Review article

Epileptic Disord 2012; 14 (1): 1-11

Therapy of encephalopathy with status epilepticus during sleep (ESES/CSWS syndrome): an update

Pierangelo Veggiotti [1], Maria Carmela Pera [1], Federica Teutonico [1], Daniela Brazzo [1], Umberto Balottin [1], Carlo Alberto Tassinari [2]

[1] National Neurologic Institute "C. Mondino", Child Neuropsychiatry Unit, University of Pavia, Italy
[2] Neuroscience Department, University of Parma, Italy

Received July 21, 2011; Accepted January 25, 2012

ABSTRACT – Electrical status epilepticus in sleep (ESES)/continuous spikes and waves during slow sleep (CSWS) is an age-related, self-limiting disorder characterised by epilepsy with different seizure types, global or selective neuropsychological regression, motor impairment, and a typical EEG pattern of continuous epileptiform activity for more than 85% of non-rapid eye movement (NREM) sleep. Although the first description of ESES/CSWS dates back to 1971, an agreement about the optimal treatment for this condition is still lacking. ESES/CSWS is rare (incidence is 0.2-0.5% of all childhood epilepsies) and no controlled clinical trials have been conducted to establish the efficacy of different antiepileptic drugs; only uncontrolled studies and case reports are reported in the literature. Treatment options for ESES/CSWS include some antiepileptic drugs (valproic acid, ethosuximide, levetiracetam, and benzodiazepines), steroids, immunoglobulins, the ketogenic diet, and surgery (multiple subpial transections). In this study, the comparative value of each of these treatments is reviewed and a personal therapeutic approach is proposed.

Key words: ESES, AEDs, steroids

Correspondence:
Pierangelo Veggiotti
Istituto Neurologico "C. Mondino",
Via Mondino 2,
27100 Pavia, Italy
<pveggiot@unipv.it>

doi:10.1684/epd.2012.0482

The first description of "subclinical electrical status epilepticus induced by sleep in children" dates back to 1971, when Patry *et al*. (1971) described a peculiar EEG pattern occurring almost continuously during sleep in six children, characterised by apparent "subclinical" spike-and-wave complexes lasting from months to years. Five of the children were mentally retarded and two had no acquired language.

The term "continuous spikes and waves during slow sleep" (CSWS) was introduced in 1989 by the Commission on Classification and Terminology of the International League against Epilepsy and "epilepsy with continuous spikes and waves during sleep" was included in

the group of syndromes of undetermined origin (focal or generalised) (Commission, 1989). Taking into account the aim of our review, it seems reasonable to consider electrical status epilepticus in sleep (ESES) and CSWS to be synonymous, although this is a debatable point of view (Tassinari and Rubboli, 2006). Regarding the aetiology, the ILAE classification reported that "*it is unknown whether these conditions are idiopathic, symptomatic or both*", however, we consider ESES/CSWS to be an EEG pattern that is present in different kinds of epilepsy (Veggiotti *et al*., 1999).
In addition, as suggested in the latest ILAE classification (2006), "*there is insufficient evidence for mechanistic differences between Landau Kleffner syndrome (LKS) and ESES/CSWS to warrant considering them separate syndromes*". However, this distinction is beyond the scope of our review and is not important for the therapeutic approach. In this review we will refer to ESES/CSWS only.
In the classic definition, ESES/CSWS is defined as a typical EEG pattern of status epilepticus during sleep, occupying more than 85% of non-rapid eye movement (NREM) sleep, and lasting for at least three EEG recordings over a period of at least one month (Morikawa *et al*., 1989; Beaumanoir, 1995; Rossi *et al*., 1999; Tassinari and Rubboli, 2006). The quantification of anomalies in terms of "spike-wave index" (SWI) has played a central role in the diagnostic criteria of ESES (Cantalupo *et al*., 2011). Although originally, threshold values of this parameter were set (Tassinari and Rubboli, 2006), currently a significant increase in EEG abnormalities during sleep with the presence of neurocognitive impairment alone is considered a hallmark of ESES. Neuropsychological impairment such as global (Dalla Bernardina *et al*., 1989; Morikawa *et al*., 1992; Tassinari *et al*., 2000) or selective cognitive or language regression (Deonna and Roulet, 1995; Debiais *et al*., 2007), motor deterioration including ataxia, dyspraxia, dystonia (Neville *et al*., 1998) or unilateral deficits (Veggiotti *et al*., 1999; Veggiotti *et al*., 2005) are reported.

Therapy

The goal of treatment is not only to control clinical seizures but also to improve neuropsychological functions and prevent potential cognitive deterioration. When the pathological EEG pattern proves to be refractory to several antiepileptic drugs (AEDs), more "aggressive" therapeutic approaches may be considered since the correlation between paroxysmal activity and neuropsychological impairment is well established. Evidence to guide therapeutic decisions, however, remains at the level of class IV studies (case reports or expert opinions) and open-label uncontrolled trials (class III).

Traditional AEDs (excluding benzodiazepines)

Since the first description of ESES/CSWS by Patry *et al*. (1971), high-dose valproate (VPA) has been considered to be a first-line therapy for patients with CSWS syndrome.
Yasuhara *et al*. (1991) reported on the efficacy of VPA or ethosuximide (ESM) in five patients and ESES disappeared after adding clonazepam (CZP). They suggested that a combination of such drugs could represent the best therapeutic option for these patients. A limitation of the study was that neither the VPA nor the CZP doses were reported. An additional critical point was that the specific drug added was not indicated and the use of either VPA or ESM was not specified. However, this is one of the few studies also taking into account the cognitive effects of pharmacological treatment.
Ribacoba *et al*. (1997) reported two patients with ESES/CSWS syndrome treated with high-dose VPA (and ESM) who had a good response when treated, a relapse when therapy was withdrawn, and a subsequent significant improvement of clinical signs and EEG pattern when treatment was reintroduced. The authors suggested that the combination of VPA and ESM can represent a first-line treatment but needs to be maintained for the long-term, *e.g*. until adolescence. The choice of AED combination without the use of monotherapy was not specified by the authors. Furthermore, the therapeutic efficacy was demonstrated only after reaching very high plasmatic dosage of both drugs. The main limitation of this trial is the small number of patients (only two), thus making the significance of their findings difficult to establish.
Recently, Inutsuka *et al*. (2006) studied the effects of traditional AEDs on the EEG pattern of 15 patients. VPA monotherapy was initially up-titrated until the serum level was above 100 μg/mL, if no side effects occurred. ESES/CSWS disappeared completely in seven patients (47%) and no relapses occurred. Subsequently, ESM was added to VPA in non-responders or when side effects occurred and was effective in three patients (43%) without any relapse. The authors found no statistically significant differences between responders and non-responders to VPA with respect to several variables, including age at onset, neuroradiological findings (presence or absence of brain lesions), spike-wave index (SWI) and serum VPA level. They concluded that VPA monotherapy should be considered as first-line therapy for patients with ESES/CSWS. Since all patients of this study had a different aetiology, the results could not be randomised. The inclusion criteria of this study were extended to patients presenting with EEG abnormalities in at least 60% of NREM sleep, without considering typical EEG patterns included in the ESES/CSWS definition (epileptiform discharges

