Review article

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Current treatment options for Encephalopathy related to Status Epilepticus during slow Sleep

Floor E. Jansen [1], Marina Nikanorova [2], Martina Peltola [3]

[1] Department of Child Neurology, Brain Center, University medical Center Utrecht, Member of the European Reference Network EpiCARE, The Netherlands
[2] Children's Department, Danish Epilepsy Centre, Dianalund, Denmark
[3] HUS Medical Imaging Center, Clinical Neurophysiology, University of Helsinki, Helsinki University Hospital and University of Helsinki, Finland

ABSTRACT – The major goal of therapy in patients with Encephalopathy related to Status Epilepticus during slow Sleep (ESES) is to prevent or reduce associated cognitive deficits. Whether or not the EEG pattern of ESES should be completely suppressed to improve cognition is unknown. In clinical practice, there are two major challenges: to establish the optimal treatment strategy in patients with ESES, and to identify the patients who will benefit most from therapy, including atypical cases. Here, we provide a comprehensive overview of the current literature on treatment efficacy in patients with ESES.

Key words: encephalopathy related to status epilepticus during slow sleep, continuous spike and waves during sleep, treatment, antiepileptic drugs, surgery, ketogenic diet, immunomodulating treatment

Almost 50 years have elapsed since the first description of Encephalopathy related to Status Epilepticus during slow Sleep (ESES) (Patry *et al*., 1971), and a well-defined treatment protocol of this condition is still lacking. There is no general agreement whether immunomodulation, benzodiazepines or antiepileptic drugs (AEDs) should be used as a first-choice medication. Nor is there consensus on the duration of treatment after which improvement may be expected, and how long treatment needs to be continued after improvement is achieved. Treatment goals in ESES include seizure control, reduction of EEG abnormalities and most importantly potential improvement, or at least prevention, of further cognitive decline. The beneficial effect of treatment on both seizure frequency and severity and on cognitive functions in relation to the reduction of epileptiform discharges in sleep has been demonstrated in many studies (Aeby *et al*., 2005; Inutsuka *et al*., 2006; Kramer *et al*., 2009; Sanchez Fernandez *et al*., 2012).

The current treatment options for ESES include "routine" AEDs, benzodiazepines, immune modulation therapy, including corticosteroids, and surgical treatment.

Correspondence:
FE. Jansen
Department of Child Neurology, Brain Center Rudolf Magnus,
University Medical Center,
Heidelberglaan 100, 3584 CX Utrecht,
Holland
<F.E.Jansen@umcutrecht.nl>

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Antiepileptic drugs

The most commonly used AEDs are sodium valproate, ethosuximide, sultiame and levetiracetam, though their effects are often temporary, partial or limited to control of clinical seizures. In a series by Inutsuka *et al*. (2006), 10 out of 15 patients (67%) responded with long-lasting seizure control and partial recovery of cognitive functions after treatment with valproate alone or in combination with ethosuximide. Liukkonen *et al* (2010) demonstrated efficacy of a combination of valproate and ethosuximide in two patients. Other investigators could not confirm these positive effects (Capovilla *et al*., 2004; Scholtes *et al*., 2005; Kramer *et al*., 2009).

Several studies have supported efficacy of levetiracetam in ESES treatment (Capovilla *et al*., 2004; Aeby *et al*., 2005; Wang *et al*., 2008; Atkins and Nikanorova, 2011; Larsson *et al*., 2012). Capovilla *et al*. (2004) observed efficacy in two of three children (all with focal structural epilepsy and ESES), followed for 15 and 12 months, respectively. Aeby *et al*. (2005) reported EEG improvement in seven of 12 children after two months of treatment, and neuropsychological or behaviour improvement in nine. In their study, levetiracetam had been discontinued after one year in four patients because of ESES relapse while on treatment.

Wang *et al*. (2008) demonstrated levetiracetam efficacy in 5 of 6 children, but 2 of 5 responders relapsed after four and five months, respectively. In a study by Atkins and Nikanorova (2011), eight out of 20 patients demonstrated a long-lasting response (more than 12 months), and three showed a partial response (6-12 months). Nine had seizures prior to levetiracetam treatment initiation. Six became seizure-free when levetiracetam was added, and in three children a significant reduction of seizure frequency was observed. The authors emphasized the higher levetiracetam efficacy in patients with structural etiology compared to unknown and genetic etiology. Sultiame has been reported as effective in small series (Wirrell *et al*., 2006; Kramer *et al*., 2009).

