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# Response to adrenocorticotropic in attention deficit hyperactivity disorder-like symptoms in electrical status epilepticus in sleep syndrome is related to electroencephalographic improvement: A retrospective study

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ABSTRACT

*Introduction:* Encephalopathy with electrical status epilepticus in sleep (ESES) syndrome is a rare epilepsy syndrome of childhood that is characterized by sleep-induced epileptiform discharges and problems with cognition or behavior. The neuropsychiatric symptoms in ESES syndrome, among which the ADHD-like symptoms are prominent, bear a close resemblance to symptoms in various developmental disorders. Positive response to adrenocorticotropic hormone (ACTH) is associated with the normalization of the EEG and improvement of neuropsychiatric function. This study aimed to determine the improvement in ADHD-like symptoms in response to ACTH and establish a relationship between improvement in clinical symptoms and EEG parameters.
*Methods:* Seventy-five patients with ESES syndrome, who had clinically displayed ADHD-like symptoms, had been treated with ACTH for ESES, and their medical records were retrospectively reviewed. Sleep EEGs were recorded at referral and follow-up visits, and short courses of ACTH were administered when spike–wave index (SWI) was ≥15%. The assessment of treatment effectiveness was based on reduction in SWI and the clinician-reported improvement in ADHD-like symptoms. Statistical analyses were conducted in order to investigate the relationship between the clinical and EEG parameters.
*Results:* Following treatment with ACTH, a reduction in SWI in all the patients was accompanied by a mean improvement of 67% in ADHD-like symptoms. Disappearance/reduction of foci and cessation/reduction of seizures were achieved in patients with formerly antiepileptic-resistant seizures. Multiple linear regressions established that pretreatment SWI and treatment delay predicted posttreatment SWI, while reduction in SWI, treatment delay, and the presence of foci predicted improvement in ADHD-like symptoms.
*Discussion:* Improvement in ADHD-like symptoms showed high correlation and was timely with the resolution of ESES. It is suggested that ESES and ADHD may be the two different expressions of a common neurobiological abnormality. With enhanced interpretation of sleep EEG, a more thorough assessment and treatment of neurodevelopmental disorders is possible.



## 1. Introduction

Electrical status epilepticus in sleep (ESES) syndrome is a rare age-related condition occurring only in childhood with an incidence of 0.2–0.5% of childhood epilepsies [1]. It consists of sleep-induced paroxysmal discharges of spike–wave complexes, and ESES syndrome is an epileptic encephalopathy often with global or selective effects of variable severity on social, behavioral, and cognitive development. In many but not all children, it is characterized by usually rare seizures associated with neuropsychiatric deficits [1–3]. Global or more selective impairments can worsen over time and may occur along a spectrum of severity. The epileptic activity is believed to contribute to neuropsychiatric impairments [4]. Severity is correlated with spike–wave index (SWI) in many studies [5,6]. Hormonal therapy is effective in ESES with reported improvements in neuropsychiatric function and outcome [7]. Both animal and human data support the view that the treatment of epileptiform discharges (ED) alleviates neuropsychiatric impairments [8–10].

*Abbreviations:* ACTH, adrenocorticotropic hormone; ADHD, attention-deficit and hyperactivity disorder; ED, epileptiform discharges; ESES, electrical status epilepticus in sleep; M, mean; SD, standard deviation; SWI, spike–wave index.

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Electrical status epilepticus in sleep syndrome is frequently associated with comorbid attention-deficit/hyperactivity disorder (ADHD) or ADHD-like symptoms, and ESES activity has been documented in various developmental disorders [11–14]. Behavioral and attentional regulation difficulties overlap with or mimic ADHD-like symptoms. Conversely, EEG displays focal or generalized ED in ADHD with an overall prevalence ranging from 6.1% to 68.8% in various studies [15–17]. Electroencephalography abnormalities contribute to cognitive impairment, and the region of the brain with intense epileptiform activity supposedly gives rise to specific neuropsychiatric symptoms [8,11,16,18,19].

Although a substantial number of publications report improvement in cognitive and behavioral impairment following treatment of ESES activity, sufficiently large series on the subject are limited in number [7]. As part of this retrospective chart review, we evaluated patients with ESES and coexisting ADHD-like symptoms. A relatively large series of patients had been followed up with sleep EEG and had been treated with ACTH. An EEG-guided treatment regimen was administered to prevent the progressive impairment of neuropsychiatric function. Our aim was to determine the improvement in ADHD-like symptoms and establish a relationship between improvement in clinical symptoms and EEG parameters.

## 2. Materials and methods

The medical records of 75 patients (50 males and 25 females) who visited our private office between 2002 and 2016 were retrospectively reviewed. Along with ADHD-like symptoms, all patients had ESES activities on their EEGs and, thus, were treated with ACTH. Patients were included if (a) they had satisfactory medical records, (b) their biochemical investigations and imaging were within the normal range, (c) they had not been using stimulant drugs in the previous 7 days prior to EEG at referral, and (d) they had sufficient treatment compliance.