occupying more than 85% of NREM sleep). The therapeutic efficacy was evaluated only considering the index point. Furthermore, the authors mentioned "high doses" without giving any further specific indication.

Kramer *et al*. (2008) studied 30 patients with ESES/CSWS between 1994 and 2007. In this sample, a worsening of seizure frequency or EEG was demonstrated after high dose of VPA (used alone or as add-on to ESM), lamotrigine (LTG), topiramate (TPM), as well as CZP.

The use of sulthiame (STM) was first assessed in 2006 (Wirrell *et al*., 2006) in a five-year-old male with language delay, nocturnal seizures and ESES/CSWS. After only one month of STM therapy (10 mg/kg/day), ESES/CSWS disappeared completely and language improved significantly. The authors suggested that STM may be indicated in cases resistant to VPA. One advantage of STM is that it can be titrated up quickly and its effect on EEG can be assessed within four weeks. Given the potentially severe adverse effects of corticosteroids, it was suggested that a brief trial of STM should be considered before using steroids in "idiopathic" ESES/CSWS cases. Despite the suggestion that the use of STM for ESES/CSWS is acceptable, it is difficult to infer general conclusions from a single case.

New AEDs

Some new AEDs, such as levetiracetam (LEV), seem to be effective as treatment for ESES/CSWS. In 2003, Hoppen *et al*. (2003) described a five-year, seven-month-old boy with pharmacological refractory ESES/CSWS which rapidly disappeared after treatment with LEV. One year later, Capovilla *et al*. (2004) used LEV in three children with symptomatic focal epilepsy and ESES/CSWS pharmacoresistant to old AEDs. ESES/CSWS disappeared completely in two children, while in the third child there was only a mild improvement of the EEG pattern during sleep. Authors defined their work as "anecdotal" since the three patients included in the study may not be representative of the ESES/CSWS population.

Aeby *et al*. (2005) studied the effects of LEV in 12 patients (seven pharmacoresistant and five non-pharmacoresistant) using a titration scheme consisting of 25 mg/kg/day during the first two weeks, followed by 50 mg/kg/day for six more weeks. Seven children (58.3%) showed a significant improvement on EEG. Three presented cognitive and behavioural improvement while two patients showed only neuropsychological improvement with no EEG changes. Eight patients (66.6%) remained on LEV for two months and four patients for one year. LEV was discontinued in four patients after 11 months because no changes in EEG occurred and no improvement in neuropsychological and/or behavioural functions were demonstrated. Four children, who initially responded to LEV, relapsed after two months and their treatment was discontinued. These observations indicate that long-term follow-up is required to study LEV efficacy in epileptic children with ESES/CSWS. Since no significant cognitive adverse effects were observed, the authors concluded that LEV represents an effective and safe treatment option for ESES/CSWS.

Wang *et al*. (2008) reported six patients with ESES/CSWS aged between five and 11 years for whom LEV was added to pre-existing therapy. The dose of LEV ranged from 30 to 50 mg/kg per day and the duration of treatment varied between six and 15 months, except for one patient who discontinued LEV due to emotional problems. Clinical improvement (more than 50% reduction in seizure frequency) with complete disappearance of ESES/CSWS was observed in five patients within two weeks from the introduction of LEV. Two children, both aged five years, who presented psychomotor regression, before starting a pharmacological treatment with LEV, showed a recurrence of atypical absence seizures and cognitive regression after four and five months of treatment, respectively. The authors suggested that relapse rate in ESES/CSWS patients is not related to the underlying aetiology but rather to an early age at onset, as proposed earlier by Veggiotti *et al*., (2002). In fact, a significant correlation was found between age at onset of ESES/CSWS and neuropsychological impairment. Wang *et al*. (2008) concluded that LEV is effective in children with ESES/CSWS syndrome, resulting in seizure reduction, improvement of alertness, and remission of ESES/CSWS. However, emotional and behavioural side effects, albeit rare, are possible and seem to be more frequent in children with pre-existing neuropsychiatric disturbances.

Kramer *et al*. (2008) demonstrated a significant difference between LEV and old generation AEDs, including VPA in 30 patients followed for a period of 13 years. In this study, occurrence of relapses was related to duration of ESES/CSWS (more than 18 months), as well as neuropsychological functions. There was a significant correlation between residual cognitive deficits and the total duration of ESES/CSWS. Moreover, there were no residual intellectual deficits in most patients with a duration of ESES/CSWS shorter than 13 months. Although the sample used in this study was representative of the ESES/CSWS population, the range of underlying aetiologies was too diverse to allow for meaningful comparisons. The treatment approach for this study may be outlined as a therapeutic flow chart: VPA was administered as first-line choice in all cases, replaced by LEV in non-responders and, finally, by steroids as a last choice. This type of approach is acceptable since it could be very useful and

appropriate in ESES/CSWS patients, when considering the wide aetiological spectrum of the population, reported by the authors.

