

# Electrical Status Epilepticus during Sleep and Evaluating the Electroencephalogram

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## Abstract

### Keywords

- electrical status epilepticus during sleep
- epileptic encephalopathy
- spike-wave index
- epileptiform activity

Electrical status epilepticus during sleep (ESES) is an age-related, self-limited epileptic encephalopathy characterized by heterogeneous clinical manifestations and a specific electroencephalographic pattern of continuous spikes and waves during slow sleep. The etiology of ESES is not completely clear, although structural brain lesions, abnormal immunological markers, and genetic mutations have been associated with the syndrome. ESES was first described in 1971 and since then, the diagnostic criteria have changed multiple times. Additionally, inconsistency between authors in how to record and evaluate the electroencephalogram also leads to variability between studies. These inconsistencies hamper objectivity, comparison, and generalization. Because of this, one of the first priorities of physicians treating this condition should be defining the parameters of this disease so that cooperative building can occur.

## Introduction

Electrical status epilepticus during sleep (ESES) is defined as an age-related, self-limited epileptic encephalopathy.<sup>1</sup> It is characterized by heterogeneous clinical manifestations and a specific electroencephalographic (EEG) pattern of continuous spikes and waves during slow sleep (CSWS). Although some authors use ESES and CSWS interchangeably, most prefer ESES to describe the electrographic pattern and CSWS to describe the clinical syndrome, where ESES is associated with deterioration of cognitive/behavioral and language functions.<sup>2</sup> This classification will be used throughout. In this review, we provide a comprehensive survey on the varying etiologies surrounding ESES. Additionally, in this article we identified the challenges involved in consistently diagnosing the ESES encephalopathies and emphasize points of consensus and disagreement surrounding its definition. Our goal is to provide physicians with the basis of a universal framework to more consistently recognize ESES in pediatric EEGs.

In Patry et al's original article, the unique characteristic defining the diagnosis was an EEG pattern that contained a

spike-wave index (SWI) of 85 to 100% during slow wave sleep.<sup>3</sup> Although Patry et al used the SWI as an inclusion criterion, he made no recommendations on how to obtain the SWI. Additionally, no consistent recommendations are made on what type of EEG to employ or how to score the EEG, leading to variability among studies. These inconsistencies among authors hamper objectivity, comparison and generalization.<sup>4</sup>

ESES presents clinically as various encephalopathies that fall along a spectrum of severity. Patients with significant risks for developing ESES should receive neuropsychological testing as early as possible to establish a cognitive baseline for comparison. This will help physicians recognize cognitive decline in patients with less severe clinical symptoms. Children affected by ESES may undergo an atypical evolution of pure benign childhood epilepsy with centrotemporal spikes (BECTS). This atypical evolution can result in atypical benign childhood focal epilepsy, status epilepticus of BECTS, Landau-Kleffner syndrome (LKS), and epileptic encephalopathy with CSWS, the latter being the most severe.<sup>5</sup> These manifestations are considered different entities, but may be

