

## Review Article

# Epileptic Encephalopathies with Status Epilepticus during Sleep: New Techniques for Understanding Pathophysiology and Therapeutic Options

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Encephalopathy with status epilepticus during sleep (ESES) is an epileptic encephalopathy, as defined by the International League Against Epilepsy (ILAE) Task Force on Classification and Terminology, that is, a condition in which the epileptic processes themselves are believed to contribute to the disturbance in cerebral function. Clinical manifestations of ESES are heterogeneous: apart from different seizure types, they consist in combinations of cognitive, motor, and behavioural disturbances associated with a peculiar electroencephalographic pattern of paroxysmal activity significantly activated during slow sleep, which culminates in a picture of continuous spikes and waves during sleep (CSWS). The pathophysiological mechanisms underlying this condition are still incompletely understood. Establishing a clear-cut correlation between EEG abnormalities and clinical data, though interesting, is very complex. Computer-assisted EEG analyses especially if combined with functional magnetic resonance imaging (EEG-fMRI) and metabolic neuroimaging have recently emerged as useful approaches to better understand the pathophysiological processes underlying ESES. Treatment of ESES is not just limited to seizures control but it should be focused on controlling neuropsychological outcome through an improvement of the continuous epileptiform activity. General agreement on treatment guidelines is still lacking. Implementation of new techniques might allow a better understanding of the pathophysiology of ESES and could enhance therapeutics options.

## 1. Introduction

Encephalopathy with status epilepticus during sleep (ESES), is an epileptic encephalopathy, “a condition in which the epileptic processes themselves are believed to contribute to the disturbance in cerebral function” (ILAE Task Force on Classification and Terminology). It is characterised by heterogeneous clinical manifestations and a specific electroencephalographic (EEG) pattern of continuous spikes and waves during slow sleep (CSWS).

“Subclinical electrical status epilepticus induced by sleep in children” was firstly described by Patry et al. in 1971 [1]; 6 children showed continuous activation of epileptic discharges in sleep without any specific abnormalities when awake. In this first description no association with clinical symptoms was hypothesised.

In 1977, Tassinari et al. proposed the term “SES” or “ESES” and suggested a connection between electroencephalographic pattern and cognitive impairment [2]. Subsequently, in 1989 the Commission of Classification and Terminology (CCT) of ILAE introduced the more descriptive term of continuous spikes and waves during slow sleep (CSWS) [3]. Currently, the two terms ESES and CSWS are often used interchangeably. Clinical variants associated with an EEG pattern of ESES/CSWS are (1) encephalopathy with CSWS/ESES, (2) Landau Kleffner syndrome (LKS), (3) acquired opercular syndrome, and (4) atypical benign childhood epilepsy with centrottemporal spikes (BECTS).

- (1) Encephalopathy with CSWS/ESES is an epileptic encephalopathy, characterized by different seizure types, combinations of cognitive, motor, and behavioural disturbances, and the peculiar electroen-

cephalographic pattern of paroxysmal activity significantly activated during slow sleep.

- (2) LKS is a rare epileptic syndrome (incidence of 0, 2% in epileptic population) with a clinical onset between 3 and 8 years of age, characterised by acquired aphasia, ESES/CSWS, seizures, neuropsychological deficit, and behavioural disturbances. Awake EEG may contain multifocal or generalised discharges, often posterotemporal; during sleep there is a marked activation as in ESES/CSWS [4]. Hallmark of the syndrome is the acquired aphasia [5]. Language impairment, which could be antecedent to seizure's onset, manifests itself after a period of normal speech development firstly through an auditory agnosia followed by an expressive language deficit.
- (3) Acquired epileptiform opercular syndrome is a rare epileptic syndrome whose onsets are around 4–8 years of age. Clinically it is characterised by oro-facio-lingual deficits, such as severe motor dysfunction, drooling, dysarthria, speech arrest, or weakness of the face and tongue. Seizures are usually focal motor seizures involving the face and occasionally rolandic, partial complex, or atypical absences. The EEG pattern presents centrotemporal bilateral or temporal spikes; sleep is characterised by spike and waves complex with secondary bilateral synchrony and up to a picture of ESES/CSWS [6].
- (4) Atypical BECTS: BECTS is the most frequent benign childhood epilepsy with an onset between 3 and 8 years. It is characterised electroclinically by infrequent nocturnal partial seizures and interictal sharp waves and spike-waves in the centrotemporal regions, significantly activated during slow sleep up to a pattern of ESES/CSWS. Clinically, presents simple partial seizures sometimes generalised which consist of brief hemi facial twitches followed by arrest of speech, drooling with preservation of consciousness. Pharmacological treatment is usually effective and a spontaneous remission often occurs at the end of childhood. Despite being defined as “benign,” long-lasting consequences such as neuropsychological deficits, behavioural problems, and learning disabilities are increasingly recognized in the course of the epilepsy and should not be considered as atypical features. Atypical features are instead early age at onset and frequent spikes or spike-wave discharges which seem to be risk factors for neuropsychological deficits but also for an atypical evolution which can lead to the appearance of severe neuropsychological impairments and continuous spikes and waves during slow sleep [7]. In the presence of these features the term Atypical BECTS is used.