In 2011, Chhun *et al*. (2011) studied 102 patients with refractory seizures in a prospective open-labelled trial in order to study the efficacy and safety of LEV as adjunctive therapy. Six patients were diagnosed with ESES/CSWS syndrome. At three and six months, patients with ESES/CSWS exhibited the highest responder rate (67%; 4/6). Three patients were seizure-free, one had 92% seizure reduction and showed behavioural and cognitive improvement, two had normal EEG, and two had persisting ESES/CSWS. The authors concluded that, in spite of a small sample, ESES/CSWS is a good candidate for a randomised-controlled trial with LEV.

Another paper published in 2011 (Atkins *et al*., 2011) evaluated the add-on effect of LEV treatment on the EEG and clinical status of 20 children with ESES/CSWS refractory to other conventional AEDs (VPA, CLB, STM, LTG, and ESM). The population was composed of seven cryptogenic, seven symptomatic and six idiopathic cases. All children received 45-50 mg/kg/day of LEV as add-on treatment for a follow-up time of 18-53 months. The authors observed an electroencephalographic response in 11 patients; eight patients demonstrated a response lasting for more than 12 months and three children showed only a partial response from six to 12 months. The authors concluded that add-on therapy with LEV is more effective in children with ESES/CSWS resulting from a known underlying structural brain lesion.

Benzodiazepines

The effectiveness of benzodiazepines (BDZs) (Kellerman, 1978; Billard *et al*., 1982; Morikawa *et al*., 1985) has been known since Patry *et al*. (1971) reported the first description of ESES/CSWS syndrome with complete remission of paroxysmal EEG activity after a rapid intravenous injection of a BDZ.

Among BDZs, clobazam (CLB) is the first choice of treatment for ESES/CSWS since Larrieu *et al*. (1986) described a 12-year-old boy with complex partial seizures evolving to ESES, who presented with a disappearance of seizures and EEG normalisation after the introduction of CLB.

Kawakami *et al*. (2007) and De Negri *et al*. (1995) investigated the effects of BDZ monotherapy on ESES electrical pattern in class III studies. Kawakami *et al*. studied the effects of flunitrazepam (FZP) in two patients, one presenting with non-convulsive status epilepticus and the other disturbances of consciousness and automatisms. Their ictal EEG showed an electrical status with continuous diffuse spike-and-wave complexes that remitted after an intravenous injection of FZP at 0.02 mg/kg. The authors commented that FZP can be effective to treat ictal status in patients with ESES/CSWS.

De Negri *et al*. (1995) studied the effect of rectal diazepam in 15 patients with ESES/CSWS, aged between five months and 14 years. A 1-mg/kg dose was given initially and EEGs were recorded for more than 60 minutes thereafter. An antiparoxysmal effect (defined as "disappearance or remission of the paroxysmal activity") was observed after l0-15 minutes in all patients and short cycles (3-4 weeks) of relatively high-dose oral DZP therapy (0.75 mg/kg/day) was subsequently administered, with blood levels ranging from 100 to 400 ng/mL. Response to treatment was classified as "positive" in nine patients (60%) who had complete remission of paroxysmal EEG activity and "almost positive" in four additional patients who had a decrease of more than 50% of paroxysmal EEG activity. A comparative neuropsychological evaluation after six months of follow-up was possible in nine of the 13 responders; intelligence quotient (IQ) improved and neuropsychological deficits decreased or disappeared in six cases, no changes were found in one case, and cognitive worsening was documented in the remaining two cases. Neuropsychological improvement appeared to be associated with complete ESES/CSWS remission, with no clear explanation for the two patients who deteriorated. The authors indicated that DZP can be used safely in ESES/CSWS patients. Side effects such as drowsiness, hypotonia and hyperactivity were minor and occurred only at the beginning of the treatment. It was remarked that the ultimate goal of therapy in ESES/CSWS, unlike other epilepsy syndromes, is not only to control clinical seizures but also stop ESES/CSWS in order to prevent potential neuropsychological deterioration. This is an interesting study, however, interpretation of results is difficult because of the lack of long-term follow-up.

Inutsuka *et al*. (2006), in a recent comparative study, investigated the effects of a short cycle of DZP therapy (0.5-1 mg/kg per day, given orally or rectally before nocturnal sleep for 6-7 days) in four patients in whom VPA or a combination of VPA and ESM had failed. DZP was initially effective in two cases, but both relapsed within a year. It was suggested that short-term treatment with DZP in ESES/CSWS patients can be valuable but, due to a lack of sustained long-term benefit, treatment should be repeated after any relapse. This approach has the advantage of avoiding long-term side effects.

The same conclusion was reached by Kramer *et al*. (2008) who used DZP at a dose of 0.75-1 mg/kg/day orally for three weeks in eight patients with ESES/CSWS. Only three patients (37%) responded to DZP and they all relapsed within six months.

Steroids and ACTH

It has been demonstrated that prednisone (2-5 mg/kg/day), methylprednisone (20 mg/kg/day for three days), and adrenocorticotrophic hormone (80 IU/day) can stop ESES/CSWS and improve neuropsychological functions.

Sinclair and Snyder (2005) studied the effect of prednisone (1 mg/kg/day for six months) in two children with ESES/CSWS. Both showed significant improvement in language, cognition and behaviour after one year of treatment without any relapse. Only rare side effects such as weight gain and hypertension were observed, which appeared to be transient and reversible. It was concluded that corticosteroids can be safe and effective in ESES/CSWS and should be considered as a treatment option for this condition. Despite the interesting results, the number of patients included in this trial was too small to suggest the use of prednisone for the entire ESES/CSWS population.

Okuyaz *et al*. (2005) reported a four-year-old girl with ESES/CSWS and epilepsy refractory to several AEDs, including VPA, BDZ, and LTG. She was treated successfully with high-dose intravenous methylprednisolone (the first three days at 30 mg/kg/day, the following two days at 20 mg/kg/day, and then gradually reduced from 10 mg/kg/day to 5 mg/kg/day over four consecutive days) with VPA, CLB, and LTG being continued at the same dose during and after corticosteroid therapy. EEG monitoring during wakefulness and sleep was performed every day during the trial. On day seven, a dramatic clinical and EEG improvement was observed. After high-dose intravenous methylprednisolone, prednisolone was administered orally (2 mg/kg, daily) for two months and then gradually discontinued. After the withdrawal of corticosteroid therapy, clinical improvement continued and no ESES/CSWS was found during routine sleep EEG performed monthly for the following six months.