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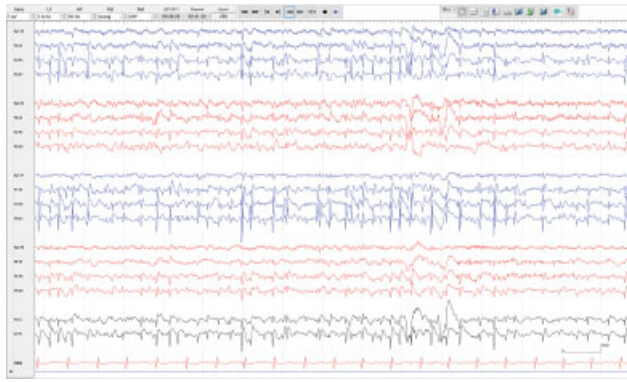
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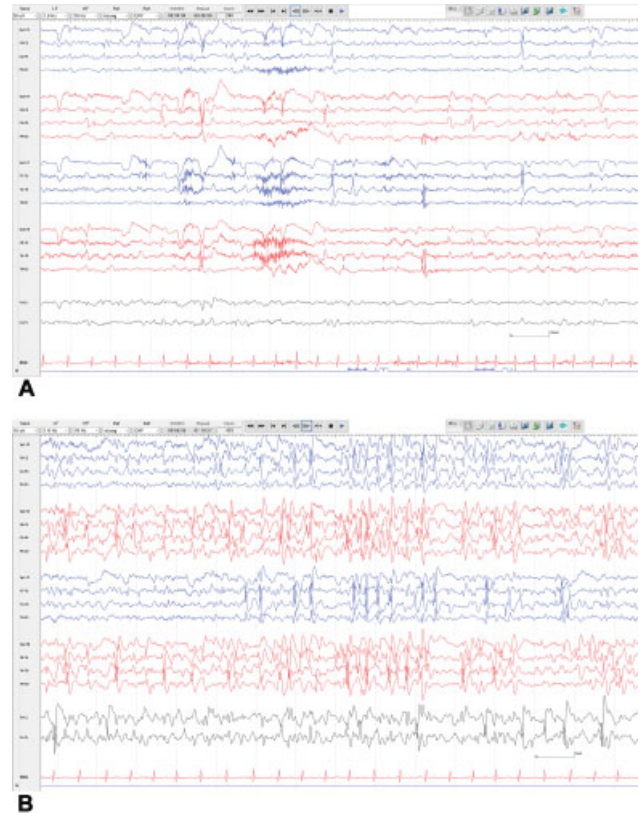


**Fig. 1** A 10-year-old patient who presented at Nationwide Children's Hospital at the age of 7 years with progressive and severe behavior deterioration and symptoms of hyperactivity/inattention. He developed episodes of atypical absence status and bilateral tonic-clonic seizures. His electroencephalogram (EEG) during wakefulness revealed a normal background with no epileptiform activity. His EEG during non-rapid eye movement sleep showed sleep activated, continuous, diffuse spike wave discharges with left-sided predominance with a spike-wave index of 100%. Magnetic resonance imaging demonstrated diffuse atrophy of left hemisphere of unknown etiology. This EEG pattern persisted despite use of steroids, high doses benzodiazepines, multiple antiseizure medications, and left frontal resection (guided by intracranial monitoring). Biopsy showed non-specific changes.

considered as part of a single spectrum of disorders arising from ESES.<sup>5,6</sup> Due to a wide range of various etiologies and an unknown pathophysiology, treatment efficacy for ESES-related syndromes remains low. Nevertheless, meta-analysis of individual patient data suggests a combination of steroids and surgery to be most effective in suitable candidates, with success percentages between 80 and 90%.<sup>7</sup> If a causative lesion is discovered, focal resection (if feasible) may be an effective surgical remedy. Multiple subpial transections may be of benefit for selected cases of LKS.<sup>8,9</sup> Benzodiazepines may also be considered as an alternative with 69% overall treatment success. Conventional antiepileptic drugs were the least effective, with a 49% treatment success percentage.<sup>7</sup>

## Etiology

ESES has various etiologies reported in the literature. The most common structural abnormalities are diffuse atrophy<sup>10</sup> (► **Fig. 1**), porencephaly, pachygyria, cortical abnormalities, and polymicrogyria.<sup>1,10,11</sup> Guerrini et al found that 8% of patients with cortical developmental disorder and seizures and 18% of patients with perisylvian polymicrogyria experienced ESES.<sup>12</sup> Hydrocephalus has also been reported in at least two separate case studies<sup>13,14</sup> and another found ESES in 33% of children with shunted hydrocephalus.<sup>15</sup> Early thalamic lesions are implicated as an etiologic factor.<sup>16,17</sup> In one study, 14% of patients with ESES showed development lesions involving the thalami compared with 2% of patients with epilepsy but no presence of ESES.<sup>18</sup> A prospective study found ESES in 83% of patients with perinatal thalamic lesions.<sup>19</sup> Furthermore, patients with ESES and normal magnetic resonance imaging demonstrated significantly smaller



