

Continuous spikes and waves during slow sleep related to sulthiame?

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Received March 19, 2021; Accepted June 19, 2021

Self-limited epilepsy with centrotemporal spikes (SLECTS) is a common and well-delineated epilepsy syndrome in childhood. Atypical evolution of SLECTS is defined by the appearance of severe neuropsychological impairment and continuous spike and waves during slow sleep (CSWSS) [1, 2]. Sulthiame was found to be useful as add-on treatment for SLECTS and CSWSS [3-5]. Here, we present two patients with SLECTS, who showed the atypical clinical manifestations associated with CSWSS which may have been induced by sulthiame, and discuss the possible pharmacological mechanisms involved. Case 1 was an 11-year-old boy who had bi-monthly right focal motor seizures, anarthria, and sialorrhea during sleep and an interictal awake and sleep EEG showing predominantly left bilateral centro-temporal spikes (*figure 1A*), compatible with SLECTS, between the ages of two and five years. Carbamazepine at 20 mg/kg/day was given without response and was discontinued. Sodium valproate at 30 mg/kg/day was started. Neurological and laboratory examinations, as well as brain MRI, were normal. At age seven, focal seizures increased. Response to topiramate at 5 mg/kg/day, lamotrigine at 6 mg/kg/day, and levetiracetam at 50 mg/kg/day was poor. At age eight, seizures continued to be frequent, but the EEG recording did not show CSWSS. Topiramate was withdrawn and sulthiame at 20 mg/kg/day was started in combination with levetiracetam at 50 mg/kg/day. The seizures increased and daily absence seizures started to occur together with beha-

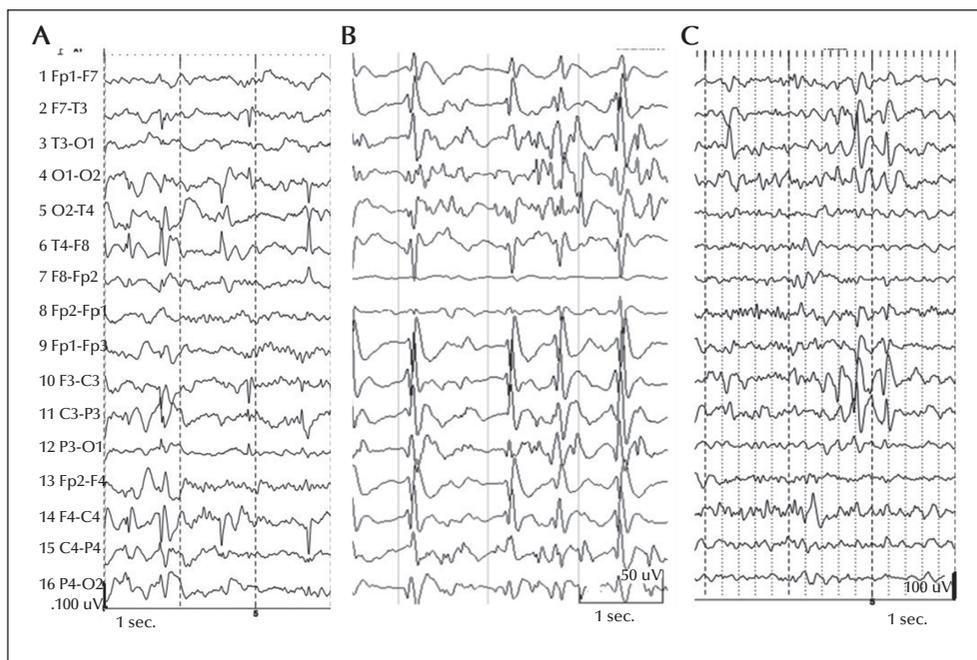
vioural disturbances. A negative myoclonus involving the neck and trunk muscles, provoking head drops and gait instability, was observed. The EEG showed CSWSS (*figure 1B*) with a spike-wave index of >85%.

At age eight, sulthiame was discontinued and the patient slowly recovered gait while the CSWSS disappeared within approximately two months. The interictal EEG recording during sleep showed frequent left temporal spikes. At age 10 years, clobazam at 0.5 mg/kg/day was added to levetiracetam at 40 mg/kg/day due to sporadic seizures. At 14 years of age, he had six-monthly focal motor seizures with normal neurological examination. His last EEG recording showed occasional central-left spikes (*figure 1C*).