In their comparative study, Inutsuka *et al*. (2006) prescribed synthetic ACTH-Z (0.01-0.04 mg/kg per day, intramuscularly) for 11-43 days to five patients who had not responded to several AEDs. This treatment was initially effective in two cases who relapsed within six months. Side effects related to ACTH-Z were observed in all patients including hypokalemia, hypertension, and weight gain (each in two patients) and anorexia, fever, hypoactivity and a convulsion (each in one patient). Because of the transient efficacy and possible serious side effects, the authors suggested that synthetic ACTH-Z therapy should be considered for the treatment of ESES/CSWS syndrome only when other possible therapeutic options have failed.

Kramer *et al*. (2008) assessed the effects of steroids in 17 patients with ESES/CSWS. Different treatment regimens were used including intravenous oral prednisone, pulse methylprednisolone or ACTH injections. Oral prednisone followed pulse methylprednisolone or ACTH injections and was continued for 6-12 months in responders. The treatment had positive effects in 11 patients (65%) but three (33%) relapsed and two (22%) became steroid-dependent. The authors concluded that the relapse rate was too high to justify long-term treatment with steroids in ESES/CSWS, even though steroids have a better short-term efficacy compared to other drugs.

In 2009, Buzatu *et al*. (2009) reported the largest series of patients, assessing the efficacy of corticosteroids in epilepsy syndromes with ESES/CSWS. They retrospectively reviewed charts of 44 children (18 symptomatic and 26 cryptogenic) who received corticosteroids for cognitive and/or behavioural deterioration associated with ESES/CSWS. Evaluation focused on effects on EEG, behaviour, and cognition. All patients received hydrocortisone (initial dose of 5 mg/kg/day in the first month) and the treatment was slowly tapered during a total duration of 21 months (4 mg/kg/day in the second month, 3 mg/kg/day in the third month, then 2 mg/kg/day as a maintenance dose for a total duration of 21 months). Mean age was seven years, mean intelligence quotient (IQ) was 65, and mean ESES/CSWS duration before corticosteroid treatment was 1.7 years. Positive response to steroids was found during the first three months of treatment in 34 of 44 patients (77.2%), with normalisation of the EEG in 21 patients. Relapse occurred in 14 patients. The association between positive response to steroids and higher IQ and shorter ESES/CSWS duration was highly significant Age, aetiology, and previous AED trials were not associated with positive response to steroids. Early discontinuation of the treatment for side effects was encountered in seven patients. The authors concluded that corticosteroids are safe and efficient for the treatment of epilepsy with ESES/CSWS. This study underlines the striking effect of steroids for the treatment of ESES/CSWS and appears to be valid since the large series (44 patients) may be assumed to be representative of the ESES/CSWS population. Furthermore, the response to treatment was assessed taking into account both the electrophysiological picture (regression of the ESES pattern) and clinical-neuropsychological improvement.

Immunoglobulins

Despite the fact that intravenous gamma-globulins (IVIGs) are part of the therapeutic protocol for patients with LKS (Mikati *et al*., 2002), they have been evaluated as a treatment option for ESES/CSWS only in the last few years. In 2008, Kramer *et al*. (2008) used IVIGs at an initial dose of 2 g/kg for two consecutive days in nine

patients with ESES. For responders, four to six additional lower-dose cycles were administered at intervals of 4-6 weeks. IVIGs were effective as monotherapy in two cases and as add-on with CLB in a third case.

Ketogenic diet

Recently, the ketogenic diet (KD) was also assessed as a potential therapy for ESES/CSWS. In 2009, Nikanorova *et al*. (2009) tested the KD in five children aged between eight and 13 years with ESES/CSWS refractory to conventional AEDs, including LEV and steroids. Concomitant AED treatment remained unchanged during the diet. EEG monitoring after 24 months showed remission of ESES/CSWS in one child and a mild decrease of SWI in another child. The KD did not seem to influence neuropsychological outcome since IQ scores were unchanged at the end of the follow-up period.

Surgery

Surgical options have also been considered for the treatment of ESES/CSWS. Multiple subpial transection (MST) is a surgical procedure sometimes applied for the treatment of language regression in LKS (Morrell *et al*., 1995) and has been suggested to also have positive effects in patients with global cognitive impairment and behavioural problems secondary to ESES/CSWS. Nass *et al*. (1999) reported improvement of autistic regression in several cases following MSTs performed over the left neocortex in temporal, parietal, and frontal regions.

In 2008, the Pediatric Epilepsy Surgery Subcommission of the ILAE conducted a survey to determine the frequency of epilepsy surgery procedures. They gathered data from 20 programs in the United States, Europe, and Australia on 543 patients (<18 years) from 2004. Only 10 children (<2%) presented with LKS (three patients) and ESES/CSWS (seven patients). One patient with LKS underwent temporal lobe resection plus MST (cortical dysplasia) and the other two received vagus nerve stimulation (VNS). Among patients with ESES/CSWS, hemispherectomy was performed in four, one child received callosotomy plus VNS, and the remaining two cases received VNS. This survey concluded that surgery is a rare therapeutic option for CSWS/ ESES.

Loddenkemper *et al*. (2009) recently investigated possible indications for surgery in 415 patients with unilateral congenital or early-acquired brain lesions associated with refractory partial seizures and ESES/CSWS. Only eight patients were considered to be candidates for surgery; six underwent hemispherectomy and two had a focal resection. Six patients became seizure-free after surgery. Two patients who had a functional hemispherectomy improved and presented with only rare seizures. Postoperative EEG documented remission of ESES/CSWS in all. The authors concluded that children with unilateral brain lesions and uncontrolled partial seizures may become seizure-free after surgery, even when the preoperative EEG shows a generalised pattern of ESES.

Based on the above findings, epilepsy surgery should be considered as an early treatment option for selected cases with symptomatic ESES/CSWS.