**Fig. 2** A 11-year-old patient evaluated at Nationwide Children's Hospital presented with right-sided focal motor seizures, bilateral tonic-clonic seizures, and symptoms of autism spectrum disorder. Seizures started at the age of 2 years. His electroencephalogram at the age of 6 years showed independent left and right centromid-temporal spikes during wakefulness (A). The spikes were greatly activated during stage 1 sleep, with a spike-wave index of 100%, consistent with electrical status epilepticus during sleep (B). Genetic testing showed a 292.09 kb loss within chromosome band 16p13.2, which contains a majority of the GRIN2A gene.

relative thalamic volumes compared with control groups.<sup>20</sup> Nevertheless, studies also demonstrated that in more than 50% of patients, no structural brain abnormalities are observed.<sup>21–23</sup> For patients with structural lesions, the ESES pattern can be strictly focal or unilateral, leading to hemispheric ESES or spreading to the homologous contralateral regions, giving a false impression of multifocality.<sup>24</sup>

Immune etiologies may also play a role. A study of 11 ESES patients demonstrated significantly higher levels of interleukin (IL)-1a, -6, -10, chemokine ligand 2, and chemokine ligand8/IL-8 when compared with controls. After immunomodulating therapy, five of these patients showed significantly decreased levels of IL-6 and improvement in the EEG and neuropsychological evaluation.<sup>25</sup>

With the availability of next-generation sequencing and functional assays, new monogenic mutations and copy number variants (CNV) have been identified in patients with ESES.<sup>26,27</sup> The most common mutation involves the GRIN2A gene and it is estimated that up to 20% of patients with Rolandic epilepsy, LKS, or CSWS harbor this mutation (► **Fig. 2**).<sup>26,27</sup> GRIN2A gene encodes for the GluN2A protein,<sup>28</sup>

which is part of a subset of N-methyl-D-aspartate (NMDA) receptors.<sup>27</sup> GRIN2A mutations are either loss-of-function, gain-of-function, or may experience multiple effects.<sup>29</sup>

Mutations in the CNKSR2 gene constitute another common cause. This gene encodes a multidomain synaptic scaffold and synaptic adaptor protein, which connects NMDA receptors associated with the GRIN2A gene to neuronal cell adhesion molecules.<sup>30,31</sup> Loss-of-function in the gene leads to loss-of-function in the synaptic protein.<sup>26</sup> Loss-of-function mutations in CNKSR2 produce intellectual disability, highly restricted speech, attentional deficits with hyperactivity, and brief childhood epilepsy.<sup>32</sup> Patients with this mutation typically experience epileptic discharges during slow wave sleep in the frontal area of the brain, spreading to central or temporal regions. This is in contrast with patients with GRIN2A abnormalities, who have epileptic discharges more posteriorly, in the centroparietal regions.<sup>31,33</sup> However, the available evidence is too limited to establish whether there are distinctive EEG patterns in the different genetically determined ESES.<sup>31</sup>

In a systematic review, 11 monogenic mutations were found to be associated with ESES: GRIN2A: (56.7%), SCN2A (10%), KCNA2 (8.3%), KCNB1 (8.3%), KCNQ2 (3.3%), CNKSR2 (3.3%), SLC6A1 (3.3%), NHE6/SLC9A6 (1.7%), DRPLA/ATN1 (1.7%), neuroserpin/SRPX2 (1.7%), and OPA3 (1.7%). From all these mutations, 86.7% were channelopathies and several CNVs were also implicated.<sup>26</sup> It is very likely that new mutations will continue to be identified, expanding the spectrum of the genetically induced ESES.<sup>26,31</sup> Newly discovered genetic mutations associated with ESES are already having implications on treatment and outcomes. One example is the development of memantine, an NMDA receptor antagonist, which has been reported to improve seizures and CSWS in patients with GRIN2A mutations.<sup>9</sup>