Recently, one study reported a very significant effect of topiramate; 16 of 21 patients showed clinical and behavioural improvement at three months, with long lasting effect in 10 (Vrielynck *et al*., 2017). Acetazolamide was reported to yield subjective clinical improvement in 5 of 6 children in whom up to 12 previous treatments had failed, when studied retrospectively (Fine *et al*., 2015). Amantidine, although not considered to have anticonvulsive effects, became of interest because of the identified *GRIN2A* variant in patients with ESES which has recently been reported in a series of 20 patients with ESES. The SW index was found to have dropped from a mean of 76% to 53% and subjective cognitive, linguistic, or behavioral benefit was noted in the majority of patients (Wilson *et al*., 2018).

Benzodiazepines demonstrate efficacy in the short term. Treatment with short cycles of high-dose diazepam (1-3 weeks) can lead to transient remission, but relapses necessitate repeated cycles (Inutsuka *et al*., 2006; Kramer *et al*., 2009). Kramer *et al*. (2009) reported a temporary response in three of eight patients after treatment with oral diazepam 0.75-1 mg/kg/day for three weeks, with a relapse within six months. In a series by Sanchez Fernandez *et al*. (2012), the mean spike wave index decreased from 77 to 41% in 29 patients with ESES after administration of 1 mg/kg oral diazepam every evening. In another study, valproate and benzodiazepines were not effective in nine out of 10 patients, and 3 patients experienced an adverse behavioural reaction (Scholtes *et al*., 2005). Chronic treatment with oral clobazam in combination with other AEDs may have a sustained effect (Larrieu *et al*., 1986). Recently, nine patients showed significant reduction of sleep spike waves after three months or daily clobazam 0.5 mg/kg (Vega *et al*., 2018). Verbal IQ scores improved, although median IQ had not changed due to an unexplained decrease in non-verbal IQ in this series.

Ketogenic diet

The data on ketogenic diet in ESES treatment are limited. Bergqvist *et al*. (1997) described three patients with Landau-Kleffner syndrome refractory to traditional therapy. All three children showed improvement of their language performance, behaviour, and seizure frequency for 26, 24, and 12 months, respectively. In another study (Nikanorova *et al*., 2009), the ketogenic diet did not appear to influence the neuropsychological outcome of ESES. Only one out of 5 patients responded with complete ESES resolution. More recently, two series were added to the literature. The combination of the KD with steroids was studied in 13 children (Ville *et al*., 2015). Of the patients, 61% were considered responders, but only one was able to discontinue steroids during follow-up. In a series by Reyes *et al*. (2015), 12 patients with ESES were treated with the ketogenic diet for a minimum of 18 months. At the end of follow-up, seven patients remained on the diet, one patient became seizure-free, and three had a significant improvement in seizure reduction. Efficacy of the ketogenic diet has been reviewed by Kelley and Kossoff in 2016. Of the 38 reported children, 41% had >50% seizure reduction, 45% had cognitive improvement, 53% had EEG improvement but only 9% had EEG normalization. Efficacy of the ketogenic diet in ESES may result from its anti-inflammatory potential or by increasing GABA that may be

particularly important since GABAergic neurons in the thalamus may be damaged in patients with ESES (Kelley and Kossof, 2016).

Activation of the immune system in patients with ESES and response to immunomodulating treatment

A growing body of evidence has recently confirmed a link between epilepsy and inflammation. Various findings indicate the involvement of the immune system, including reduced serum levels of IgA and IgG subclasses but also elevated cerebrospinal fluid levels of IgG, IgM, as well as positive antinuclear antibodies, antibrain, antimyelin, and antiglutamate receptor antibodies in serum (Boscolo *et al*., 2005; Connolly *et al*., 2006; de Vries *et al*., 2016). The inflammatory process is mediated by cytokines, chemokines and proteases. To date, IL-1beta and HMGB1 overexpression has been found in resected focal cortical dysplasia, mesial temporal sclerosis and tubers (Connolly *et al*., 2006). Further, increased levels of IL-6 have been found in a number of epilepsy-related etiologies making it a consistent finding. However, there are only two studies of ESES that investigated cytokine profiles (Lehtimaki *et al*., 2011; van den Munckhof *et al*., 2016). Van den Munckhof found significantly higher levels of IL-1α, IL-6, IL-10, chemokine (C-C motif) ligand (CCL)2 and chemokine (C-X-C motif) ligand (CXCL)8/IL-8 in 11 patients with ESES as compared to controls. Further, IL-6 changes were accompanied by clear improvement of electroencephalography (EEG) patterns and neuropsychological evaluation after immunomodulating treatment. As seizures may be infrequent in ESES, it is suggested unlikely that IL-6 elevation and chronic inflammatory system activation result from recurrent seizures alone. Although it has been suggested that continuous epileptiform activity may also cause inflammatory system activation, the exact relationship-cause or consequence- is not known.