Battaglia *et al*. (2009) documented the effects of hemispherectomy in two patients with refractory symptomatic epilepsy due to an early brain injury involving the thalamus and complicated by ESES/CSWS. Surgery appeared to be strikingly efficacious since seizures and ESES/CSWS disappeared immediately and were followed by a significant cognitive and behavioural improvement. The authors concluded that the disconnection of the injured hemisphere could prevent the controlateral diffusion of epileptiform discharges, thus allowing a normal function of thalamo-cortico-thalamic circuits in the healthy hemisphere.

Drug exacerbation

Studies have demonstrated that some AEDs can worsen ESES/CSWS. In particular, phenobarbital (PB) and carbamazepine (CBZ) may reduce seizures but they are usually not indicated for patients with ESES/CSWS because they can have negative effects on neuropsychological outcome and EEG pattern (Lerman, 1986; Caraballo *et al*., 1989; Van Lierde, 1992). Snead and Hosey (1985) investigated the use of CBZ in 15 children with ESES; CBZ exacerbated daily seizures in all and had no effect on the EEG. The authors suggested that CBZ should be considered as a causative agent in any child with a clinical worsening of generalised convulsive or absence seizures.

Conclusion

This review highlights the major limitations of available evidence concerning the treatment of ESES/CSWS. The results of the cited articles discussed are summarised in *table 1*. Firstly, no randomised Class I and II studies have been performed. Except for a few prospective Class III studies that investigated the effects of BDZs (Kellerman, 1978; Billard *et al*., 1982), studies were retrospective (Class IV) or limited to case reports, and many publications simply reflect expert opinion based on personal experience. Even in formal studies, the number of patients was usually small. These limitations are explained, to a large extent, by the fact that ESES/CSWS is a rare syndrome with different aetiologies, making randomised trials difficult to perform. Secondly,

Table 1. Summary of reported studies.

Reference	Type of studies	Nº of patients	Goal therapy	Failed therapies	Response (seizures/neurocognition)
Larrieu *et al*.(1986)	Retrospective	1	CLB		Positive
Yasuhara *et al*.(1991)	Retrospective	5	VPA + CZP		Positive in 5
De Negri *et al*.(1995)	Prospective	15	DZP		Positive in 13 (for seizures) Positive in 6 (for neurocognition)
Ribacoba *et al*.(1997)	Retrospective	2	VPA + ESM		Positive in 2
Hoppen *et al*. (2003)	Retrospective	1	LEV	Old AED	Positive
Capovilla *et al*. (2004)	Retrospective	3	LEV	Old AED	Positive in 2
Aeby *et al*. (2005)	Prospective	12	LEV	Old AED	Positive in 4
Inutsuka *et al*. (2006)	Prospective	15	VPA VPA + ESM DZP	ACTH	Positive in 7 Positive in 3 Positive in 2
Wirrell *et al*. (2006)	Retrospective	1	STM		Positive
Kawakami *et al*. (2007)	Prospective	2	FZP		Positive in 2
Wang *et al*. (2008)	Prospective	6	LEV	Old AED	Positive in 3
Kramer et al. (2008)	Prospective	30	LEV CLB STM DZP Steroids IVIG (+CLB)	VPA VPA + ESM LTG/ TPM / CZP	Positive in 12 Positive in 9 Positive in 5 Positive in 3 Positive in 8 Positive in 2 (+1)
Atkins *et al*. (2011)	Prospective	20	LEV	VPA/LTG/STM/ CLB/ESM	Positive in 11
Sinclair and Snyder (2005)	Prospective	2	Steroids		Positive in 2
Okuyaz *et al*. (2005)	Prospective	1	Steroids	VPA/LTG/BDZ	Positive
Buzatu *et al*. (2009)	Retrospective	44	Steroids		Positive in 34
Nikanorova *et al*. (2009)	Prospective	5	KD		Positive in 1 (for seizures)
Loddenkemper *et al*. (2009)	Retrospective	8	Surgery		Positive in 8
Battaglia *et al*. (2009)	Retrospective	2	Surgery		Positive in 2
Varga *et al*. (2011)	Prospective	5		tDCS*	Positive in 0

*transcranial direct current stimulation.

patients included in published studies usually had the common EEG pattern typical of ESES/CSWS, but a more precise characterisation of the treatment response based on other clinical features (*i.e.* aetiology, age at onset, duration of ESES/CSWS) was only rarely considered. Thirdly, many studies investigated the efficacy of different treatments based only on changes in EEG pattern and seizure frequency without taking into consideration the cognitive and neuropsychological aspects.

The correlation between continuous EEG discharges during sleep/seizures and neuropsychological impairment is well established and should be included as a main feature in the definition of this syndrome.

Taking into account the limitations discussed above, some AEDs, particularly VPA, BDZs, and LEV, appear to be valuable for the treatment of ESES/CSWS. Steroids also seem to have a powerful effect. On the other hand, some AEDs, most notably PB and CBZ, are known to increase synchronous bilateral epileptic discharges and to worsen clinical manifestations.

Based on a review of the literature and our own clinical experience, we propose a diagnostic algorithm that considers all the characteristic features of the syndrome, including the cognitive and neuropsychological aspects that represent an important component of the child's development (*figure 1*).

In the absence of shared protocols and clear indications emerging from the literature, we suggest a therapeutic approach, depicted as a flow chart in *figure 2*, which aims to stop the EEG pattern in question and avoid neurocognitive impairment. The flow chart is divided into two sections: 1) structural, metabolic, and unknown causes of epilepsy; and 2) idiopathic epilepsy. The therapeutic approach proposed in our algorithm for structural, metabolic, and unknown causes of epilepsy (Berg *et al.*, 2010) might be interpreted as "aggressive", however, the purpose is to immediately stop a status condition in order to prevent cognitive and neuropsychological deterioration