## Epidemiology

ESES is a rare age-dependent and self-limiting condition that occurs only in children and adolescents. In one retrospective study, 1 out of 440 (0.2%) children with epilepsy had ESES.<sup>34</sup> In tertiary epilepsy centers, this number increases to 0.5 to 0.6%.<sup>23</sup> There is also a male predominance (60% of affected patients).<sup>21,35,36</sup> Family history of epilepsy is found in 20%.<sup>35</sup> The mean age of onset is 6 years with a duration of 3 to 26 months. Longer ESES duration correlates with more severe cognitive deficits. Seizures occur before the onset of ESES in around 90%.<sup>36,37</sup>

## Diagnosis and Scoring System

### Changing Definition and Diagnosing Criteria

Landau and Kleffner provided the first clinical manifestation of ESES in 1957 when describing five children with acquired aphasia associated with a convulsive disorder.<sup>38</sup> In 1971, Patry et al provided the first electrographic description of subclinical ESES. Their study focused on six children in whom sleep induced a dramatic modification of the EEG without any clinical accompaniment nor changes in sleep pattern. The inclusion criteria for their study were twofold. First, the

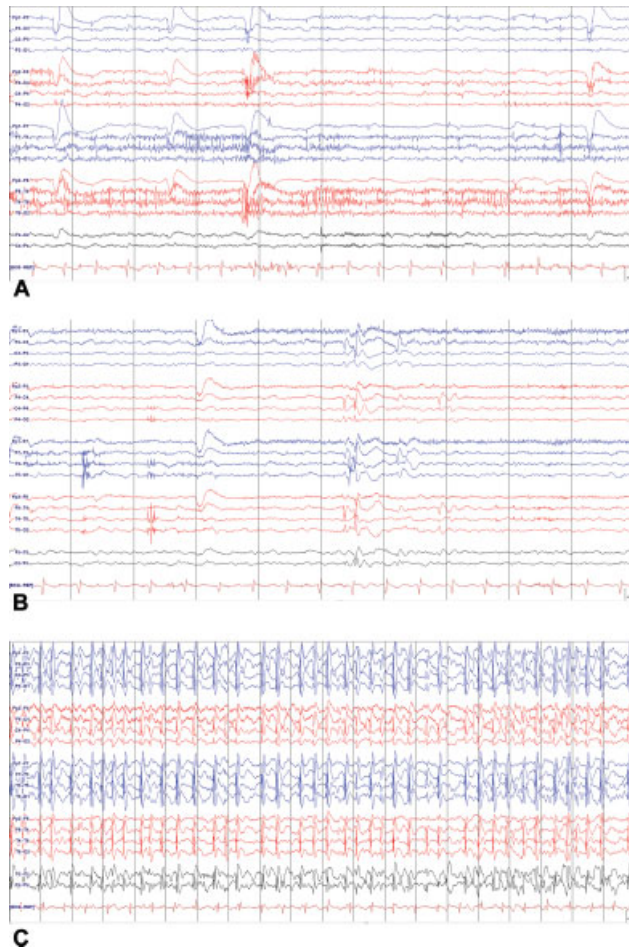
EEG abnormalities had to occupy at least 85% of the slow sleep tracing, measured by the SWI, although no methods were provided for calculating the SWI. Next, these findings had to be repeated on three or more occasions over a period of at least 1 month.<sup>3</sup>