In addition to measuring the inflammatory process, effective response to immunomodulating therapy in patients with ESES provides further evidence for the role of immune system activation (Walker and Sills, 2012), although the mechanisms of action are not completely understood.

Intravenuous immunoglobins (IVIG)

IVIG was first used in the treatment of childhood epilepsy in 1977 (Pechadre *et al*., 1977). Since then, successful treatments with intravenous immunoglobulin (IVIG) in LKS or CSWS/ESES syndrome have been published in a few case reports (Pechadre *et al*., 1977; Fayad *et al*., 1997; Mikati *et al*., 2002; Arts *et al*., 2009). Arts *et al*. reported the use of IVIG in six children with LKS or CSWS/ESES who were studied in a prospective manner. Only one of the six patients showed a clear, temporal, positive response to IVIG. The other children did not respond, and four of them were treated subsequently with prednisone.

Corticosteroids

Corticosteroids seem to offer better efficacy and more long-lasting effect than conventional AEDs. Different steroid modalities and schemes have been reported over years and again, results are mostly restricted to small case series. Lerman *et al*. described successful long-term treatment of ACTH and corticosteroids in four patients (Lerman *et al*., 1991). Repeated pulses with intravenous methylprednisolone was effective in two patients (Tsuru *et al*., 2000); they showed a maintenance of improved language performance with subsequent continuous oral prednisolone administration. Another nine out of ten patients manifested significant long-lasting improvement in language, cognition, and behavior after 6 months treatment with oral prednisolone 1 mg/kg/day (Sinclair and Snyder, 2005). Only few and reversible side effects were noted. Haberlandt *et al*. (2010) showed that pulsatile corticoid therapy with dexamethasone was an effective alternative treatment to adrenocorticotropic hormone for a number of epilepsy syndromes, including ESES. Dexamethasone was also considered effective in a study by Chen *et al*. (2016) with seven out of 15 responders, although relapses were seen in 4 when dexamethasone was discontinued after one month. Kramer *et al* (2009) concluded that the 64% (11 of 17 patients) short-term efficacy of steroid therapy was greater than the efficacy of any other agents (including AEDs, benzodiazepines and immunoglobulins). However, of those, 33% eventually relapsed and 22% became steroid dependent. Two centers combined their experience with corticosteroid treatment in a large retrospective cohort of 44 patients with CSWS or LKS (Buzato *et al*., 2009). All but two patients were administered daily hydrocortisone, in a scheme lasting up to 21 months. Initial positive response was found in 34 of 44 patients (77.2%), with normalization of the EEG in 21 patients. Although relapses occurred (14 of 34), 20 patients (45.4%) were found to be long-term responders. Higher IQ/DQ and shorter CSWS duration were significantly related to positive treatment response. Recently, the electroclinical spectrum and treatment efficacy was reported in a large cohort of 44 Turkish patients with ESES (Gencpinar *et al*., 2016). Patients treated with a minimum of two AEDs did not differ from patients treated with AEDs and ACTH with respect to

seizure outcome, SWI and cognitive outcome. On the other hand, van den Munckhof *et al*. (2018) and Altunel *et al*. (2017) did find steroid treatment to be most successful. Altunel reported the effects on SWI in sleep EEGs and ADHD symptoms in 75 patients treated with ACTH (with repeated cycles when SWI remained > 15%). They found a reduction in SWI in all the patients that was accompanied by a mean improvement of 67% in ADHD-like symptoms after treatment with ACTH. Van den Munckhof reported improved cognitive performance in a series of 47 patients with ESES. More so, improvement of daily functioning after treatment was strongly associated with SWI decrease. Pooling individual patient data yielded treatment success (for EEG or cognitive improvement) in 81 % of ESES cases for steroids, as compared to 68% for benzodiazepines and 49% for other AEDs (van den Munckhof *et al*., 2015).