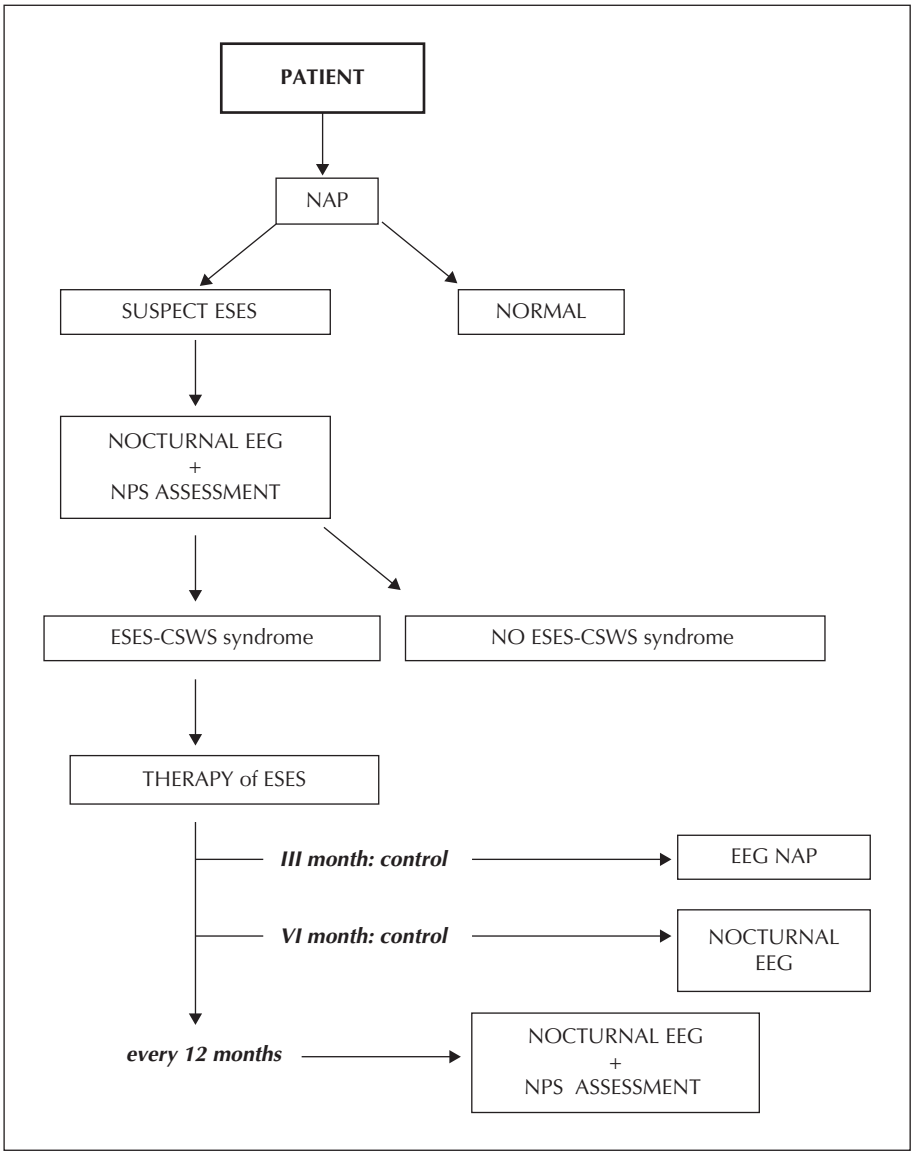

Figure 1. Diagnostic algorithm.
NAP: sleep EEG recorded during afternoon; NPS: neuropsychological evaluation.

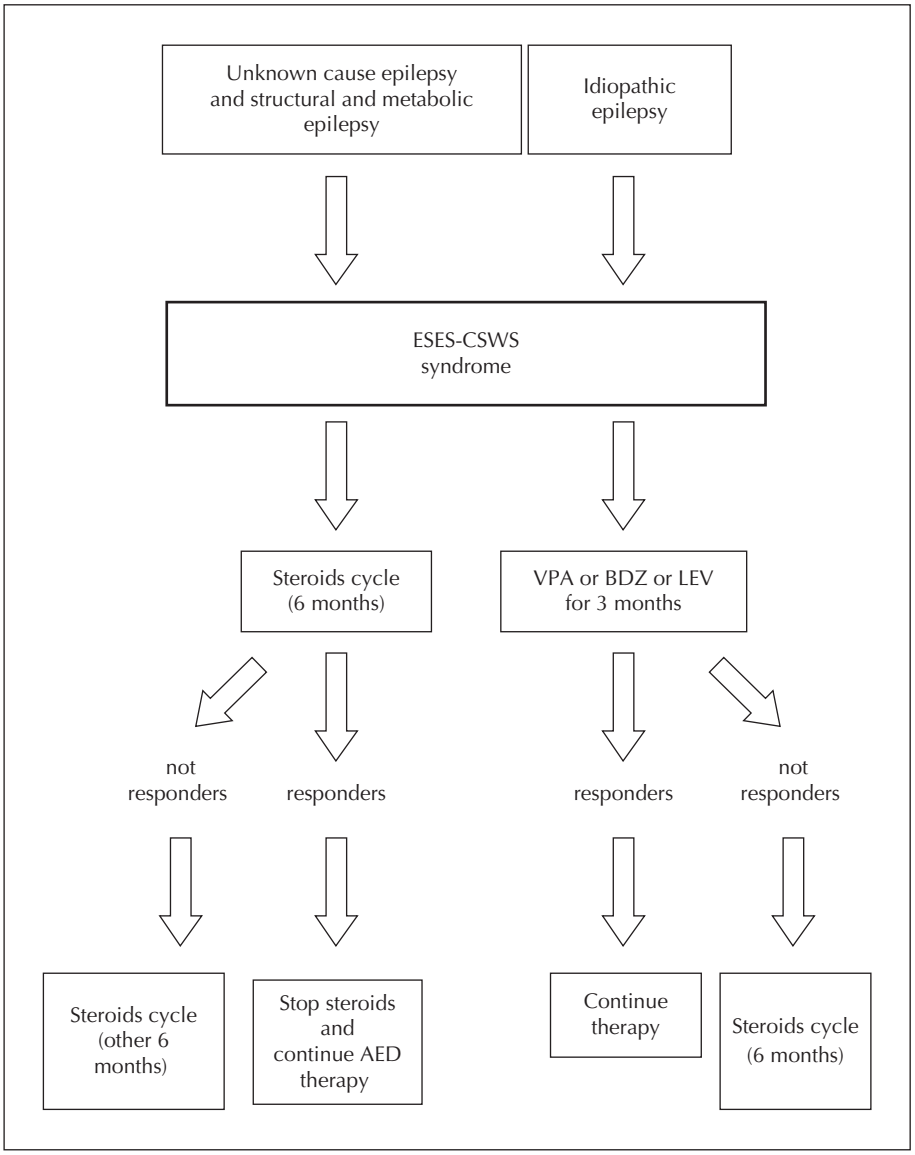

Figure 2. Therapeutic approach.

secondary to long-term EEG abnormalities. Based on the literature and in our experience, it is clear that extending to AED therapy does not lead to disappearance of the EEG pattern and, thus, the early use of corticosteroids is crucial, as is the case for other epileptic encephalopathies such as West syndrome.