Since then, the definition and diagnostic criteria for the condition have changed multiple times. Six years after the first description, Tassinari et al introduced the terms “encephalopathy related to electrical status epilepticus during slow sleep” and “electrical status epilepticus during slow sleep” to also describe the condition.<sup>39,40</sup> In 1989, the Commission on Classification and Terminology of the International League Against Epilepsy (ILAE) included the term “continuous spikes and waves during slow sleep” (CSWS) as a synonym of status epilepticus during sleep. In the Commission, “epilepsy with CSWS” is included among epilepsies and syndromes undetermined as to whether they are focal or generalized, with the following definition: “Epilepsy with continuous spike-waves during slow sleep results from the association of various seizure types, partial or generalized, occurring during slow sleep, and atypical absences when awake. Tonic seizures do not occur. The characteristic EEG pattern consists of continuous diffuse spike-waves during slow wave sleep, which is noted after onset of seizures. Duration varies from months to years. Despite the usually benign evolution of seizures, prognosis is guarded, because of the appearance of neuropsychologic disorders.”<sup>41</sup>

In 2000, Tassinari et al developed a set of criteria to consistently define ESES. He defined ESES as an age-related and self-limited disorder, whose etiology is unknown, characterized by the following: (1) neuropsychological impairment, in the form of global or selective regression of cognitive or expressive functions, such as acquired aphasia; (2) motor impairment, in the form of ataxia, dyspraxia, dystonia or unilateral deficit; (3) epilepsy, with focal and/or apparently generalized seizures (unilateral or bilateral clonic seizures, tonic-clonic seizures, absences, partial motor seizures, complex partial seizures or epileptic falls); (4) status epilepticus during sleep (SES) occurring during at least 85% of slow wave sleep and persisting on one or more records over a period of at least 1 month.<sup>1</sup> This definition is generally accepted by neurologists and is used to diagnose ESES encephalopathies in epileptic pediatric patients.

However, there is currently disagreement around the criteria requiring SES during at least 85% of the slow sleep cycle. Several case studies have noticed cognitive/mental decline in patients where SES occupied less than 85% of slow sleep. There are reports of cognitive/mental deterioration in patients with a minimum SWI threshold of 25,<sup>21</sup> 30,<sup>42</sup> 50,<sup>43–45</sup> and 60%.<sup>46</sup> Because of this evidence, in 2019, Tassinari et al revised the criteria requiring >85% SES to a less rigid definition. This new definition concludes that a minimum SWI threshold is not necessary for diagnosing ESES once the occurrence of cognitive deterioration associated with sleep-enhanced epileptic activity is demonstrated.<sup>47</sup> This less rigid criterion is more consistent with the ILAE 1989 definition of the syndrome. Because of this, SWIs as low as 25% can be used to diagnose patients with ESES encephalopathies, if matched with an appropriate clinical





**Fig. 3** A 4-year-old girl child patient presented at Nationwide Children's Hospital with subacute onset of "verbal auditory agnosia" (difficulty understanding spoken language), behavioral deterioration, impulsivity, and hyperactivity. Electroencephalogram during wakefulness was normal with no epileptiform activity (A). During sleep, bilateral temporal discharges (more frequent on the left hemisphere) were observed with a spike-wave index (SWI) of 50% (B). The phenotype was consistent with Landau-Kleffner syndrome. She responded acutely to high dose benzodiazepine treatment. However, a few months later, she recurred and the sleep record showed an SWI of 100% (C).

picture.<sup>46</sup> It is also important to consider that ESES is an evolving pattern and EEGs can be performed at different stages of evolution (► Fig. 3). Cognitive outcome is not solely dependent on the resolution of the epileptiform activity alone. Although there was a trend toward those experiencing resolution of ESES to be more likely to experience improvement in language and behavior, data suggests no direct correlation between ESES and a patient's functioning. Because of this, establishing baseline neuropsychological evaluations in the form of parent interviews, behavioral observations, and qualitative language samples is paramount in determining the efficacy of a treatment course and improvements in these areas should be viewed in combination with improvements in the EEG.<sup>48</sup>

### Scoring Techniques

Patry et al, during the first electrographic descriptions of ESES, provided no method for calculating the SWI nor the

type of EEG to employ.<sup>3</sup> Various techniques have been used to quantify the SWI, although no method is consistently recommended in the literature. Therefore, greater consensus in the community is needed before a standardized SWI cutoff can be made. This review article observed that perhaps only epileptiform activity during sleep is needed, if accompanied with the proper clinical manifestations. Because of this, it could be recommended that shorter recordings may be just as valid as overnight recordings.

