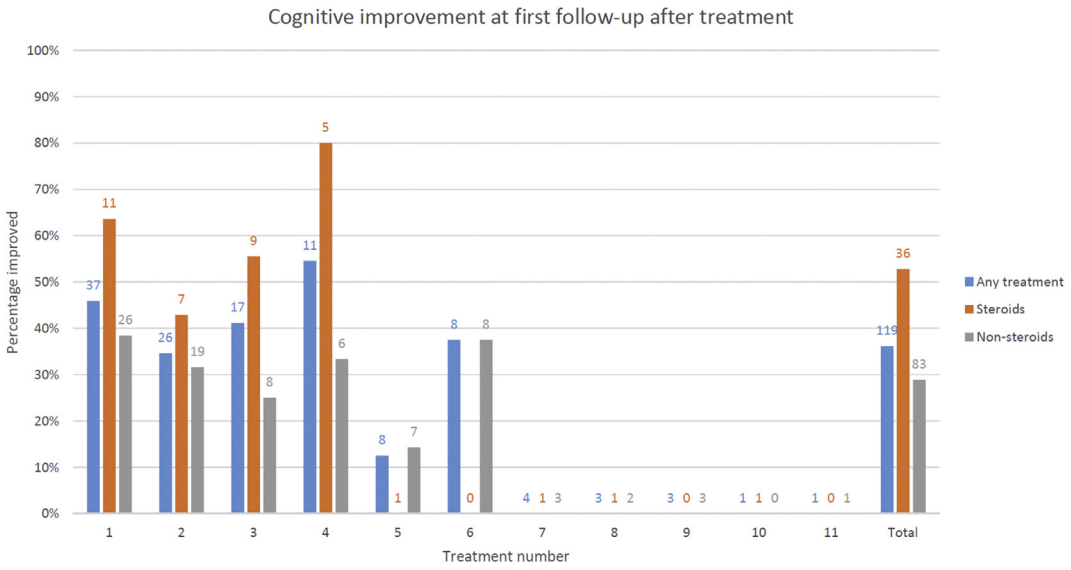

Fig. 2 – Cognitive improvement at first follow-up after treatment, related to the treatment number after the diagnosis of ESES. The treatment number refers to the order in which treatments were given, i.e. the first treatment is treatment 1, the fifth treatment is treatment 5. The height of the bars reflects the percentage of treatments that was effective, the number on top of the bars reflects how many patients received this number of treatments, i.e. a fifth treatment was given in 8 patients, of which 7 had a non-steroid and 1 a steroid treatment and 12.5% of fifth treatments were successful.

3.8. *Secondary outcomes: behavior, seizure frequency and side effects*

Due to small numbers of patients in the different treatment categories we limited the analysis of secondary outcomes to a comparison of steroid vs. non-steroid treatments. No significant differences were found in the effect of treatment on behavioral problems, seizure frequency and side effects between steroid treatments and non-steroid treatments.

Table 4 – Possible predictors of cognitive improvement at last follow-up.

Treatment category	OR (95% CI) Univariate CC	OR (95% CI) Univariate MI
AED	Reference	Reference
Benzodiazepines	0.7 (0.2–2.0)	0.6 (0.2–2.1)
Steroids	1.6 (0.5–5.5)	1.2 (0.2–6.8)
Surgery	N/A (2/2 positive)	N/A (2/2 positive)
IVIG	0.7 (0.2–2.9)	0.6 (0.1–2.7)
Other	0.8 (0.2–3.5)	0.7 (0.1–3.5)
Patient/treatment characteristics		
Male gender	0.9 (0.4–2.2)	1.0 (0.4–2.4)
Age at diagnosis	**1.02 (1.01–1.04)**	1.02 (0.99–1.04)
Interval diagnosis – treatment	1.00 (0.98–1.02)	1.00 (0.98–1.03)
Abnormal development before ESES onset	0.6 (0.3–1.3)	0.7 (0.2–2.2)
MRI abnormalities	1.6 (0.7–3.6)	1.5 (0.6–3.6)
Number of previous treatments	0.85 (0.70–1.03)	0.90 (0.75–1.07)

95% CI = 95% confidence interval, CC = complete case analysis, MI = analysis of multiple imputation dataset. N = 94 for complete case analysis, n = 147 for analysis after multiple imputation. Statistically significant findings ($p < 0.05$) are shown bold.
Note: No multivariate analysis after multiple imputation is reported because only for age the p-value is < 0.2 in univariate after multiple imputation.

4. Discussion

In this study we investigated the effect of treatment on – subjectively assessed – cognitive functioning, IQ test results and spike-wave index in 47 patients with ESES syndrome treated in our center. We found that, in general, cognitive improvement is reported after a minority of treatments (36% at first follow-up and 45% at last follow-up). IQ results showed on average no clear change after treatment, while the EEG on average revealed a decrease in spike-wave index (−21 and −24% at first and last follow-up respectively). Subjectively reported cognitive improvement was significantly related to SWI decrease but not to IQ changes. Corticosteroids were found to be significantly associated with improvement at first follow-up, as compared to all other treatment categories, while at last follow-up higher age at diagnosis was associated with improvement. The number of previous treatments seemed to be inversely correlated to improvement.