Also, it is important to remind ourselves that previous pharmacological therapy should be maintained along with steroids for the entire clinical and EEG follow-up period.

From the literature and our own clinical practice, several data demonstrate the efficacy of antiepileptic drugs (VPA, BDZs, and LEV) for the idiopathic forms of ESES, indicating that they could be considered as first-line therapy in these cases. However, in the event of ineffective treatment after six months, the use of steroids is applicable.

Controlled trials and new studies taking into account a variety of clinical variables should be performed in order to provide an improved evidence basis for a rational approach for the treatment of ESES. □

Disclosures.
None of the authors of this study has any conflicts of interest in relation to this work.

References

Aeby A, Poznanski N, Verheulpen D, Wetzburger C, Van Bogaert P. Levetiracetam efficacy in epileptic syndromes with continuous spikes and waves during slow sleep: experience in 12 cases. *Epilepsia* 2005; 46: 1937-42.

Atkins M, Nikanorova M. A prospective study of levetiracetam efficacy in epileptic syndromes with continuous spikes-waves during slow sleep. *Seizure* 2011; 20: 635-9.

Battaglia D, Veggiotti P, Lettori D, *et al*. Functional hemispherectomy in children with epilepsy and CSWS due to unilateral early brain injury including thalamus: sudden recovery of CSWS. *Epilepsy Research* 2009; 87: 290-8.

Beaumanoir A. EEG data. In Beaumanoir A, Bureau M, Deonna T, Mira L Tassinari CA. *Continuous spikes and waves during slow sleep*. London: John Libbey, 1995: 217-23.

Berg AT, Berkovic SF, Brodie MJ, *et al*. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. *Epilepsia* 2010; 51: 676-85.

Billard C, Autret A, Laffont F, Lucas B, Degiovanni F. Electrical status epilepticus during sleep in children: a reappraisal from eight new cases. In: Sterman MB, Shouse MN, Passouant P. *Sleep and epilepsy*. New York: Academic Press, 1982: 481-91.

Buzatu M, Bulteau C, Altuzarra C, Dulac O, Van Bogaert P. Corticosteroids as treatment of epileptic syndromes with continuous spikes-waves during slow-waves sleep. *Epilepsia* 2009; 50(Suppl.7): 68-72.

Cantalupo G, Rubboli G, Tassinari CA. Night-time unravelling of the brain web: Impaired synaptic downscaling in ESES - The Penelope syndrome. *Clin Neurophysiol* 2011; 122: 1691-2.

Capovilla G, Beccaria F, Cagdas S, Montagnini A, Segala R, Paganelli D. Efficacy of levetiracetam in pharmacoresistant continuous spikes and waves during slow sleep. *Acta Neurol Scand* 2004; 110: 144-7.

Caraballo R, Fontana E, Michelizza B, *et al*. Carbamazepina, "assenze atipiche", crisi "atoniche" e stato di PO continua del sonno (POCS). *Bollettino della Lega Italiana contro l'Epilessia* 1989; 66/67: 379-81.

Chhun S, Troude P, Villeneuve N, *et al*. A prospective open-labeled trial with levetiracetam in pediatric epilepsy syndrome: Continuous spikes and waves during sleep is definitely a target. *Seizure* 2011; 20: 320-5.

Commission on Classification and Terminology of the International League against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia* 1989; 30: 389-99.

Dalla Bernardina B, Fontana E, Michelizza B, Colamaria V, Capovilla G, Tassinari CA. Partial epilepsies of childhood, bilateral synchronization, continuous spike-waves during slow sleep. In: Manelis S, Bental E, Loeber JN, Dreifuss FE. *Advances in epileptology*. New York: Raven Press, 1989: 295-302.

Debiais S, Tuller L, Barthez MA, *et al*. Epilepsy and language development: the continuous spike-waves during slow sleep syndrome. *Epilepsia* 2007; 48: 1104-10.

De Negri M, Baglietto MG, Battaglia FM, Gaggero R, Pessagno A, Recanati L. Treatment of electrical status epilepticus by short diazepam (DZP) cycles after DZP rectal bolus test. *Brain Dev* 1995; 17: 330-3.

Deonna T, Roulet E. Acquired epileptic aphasia (AEA): definition of the syndrome and current problems. In: Beaumanoir A, Bureau M, Deonna T, Mira L, Tassinari CA. *Continuous spikes and waves during slow sleep – electrical status epilepticus during slow sleep*. London: John Libbey, 1995: 37-45.

Hoppen T, Sandrieser T, Rister M. Successful treatment of pharmacoresistent continuous spike wave activity during slow sleep with levetiracetam. *Eur J Pediatr* 2003; 162: 59-61.

Inutsuka M, Kobayashi K, Oka M, Hattori J, Ohtsuka Y. Treatment of epilepsy with electrical status epilepticus during slow sleep and its related disorders. *Brain Dev* 2006 28: 281-6.

Kawakami Y, Matsumoto Y, Hashimoto K, *et al*. Treatment with flunitrazepam of continuous spikes and waves during slow wave sleep (CSWS) in children. *Seizure* 2007; 16: 190-2.

Kellerman K. Recurrent aphasia with subclinical bioelectric status epilepticus during sleep. *Eur J Pediatr* 1978; 128: 207-12.