### Type of Recording

Several methods to register epileptiform EEG activity during sleep relating to ESES have been reported. Yan Liu and Wong and Pavlidis et al used ambulatory 24-hour EEG sleep recordings of patients.<sup>33,49</sup> Several studies employed polysomnography with or without video.<sup>46,50</sup> Whole night EEGs<sup>21,44,45</sup> and nap EEGs<sup>42</sup> were also employed and some used both.<sup>51</sup> Other studies did not specify the type of EEG<sup>1,52</sup> or only noted a continuous EEG.<sup>53</sup>

### Evaluating the EEG

Different portions of the EEG have been analyzed when looking for ESES and no exact method is sometimes specified.<sup>1,54</sup> Previous studies have measured epileptiform activity during the whole night non-rapid eye movement (non-REM) sleep,<sup>39</sup> at least 15 minutes of slow wave sleep,<sup>55</sup> the total duration of each cycle of slow wave sleep,<sup>56</sup> the first 30 minutes of non-REM sleep of the first and last sleep cycles,<sup>57</sup> the first 100 seconds of sleep,<sup>58</sup> the first 5 minutes of non-REM sleep,<sup>59</sup> at least one sleep-wake cycle,<sup>60</sup> the whole-night, first non-REM cycle or nap EEG.<sup>46</sup> Nevertheless, these studies showed that the highest SWI is usually during the beginning of sleep and gradually decreases over the course of sleep.<sup>35</sup> As most of these studies utilized a small sample size, further investigation is needed to determine the validity of this conclusion.

Along with discrepancies about what portion of the EEG to investigate, the method to score the EEG is often varied among studies. Many studies implement the SWI but provide different methods to calculate it. A common, reproducible method to determine the SWI is to quantify the percentage of 1-second bins with at least one spike-wave in them divided by the total seconds observed.<sup>57,59</sup> However, in a survey of 219 neurologists from the Child Neurology Society and the American Epilepsy Society, multiple "short-cut" methods have been used to calculate the SWI, including visual assessment estimation,<sup>35</sup> seconds of epileptiform activity per page, and amount of 1-second bins with spikes per 20 seconds.<sup>2</sup> An additional method being explored is spike frequency (SF), which is the average number of spike wave complexes every 100 seconds. One benefit of using SF is that it does not contain a ceiling effect (SWI cannot exceed 100%). This could be beneficial in situations with high epileptiform activity. However, the clinical significance of this difference has yet to be determined.<sup>59</sup> Semiautomated spike detection software was also recently developed to compare with human readers with no significant differences in the calculated SWI, suggesting an automated approach may be used in the future to more consistently and accurately calculate the SWI.<sup>61,62</sup>

## Conclusion and Future Direction

Although ESES was first described clinically in 1957 and electrographically in 1971, a considerable amount of heterogeneity exists regarding the condition. A precise definition, consistent scoring techniques, and agreement about appropriate treatment paradigms still elude the medical community as a whole. As a result, collaboration and research are made more difficult because of the lack of a common language. One of the first priorities of the community of physicians treating this condition should be defining the parameters of this disease so that cooperative building can occur.

ESES can rob children of the restorative powers of slumber. Therefore, further research in the varying etiologies of ESES is necessary and fortunately rapidly evolving. This research may yield further insight into the varying etiologies that can cause ESES, which may lead to promising treatment targets.

### Conflict of Interest

None declared.

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