## 2. EEG Pattern, Clinical Manifestations, and Aetiology

An increase in epileptiform discharges during sleep is described in many epileptic syndromes; the prototype

of which is encephalopathy with CSWS/ESES. Since the hallmark of this condition is its electroencephalographic features, a clear definition of EEG pattern is compulsory to define the syndrome. In wakefulness, EEG is usually abnormal and shows epileptiform discharges that are focal, multifocal, or diffuse, often with frontotemporal or fronto-central predominance [8, 9].

The quantification of anomalies during sleep has played a central role in the diagnostic criteria of ESES/CSWS. Percentage of epileptiform activity during sleep can be expressed as spike-wave index (SWI), which is obtained as the total number of minutes of all spike and slow-wave abnormalities divided by the total number of minutes of nonrapid eye movement sleep (NREM) and multiplied by 100. In the first report by Patry et al. [1] “continuous” referred to a SWI of 85%–100% in 3 or more recordings over a period of 1 month. Although threshold values of this parameter were set as 90% [10], >85% [8], 60% [11], 50% [12], and 25% [13], currently a huge increase in EEG abnormalities during sleep associated with clinical symptoms of gradual cognitive and behavioural deterioration is sufficient and considered a hallmark of ESES/CSWS [14]. Recently, a disruption in the downscaling process of slow wave during NREM sleep across the night has been suggested as being involved in the psychomotor regression [15].

Clinical manifestations of ESES/CSWS include various seizure types (partial simple or complex, generalised tonic clonic, and typical and atypical absences seizures) [16] associated with cognitive, motor, and behavioural disturbances. Main clinical feature is the global regression in a wide spectrum of general cognitive impairment which includes deficit in language [17–19], temporospatial skills, [10], and short-term memory [20, 21]. Hyperactivity, instability, disorientation, and aggressiveness have been described [22]. In addition, motor deficits such as ataxia, dystonia, dyspraxia bilateral, or unilateral have also been reported [23].

Longer duration of ESES/CSWS and presence of frontal anomalies superimposed to the typical EEG pattern plus frontal neuropsychological deficit [24] are considered the main predictors for a poor outcome.

Although the majority of the cases have unknown aetiology-cryptogenic cases [25], ESES/CSWS has been sometimes associated with identifiable brain pathology such as migrational disorders [26], shunted hydrocephalus [27], polymicrogyria [28], porencephaly [9], and thalamic lesions [29]. Recently, it has been found that particular types of chromosome aberration, such as 8p deletion, 9p duplication [30, 31], and dup X (p11.22-p11.23), may have propensity to develop a neurological phenotype characterised by ESES/CSWS [32].

## 3. ESES/CSWS New Techniques: Understanding Pathophysiology

The typical presentation of ESES/CSWS, which shows an acute phase with specific EEG pattern, variable seizures types, and psychomotor delay, followed by a recovery phase

with neuropsychological and electrical improvement, seems to suggest the role of continuous interictal activity in determining the psychomotor delay. However, some authors still consider ESES/CSWS activity as an epiphenomenon mirroring the underlying brain pathology, rather than the direct cause of the psychomotor regression [33]. Although the most plausible hypothesis establishes a correlation between interictal EEG activity and neuropsychological impairment, a direct relationship has yet to be defined. This is partly due to intrinsic characteristics of epileptiform discharges, which appear with considerable variability (in terms of topography, amplitude, spatial, and temporal distribution) both during their evolution in the same subject, and across different subjects. Moreover, in the literature large prospective studies are lacking, while there is a prevalence of small series and case reports in which clinical syndromes, EEG criteria, and assessment methods are extremely inconsistent. In the literature, there is only one paper on a large series, just recently published. The authors studied the correlation between clinical features of patients with ESES/CSWS and focal or generalized increase of epileptiform activity (50% or more during nonrapid eye movement sleep compared with wakefulness). They concluded that focal or generalized activation of epileptiform activity in sleep is not related to any significant difference in the clinical features of patients [34].