Epilepsy surgery

Hemispherectomy and lobar or multilobar resection has been found effective for selected children and adolescents with a congenital or early-acquired brain lesion, despite abundant generalized or bilateral epileptiform discharges on EEG (Wyllie *et al*., 2007). Pooled data from several studies shows the effect of 14 hemispherectomies or hemispherotomies and four resections in patients with structural and pharmacoresistant ESES (Wyllie *et al*., 2007; Battaglia *et al*., 2009; Kallay *et al*., 2009; Loddenkemper *et al*., 2009; Roulet-Perez *et al*., 2010; Peltola *et al*., 2011; Fournier-Del Castillo *et al*., 2014). Fifteen of 18 patients had strictly unilateral brain lesions. In the other patients, the lesion was predominantly unilateral. The etiology of lesions was perinatal vascular with or without thalamic injury in the majority of the patients. Two of 18 patients presented with hemispheric or lobar polymicrogyria. Age at the hemispherotomy or hemispherectomy varied between 3.6 and 6.2 years (median: 6.9 years), and at the resection between 4.7-14.9 years (median: 4.9 years). Minimum duration of postsurgical follow-up was 18 months. Good response after surgery was seen with seizure freedom in 14 of 17 patients with preoperative seizures, resolution of ESES in all except one patient, who had residual regional ESES, and behavioural and cognitive improvement in all. Cognitive catch-up with increment of IQ or DQ with greater than or equal to 10 points was verified by comparable pre- and postoperative IQ/DQ measurements in nine of 14 patients after hemispherotomy or hemispherectomy and in three of four patients after resection. In 2017, Jeong *et al*. (2017) reported hemispherotomy resulting in complete seizure control in all nine children with ESES and resolution of continuous spike-and-wave discharge in six of six patients in whom postoperative EEG recordings were available. Regression of skills was stopped in all patients and in four of them developmental and academic gains were noted in parental reports.

Factors that are suggestive of favorable outcome are a strictly unilateral MRI lesion in patients considered for resective or disconnective surgery, preoperative propagation of SES from one hemisphere to another and normal or near-normal cognitive development before or at the diagnosis of ESES (Loddenkemper *et al*., 2009; Roulet-Perez *et al*., 2010; Peltola *et al*., 2011). The meta-analysis by van den Munckhof confirms surgery to be the most effective treatment in patients with structural etiology (van den Munckhof *et al*, 2015).

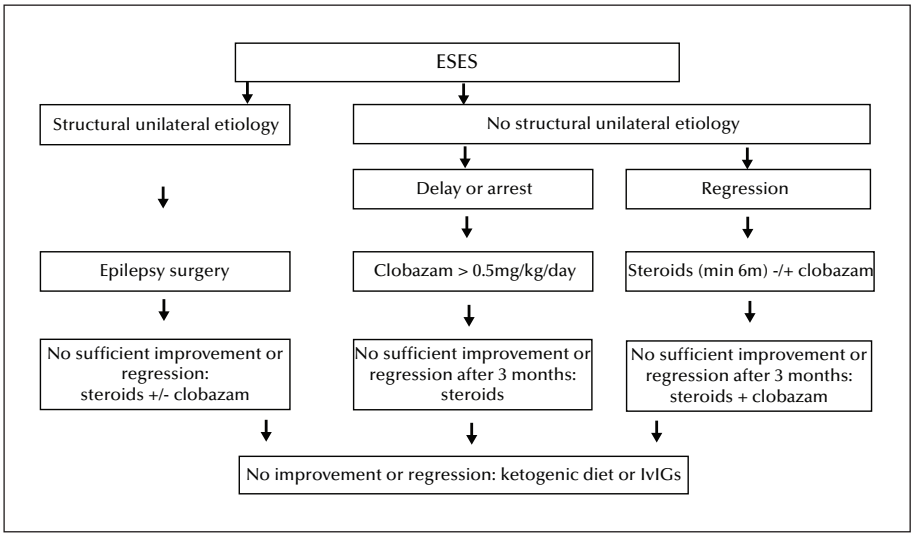

Figure 1. Flow chart of therapeutic approach, based on review of the literature and expert opinion.

Conclusions

In patients with ESES, different treatment regimens have been advised and responses are unpredictable. Here, we reviewed the current literature. Many of the studies are small or retrospective, and may have been published only because of an exceptionally good or bad treatment effect. Next, most of these studies used qualitative outcome data only, not analyzing structured and serial neuropsychological assessments. Furthermore, series published to date used very different schemes of steroid treatment, making comparisons difficult. Finally, data on relapse rates and adverse events were largely missing.

Based on the comprehensive review of the literature and our own clinical experience, we propose a therapeutic approach (*figure 1*). Since epilepsy surgery was found to be most effective, children with ESES due to unilateral structural abnormalities should be discussed for surgery immediately. We propose to start with clobazam in patients without regression but consider steroids in cases who regressed. In addition to this flow chart, individual choices can be made depending on the epilepsy syndrome, for example sultiam could be first chosen in children with atypical benign focal epilepsy of childhood and ethosuximide could be effective in children with solitary thalamic injury. Further research to provide definite answers regarding treatment of children with ESES is warranted. For this goal, a European randomized controlled trial has been undertaken. RESCUE ESES (Randomized European trial of Steroids *versus* Clobazam Usage for Encephalopathy related to Status Epilepticus during slow Sleep) is a multicenter trial comparing treatment with either corticosteroids or clobazam in newly diagnosed patients. Quantitative cognitive and EEG outcome and possible predictors of treatment response will be assessed. □

Disclosures.
None of the authors have any conflict of interest to declare.

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