Kramer U, Sagi L, Goldberg-Stern H, Zelnik N, Nissenkorn A, Ben-Zeev B. Clinical spectrum and medical treatment of children with electrical status epilepticus in sleep (ESES). *Epilepsia* 2008; 50: 1517-24.

Larrieu JL, Lagueny A, Ferrer X, Jullien J. Épilepsie avec décharges continues au cours du sommeil lent. Guérison sous clobazam. Revue d'EEG. *Neurophysiologie Clinique* 1986; 16: 383-94.

Lerman P. Seizures induced or aggravated by anticonvulsants. *Epilepsia* 1986; 27: 706-10.

Loddenkemper T, Cosmo G, Kotagal P, *et al*. Epilepsy surgery in children with electrical status epilepticus in sleep. *Neurosurgery* 2009; 64: 328-37.

Mikati MA, Saab R, Fayad MN, Choueiri RN. Efficacy of intravenous immunoglobulin in Landau-Kleffner syndrome. *Pediatr Neurol* 2002; 26: 298-300.

Morikawa T, Seino M, Osawa T, Yagi K. Five children with continuous spike-waves discharges during sleep. In: Roger J, Dravet C, Bureau M, Dreifuss FE, Wolf P. *Epileptic syndromes in infancy, childhood and adolescence*. London: John Libbey, 1985: 205-12.

Morikawa T, Seino M, Watanabe Y, Watanabe M, Yagi K. Clinical relevance of continuous spike-waves during slow wave sleep. In: Manelis S, Bental E, Loeber JN, Dreifuss FE. *Advances in epileptology*. New York: Raven Press, 1989: 359-63.

Morikawa T, Seino M, Yagi K. Long-term outcome of four children with continuous spike-waves during sleep. In: Roger J, Bureau M, Dravet C, Dreifuss FE, Perret A, Wolf P. *Epileptic syndromes in infancy, childhood and adolescence*. 2nd ed. London: John Libbey, 1992: 257-65.

Morrell F, Whisler WW, Smith MC, *et al*. Landau-Kleffner syndrome. Treatment with subpial intracortical transection. *Brain* 1995; 118: 1529-46.

Nass R, Gross A, Wisoff J, Devinsky O. Outcome of multiple subpial transections for autistic epileptiform regression. *Pediatr Neurol* 1999; 21: 464-70.

Neville BG, Burch V, Cass H, Lees J. Motor disorders in Landau-Kleffner syndrome (LKS). *Epilepsia* 1998; 39: 123.

Nikanorova M, Miranda MJ, Atkins M, Sahlholdt L. Ketogenic diet in the treatment of refractory continuous spikes and waves during slow sleep. *Epilepsia* 2009; 50: 1127-31.

Okuyaz C, Aydin K, Gücüyener K, Serdarolu A. Treatment of electrical status epilepticus during slow-wave sleep with high-dose corticosteroid. *Pediatr Neurol* 2005; 32: 64-67.

Patry G, Lyagoubi S, Tassinari CA. Subclinical electrical status epilepticus induced by sleep in children. *Arch Neurol* 1971; 24: 242-52.

Ribacoba R, Salas-Puig J, Solar DM, Otero B, Herranz JL. The efficacy of the valproic acid-ethosuximide combination in the continuous slow point wave syndrome during sleep. *Neurologia* 1997; 12: 335-8.

Rossi PG, Parmeggiani A, Posar A, Scaduto MC, Chiodo S, Vatti G. Landau-Kleffner syndrome (LKS): long-term follow-up and links with electrical status epilepticus during sleep (ESES). *Brain Dev* 1999; 21: 90-8.

Sinclair DB, Snyder TJ. Corticosteroids for the treatment of Landau-kleffner syndrome and continuous spike-wave discharge during sleep. *Pediatr Neurol* 2005; 32: 300-6.

Snead OC 3rd, Hosey LC. Exacerbation of seizures in children by carbamazepine. *N Engl J Med* 1985; 313: 916-21.

Tassinari CA, Rubboli G. Cognition and paroxysmal EEG activities: from a single spike to electrical status epilepticus during sleep. *Epilepsia* 2006; 47:40-3.

Tassinari CA, Rubboli G, Volpi L, *et al*. Encephalopathy with electrical status epilepticus during slow sleep or ESES syndrome including the acquired aphasia. *Clin Neurophysiol* 2000; 111: S94-102.

Van Lierde A. Therapeutic data. In: Roger J, Bureau M, Dravet C. *Epileptic Syndrome in Infancy, Childhood and Adolescence*. Eastleigh: John Libbey, 1992: 225-7.

Varga ET, Terney D, Atkins MD, *et al*. Transcranial direct current stimulation in refractory continuous spikes and waves during slow sleep: a controlled study. *Epilepsy Res* 2011; 97: 142-5.

Veggiotti P, Beccaria F, Guerrini R, Capovilla G, Lanzi G. Continuous spike-and-wave activity during slow-wave sleep: syndrome or EEG pattern? *Epilepsia* 1999; 40: 1593-1601.

Veggiotti P, Termine C, Granocchio E, Bova S, Papalia G, Lanzi G. Long-term neuropsychological follow-up and nosological considerations in five patients with continuous spikes and waves during slow sleep. *Epileptic Disord* 2002; 4: 243-9.

Veggiotti P, Cardinali S, Granocchio E, Avantaggiato P, Papalia G, Cagnana A, Lanzi G. Motor impairment on awakening in a patient with an EEG pattern of "unilateral, continuous spikes and waves during slow sleep". *Epileptic Disord* 2005; 7: 131-6.

Wang SB, Weng WC, Fan PC, Lee WT. Levetiracetam in continuous spike waves during slow-waves sleep syndrome. *Pediatr Neurol* 2008; 39: 85-90.

Wirrell E, Ho AW, Hamiwka L. Sulthiame therapy for continuous spike and wave in slow-wave sleep. *Pediatr Neurol* 2006; 35: 204-8.

Yasuhara A, Yoshida H, Hatanaka T, Sugimoto T, Kobashi Y, Dyken E. Epilepsy with continuous spike-waves during slow sleep and its treatment. *Epilepsia* 1991; 32: 59-62.