Improvement of new techniques of investigations and large perspective studies are needed to better understand pathophysiological processes underlying ESES/CSWS. Among neuroimaging techniques, recently emerging useful approaches seem to be the computer-assisted EEG analyses especially if combined with functional magnetic resonance imaging (EEG-fMRI) and metabolic investigations such as positron emission tomography (PET) and single-photon emission-computed tomography (SPECT). Modern methods of EEG source localization (EEG source localization (ESL)) are able to provide information, with temporal resolution in the order of milliseconds, regarding the power source at the onset and during the propagation of epileptic discharges [35]. Valuable tools to analyse the multifocal nature of the EEG signal are the so-called “Blind Source Separation” methods such as independent component analysis (ICA). This technique allows separating in time series, the statistically independent components of an EEG signal using an information-maximization approach [36, 37]. By using this method, it becomes possible to obtain and to separate space-temporal components with a constant topographic pattern over time, but with temporal patterns maximally unrelated to each other. In the literature, there are several studies showing that ICA, despite being “blind” to the waveform of input data, is able to provide more information on the nature of the temporal evolution of bioelectric phenomena than expected. Moreover, ICA has been largely applied to EEG data since it is able to reflect the evolution of space-temporal EEG field [38, 39]. It has also been used to remove ballistocardiogram and ocular artefact which are the two mainly artefacts contaminating EEG data recorded during MRI scan. In LKS and ESES/CSWS EEG, source analysis applied to magneto-encephalographic data

has shown a bilateral spikes generator in or propagate to the perisylvian cortex [40, 41].

Functional magnetic resonance imaging (fMRI) has obtained recognition for being a useful research tool able to map cortical activity in a noninvasive manner. A multimodal approach combining EEG and fMRI (EEG-fMRI) is also a promising technique which may be applied to patients with epilepsy for investigating hemodynamic changes associated with interictal epileptiform discharges (IED). This technique has been already applied to identify neuronal network in primary and secondary generalised epileptiform activity [42] and focal epilepsy [43]. EEG source analyses can contribute to the comprehension of the complex relationships between bioelectric and hemodynamic changes related to interictal spikes. By combining the two techniques—EEG source analysis and EEG-fMRI—it is possible to obtain new information on the dynamics of epileptic networks. EEG source analysis in fact provides high temporal resolution which can improve the localising value of EEG-fMRI, while the spatial definition of the BOLD activity may increase the power of source localization [44].

Furthermore, metabolic investigations such as SPECT as well as PET allow underpinning seizure-related changes of cerebral perfusion, glucose metabolism, and neuroreceptor status. The application of such new techniques in LKS and ESES/CSWS has already suggested, with interesting findings. In LKS, an EEG-fMRI study has shown that spike-wave discharges involve more complex networks than Heschl’s gyrus alone, as suggested in previous literature, and are associated with increased blood-oxygenation level-dependent (BOLD) response in primary and associative auditory cortex, as well as temporoparietal junction [45]. More recently, activation in the perisylvian/prefrontal network associated with both activation and deactivation in the thalamocortical network has also been reported [46].

Similar results have also been demonstrated with metabolic studies. De Tieghe et al. performed a PET study using 18F-fluorodeoxyglucose (FDG) in 9 children during acute and recovery phases of ESES/CSWS. They showed an increased metabolism at the site of epileptic focus and hypometabolism in connected area, in particular prefrontal cortex. Interestingly during the recovery phase a complete or almost complete regression of both hypermetabolic and hypometabolic abnormalities observed during the acute phase was observed. These findings together with the natural history of the disease led the authors to hypothesize the mechanism of remote inhibition to describe the psychomotor regression in ESES/CSWS [47, 48].