Six patients exhibited seizures as manifesting complaints, and the remaining 69 patients were referred to our office because of uncontrolled seizures and/or uncontrolled neuropsychiatric symptoms, among which the ADHD-like symptoms (inattentiveness, hyperactivity, and impulsiveness) were most prominent. The 69 patients had been previously followed up at other centers (the child psychiatry and child neurology units of several university hospitals) but had never received ACTH therapy antecedently.

### 2.1. Clinical assessment and EEG recording

Neurological history and examination were carried out by one of the authors of this study. Neuropsychiatric tests and previous EEG recordings (if present) were evaluated. Treatment histories, especially antiepileptic drugs preceding ACTH, were recorded. Questions at referral addressed age, the onset of ADHD-like symptoms, and the number of epileptic seizures per month. Information regarding subtle seizures, febrile convulsions, and treatment delay (defined in Table 1) was gathered.

Experienced in pediatric epileptology, one of the authors of this study examined the EEG recordings. Sleep EEGs, encompassing a minimum of 30-min nonrapid eye movement sleep, were recorded without sedation upon referral and at follow-up visits. The international 10–20 electrode placement system was used for all EEGs. The percentage of epileptiform activity, expressed as SWI, was measured, and reduction in SWI was calculated (Table 1). Despite the name SWI, ESES/epileptiform paroxysmal activities included both the typical and atypical spike–wave paroxysms. Some EEG samples had been presented in a previous study [20]. The number of EEG recordings and the number, site, and spread of foci were noted for each patient.

In our previous study, we have illustrated that the onset or recurrence of neuropsychiatric symptoms is associated with the progressing epileptiform activity; when SWI is around 10–15%, neuropsychiatric symptoms appear [20]. Our argument is that without treatment, lower levels of SWI gradually evolve to higher levels where the drop in neuropsychiatric performance becomes more pronounced [20]. Treating ESES when SWI is low may improve the neuropsychiatric outcome. Shared protocols regarding treatment are absent in the literature [7]. Based on our clinical experience, we believe that prolonged ACTH administration is unwarranted. Despite prolonged ACTH use, many patients relapse following treatment discontinuation. Thus, similar to the approach in West Syndrome EEG, guided and repeated short-term ACTH administrations have been considered. In order to treat the ESES syndrome with the gradual build-up of spike–wave activity and the related neuropsychiatric symptoms, patients received short courses of ACTH when SWI was ≥15%: 0.03 mg/kg/day if the patient's body weight was <30 kg, 1 mg/day if the patient's body weight was >30 kg, 6–10 days if SWI was 15–30%, and 12–15 days if SWI was >30%. Following a course of treatment, SWI falls (and symptoms subside) usually to rise again after some time specific to the patient. Recurrent relapses (Table 1) occur both electroencephalographically and clinically. This, we believe, necessitates the repeated short courses of ACTH.

Neuropsychiatric symptom improvement following treatment was assessed according to patient/caregiver interviews at follow-up visits. Interviews focused not only on the reduction of ADHD-like symptoms but also on measures of functionality, school performance, social and emotional problems, inappropriate behavior, executive functions, and adaptive life skills [21]. Based on this interview to collect patient/caregivers' view about the improvement in behavior following treatment with ACTH, one of the authors of this study determined the percentage of improvement according to the assessment at follow-up visits.

At referral, patients/caregivers were informed about the fluctuating course through treatment and that recurrence frequency and improvement levels were different among different patients but similar within the same patient. Initial follow-up visits were planned either for 2 months subsequent to the initial ACTH, or for earlier, if neuropsychiatric symptoms/seizures recurred. Patients/caregivers were asked to note the time of onset of improvement and recurrence, onset and duration of maximum improvement, and the period with strongest response in between the two visits. Treatment effectiveness was based on this

**Table 1**
Table of definitions.

| Terms | Definitions |
|---|---|
| ESES/epileptiform paroxysmal activity | Includes both the SW paroxysms and other generalized pathological paroxysms without the typical SW configuration, such as the 'newly onset' SW paroxysms, lower in amplitude and higher in frequency (<3/s) than mature paroxysms, or the morphologically typical and/or atypical SW paroxysms without spikes which are of higher amplitude than baseline activity |
| Spike–wave index (SWI) (%) | The percentage of epileptiform paroxysmal activity, which is defined as the total duration of epileptiform paroxysms relative to total slow sleep duration with the exception of the REM phase |
| Treatment delay | Time elapsed between the onset of ESES syndrome and the initial ACTH therapy |
| Relapse | Either SWI ≥ 15% or symptom recurrence or deterioration (≥1 month following the end of treatment with ACTH) |
| Reduction in SWI (%) | The percentage of decrease from the pretreatment to the posttreatment SWI (e.g., if pretreatment SWI is 80% and posttreatment SWI is 20%, then reduction in SWI is 75%) |

SW, spike and wave; SWI, spike–wave index; REM, rapid eye movement; ACTH, adrenocorticotropic hormone.