Case 2 had a brief right hemifacial clonic seizure, anarthria, and sialorrhea during sleep associated with frequent left centro-temporal spikes on sleep EEG, compatible with SLECTS, at age seven. The patient had no personal or family history of epilepsy. Neurological and laboratory examinations, as well as brain MRI, were normal. Six months later, he had another brief focal seizure with similar features during sleep. Clobazam at 0.5 mg/kg/day was started. At age eight years, the number of focal seizures increased and levetiracetam at 30 mg/kg/day was added. Sleep EEG showed frequent independent bilateral spikes. Eight months later, the seizure rate again increased with a high frequency of synchronous bilateral spikes on EEG. Clobazam was withdrawn and sulthiame at 20 mg/kg/day was added

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doi:10.1684/epd.2021.1359



■ **Figure 1.** (A) The EEG recording during sleep shows bilateral spikes before sulthiame was introduced (A), continuous spikes and waves during slow sleep after sulthiame was introduced (B), and left centro-temporal spikes after sulthiame was discontinued (C).

to levetiracetam. Focal seizures started to occur daily together with behavioural disturbances. The EEG showed CSWSS with a spike-and-wave index of >85%. Therefore, sulthiame was discontinued and behavioural disturbances and CSWSS disappeared. The interictal sleep EEG showed right centrotemporal spikes.

At age 13 years, he received levetiracetam at 20 mg/kg/day. He had sporadic focal motor seizures, normal neurological examination, and occasional bilateral spikes on EEG.

The two patients presented here had electroclinical features of SLECTS with an atypical clinical evolution characterized by increased seizure frequency, negative myoclonus, absence seizures, and behavioural disturbances associated with CSWSS, possibly induced by sulthiame. The appearance of clinical symptoms when sulthiame was started and their disappearance soon after the antiseizure medication was discontinued led to the suspicion of sulthiame as the culprit.

An inverse pharmacodynamic effect may be due to an incorrect diagnosis of the seizure type or syndrome, an incorrect drug, or a consequence of drug intoxication due to excessive dosage or drug combinations [6], however, none of these were

plausible explanations in our patients. Exacerbation of seizures may also be due to an adverse interaction between the mode of action of a drug and the pathogenetic mechanisms underlying specific seizure types or syndromes. This seizure exacerbation may occur at therapeutic dosages and in patients with epilepsy types that generally respond well to the drug in question [7]. In our patients, the latter mechanism may have been involved.

These cases are an example of the need for close monitoring of the pharmaceutical management that may lead to CSWSS in our patients.

In our patients with SLECTS, seizure aggravation associated with CSWSS might have been induced by sulthiame, however, different mechanisms should be considered. Sulthiame remains a valuable option in the treatment of SLECTS and CSWSS. ■

Supplementary material.

Summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

Disclosures.

None of the authors have any conflicts of interest to disclose.

References

1. Fejerman N, Caraballo RH. *Benign focal epilepsies in infancy, childhood and adolescence*. Montrouge: John Libbey Eurotext, 2007.
2. Fejerman N, Caraballo R, Tenembaum SN. Atypical evolutions of benign localization-related epilepsies in children: are they predictable? *Epilepsia* 2000; 41(4): 380-90.
3. Fejerman N, Caraballo R, Cersósimo R, Ferraro SM, Galicchio S, Amartino H. Sulthiame add-on therapy in children with focal epilepsies associated with encephalopathy related to electrical status epilepticus during slow sleep (ESES). *Epilepsia* 2012; 53(7): 1156-61.
4. Topçu Y, Kılıç B, Tekin HG, Aydın K, Turanlı G. Effects of sulthiame on seizure frequency and EEG in children with electrical status epilepticus during slow sleep. *Epilepsy Behav* 2021; 116: 107793.
5. Kanmaz S, Simsek E, Serin HM, Yilmaz S, Aktan G, Tekgul H, Gokben S. Sulthiame add-on treatment in children with epileptic encephalopathy with status epilepticus: an efficacy analysis in etiologic subgroups. *Neurol Sci* 2021; 42(1): 183-91.
6. Guerrini R, Belmonte A, Genton P. Antiepileptic drug-induced worsening of seizures in children. *Epilepsia* 1998; 39 (Suppl 3): S2-10.
7. Perucca E, Gram L, Avanzini G, Dulac O. Antiepileptic drugs as a cause of worsening seizures. *Epilepsia* 1998; 39(1): 5-17.

TEST YOURSELF

(1) What are the three main explanations for an inverse pharmacodynamic effect?

(2) What are the main indications for sulthiame?

(3) Should sulthiame still be considered a valuable option for the treatment of CSWSS?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.