A better understanding of the complex pathophysiological mechanisms of ESES/CSWS gained with the assistance of these new techniques can shed light on the possible therapeutic approaches for the treatment of ESES/CSWS. Knowing the epileptic networks likely to be involved in generating the typical EEG pattern of ESES/CSWS and possibly responsible for the psychomotor regression and deficit in language, cognition, and behavior can be a starting point for considering therapeutics options from a different perspective. This might be the case of nonconventional pharmacological options such as vagus nerve stimulation, surgery, and

corticosteroids therapy which are part of the comprehensive therapeutic approach for ESES/CSWS. The hypothesis that seizures but mainly epileptic activity are responsible for cognitive, behavioural, and language deterioration seems to be demonstrated by the recent findings acquired using new techniques. It is getting more evident that EEG abnormalities lead to dysfunctions in different domains and therefore the treatment of encephalopathy with ESES/CSWS requires the reversal of the ESES/CSWS pattern on EEG.

#### 4. Therapy

There is little evidence to guide treatment since only uncontrolled studies and case reports on the efficacy of different antiepileptic drugs (AEDs) are present in literature.

Treatment options for ESES include some “old” AEDs (Valproate [49], Ethosuximide [50], and Benzodiazepines [51, 52]) and “new” AEDs (Levetiracetam [53, 54]). However, evidence to guide therapeutic decisions about these AEDs remains on class IV studies (case reports or expert opinions) and open-label uncontrolled trials (class III). Despite the interesting results, it appears difficult to infer general conclusions from single cases: the number of patients included in these trials in fact is too small to suggest the use of a specific therapy in the whole population. Due to the poor response to a single antiepileptic drug, epileptic syndromes with ESES/CSWS are since the beginning treated with a polytherapy of antiepileptic drugs, such as valproate (VPA) or ethosuximide (ESM) with benzodiazepines [55].

Nonconventional pharmacologic treatment options such as intravenous immunoglobulins [56], ketogenic diet [57], vagus nerve stimulation [58], and epilepsy surgery with multiple subpial transaction [59] have shown efficacy in small case series and are part of the comprehensive treatment plan for children with ESES. Several studies have demonstrated that some AEDs such as phenobarbital (PB) and carbamazepine (CBZ) can worsen ESES/CSWS. Although they may reduce seizures, they are usually not indicated for patients with ESES/CSWS due to the negative effects on neuropsychological outcome and EEG pattern [60–62].

Efficacy and tolerability of steroids in epileptic syndromes with ESES/CSWS have been demonstrated as well [63, 64]. Children who received corticosteroids for cognitive and/or behavioural deterioration associated with ESES/CSWS were retrospectively reviewed. Positive response was found in terms of normalization of the EEG and improvement of neuropsychological function. Urbain et al. [65] reported a normalization of EEG together with the normalization of overnight memory performance in one patient with ESES/CSWS who was treated with corticosteroids therapy. Although in one single case, the hydrocortisone effectiveness in obtaining a normalization of EEG and in positively influencing neuropsychological performances is confirmed. The use of corticosteroids in the treatment of ESES/CSWS seems to be the most effective approach; however, some questions arise. First of all, which is the best option between ACTH and Hydrocortisone? Second, when is it appropriate to start? Third, which dose is the correct one? And finally, for how long the therapy should last?

In the lack of shared protocols the oral therapy (Hydrocortisone) appears to be the most utilized; however, dose and duration are extremely variable. From the literature [66], it is clear that extending the range of AEDs to a large number of drugs does not lead to any results in terms of disappearance of EEG pattern and that the early use of hydrocortisone is crucial as in other epileptic encephalopathies [67]. Studies of long-term followup in ESES/CSWS [68] have shown that the permanent cognitive impairment which most patients experience can be predicted by the absence of response to drug treatment and relapse and longer duration of ESES/CSWS appears to be the major predictor factor of poor outcome. Therefore, it is important to use an appropriate dose of medication to normalize the EEG pattern and repeat a cycle of therapy whenever the EEG pattern should return.

In consideration of the side effects related to high and/or prolonged use of corticosteroid therapy, a possible alternative approach is represented by the use of pulse therapy for short cycles (high e.v. dose for three–five days repeated every three–four weeks) which could be undertaken for long time in relation to the EEG pattern. This approach has been used for other neurological conditions and its effectiveness has been also reported in ESES/CSWS [69, 70]. The aim of this procedure is to prevent the side effects associated to prolonged corticosteroids therapy using high dose for a short time and repeat it several times if the EEG pattern does not disappear or comes back.

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

#### Conflict of Interests

None of the authors of this study has any conflict of interests in relation to this work.

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