In clinical practice, subjective judgment of cognitive functioning and sleep EEG recordings are generally used to evaluate treatment effect, as these are more readily available than repeated neuropsychological assessments and not influenced by re-test bias. We investigated whether subjective cognitive improvement is accompanied by IQ improvement. Although an increase in IQ was seen in patients who were reported to have improved and a decrease in patients who did not improve, we found no significant association between subjective improvement and changes in IQ scores. A first possible explanation is that total IQ values are not a

sensitive marker for cognitive functioning in children with ESES and can only be used to evaluate the course during long-term follow-up. Subjective improvement of functioning can be can be clinically very relevant, even if this does not lead to IQ improvement. Second, most children start treatment because of cognitive deterioration and in this setting an unchanged IQ after treatment (i.e. the child gains skills and remains stable compared to other children of the same age) can be seen as successful treatment and can be confirmed by parents as improvement in functioning. Another explanation may be that we analyzed IQ changes of only 33 treatments, because these were the only treatments that were evaluated with a neuropsychological test before any other treatment was started. This inherently resulted in reduced statistical power and may have caused selection bias. EEG evolution, however, showed a strong association with subjective cognitive improvement. Although SWI change was not correlated to IQ change at first follow-up, at last follow-up a correlation between SWI change and IQ change was seen that suggests that a decrease in SWI is correlated to a decrease in IQ. Although this correlation was statistically significant, we feel that due to the very small number of treatments ($n = 7$) in this analysis and the probable influence of selection bias, this finding should be interpreted with caution. Previous studies found that location, severity and duration of EEG abnormalities are correlated to cognitive performance and prognosis.[6,21,22] Our study adds that SWI change is correlated to cognitive improvement, despite the fact that about half of the patients with cognitive improvement still had a SWI above 50%.

We found that steroid treatment was significantly correlated to cognitive improvement at first follow-up, in contrast with all other treatment categories. At last follow-up this difference was not significant. The results of our treatment analysis are consistent with a recent pooled analysis of 575 ESES cases.[8] In this meta-analysis of the literature, steroid treatment was found to be associated with cognitive and EEG improvement compared to non-steroid medical treatment, although no directly comparing studies were included. The underlying mechanism explaining efficacy of steroids in patients with ESES is incompletely understood. Alterations in cytokine profiles have been found in children with ESES and an underlying inflammatory process has been suggested.[13,23] Corticosteroids may be of benefit by interfering in this pro-inflammatory state. A possible explanation for the non-significance at last follow-up could be that corticosteroids can lead to a temporary response by suppressing an inflammatory process, while after completing steroid pulses or after tapering oral steroids the inflammation and ESES related cognitive deficits re-emerge. This is consistent with long-term relapses found in a previous cohort of ESES patients treated with corticosteroids.[14]

Our results have to be interpreted with some caution. First, the retrospective design of the study is inevitably associated with missing data. Especially, for many individual treatments neuropsychological follow-up was insufficient for a before-after comparison. This reflects that IQ measurements cannot reliably be repeated shortly after the first measurement, which limits their utility in the context of (the treatment of) ESES. Second, the lack of a placebo control group makes it impossible to distinguish true treatment effect from fluctuations in the natural course that are often seen in ESES patients. This may have influenced our comparison of the different treatment options for ESES. Third, the evaluation of non-steroid treatments was often earlier (after reaching the intended dosage) than for steroids (in many cases after completing the intended number of pulses). Therefore a slow response to an AED or benzodiazepine may have remained unnoticed at first follow-up, while a slow response to a steroid treatment was included. In addition, this longer interval allows more time for spontaneous recovery.

Despite these challenges, our study provides valuable information. To our knowledge, it is the largest single center study describing treatment effect in patients with ESES syndrome. Also, it is the first cohort study statistically comparing different methods (subjective assessment, neuropsychological assessment, EEG) used for the follow-up of treatment in a relatively large group of patients with ESES syndrome.

For definite conclusions regarding the treatment of ESES syndrome, adequately sized Randomized Controlled Treatments are required. EEGs and neuropsychological assessments need to be performed at pre-specified time-points. RESCUE ESES is a European multicenter randomized controlled trial, currently comparing treatment with corticosteroids to treatment with clobazam.

Competing interests

Dr. van den Munckhof and Dr. Jansen report grants from the Dutch Epilepsy Fund (epilepsiefonds) and Wilhelmina Children's Hospital Research Fund and non-financial support by the European Clinical Research Infrastructure Network (ECRIN) during the conduct of the study. The other authors have no potential conflicts of interest to declare.

Acknowledgments

This work was supported by grants from the Dutch Epilepsy Fund (13-17) and the Wilhelmina Children's Hospital Research Fund (R2634). The funding sources had no direct involvement in this study.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejpn.2017.08.006.

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