

# Encephalopathy with status epilepticus during sleep (ESES) induced by oxcarbazepine in idiopathic focal epilepsy in childhood

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## Summary

**Encephalopathy with status epilepticus during sleep (ESES) is an age-related disorder characterized by neuropsychological regression, epilepsy and a typical EEG pattern of continuous epileptiform activity (> 85%) during NREM sleep. Cases of worsening or induction of ESES with phenytoin, carbamazepine and phenobarbital have been reported. We describe a child with benign epilepsy with centrotemporal spikes (BECTS) in whom treatment with oxcarbazepine (OXC) induced ESES. The patient was studied through repeated clinical-neuropsychological evaluations and 24-hour EEG recordings. He was treated with OXC two months after epilepsy onset. One month after starting OXC, he developed an abrupt and severe cognitive deterioration. A 24-hour EEG and neuropsychological tests showed an electroclinical picture compatible with ESES. Withdrawal of OXC and introduction of other drugs were followed by a prompt improvement. Five months after ESES onset, a 24-hour EEG was normal. Our report indicates that OXC can induce ESES in BECTS.**

**KEY WORDS:** antiepileptic drugs (AEDs), benign epilepsy of childhood with centrotemporal spikes (BECTS), encephalopathy with status epilepticus during sleep (ESES), idiopathic focal epilepsies of childhood, oxcarbazepine (OXC).

## Introduction

Encephalopathy with status epilepticus during sleep (ESES) is an age-related disorder characterized by epilepsy with different seizure types, neuropsychological regression, motor impairment and a typical EEG pattern of continuous epileptiform activity for more than 85% of non-rapid eye movement (NREM) sleep (Tassinari et al., 2012). The epilepsy is usually well controlled by antiepileptic treatment and tends to resolve with age, whereas the prognosis of the cognitive deficits and behavioral disturbances is guarded and deficits can often persist until adulthood. Antiepileptic drugs (AEDs) commonly used in ESES are valproate, ethosuximide, levetiracetam, sulthiame and benzodiazepines, whereas other AEDs, such as phenytoin, carbamazepine and phenobarbital, can worsen the ESES electroclinical picture, or even induce the appearance of ESES in benign focal epilepsies of childhood [for a review see Tassinari et al., 2012]. Oxcarbazepine (OXC) is a new AED that has been shown to be effective and well tolerated for the treatment of children with focal epilepsies, particularly benign epilepsy of childhood with centrotemporal spikes (BECTS) (Coppola et al., 2007). However, some reports have shown that OXC may aggravate seizures and worsen the EEG picture in children with idiopathic focal epilepsies of childhood (IFEC), including BECTS (Chapman et al., 2003; Grosso et al., 2006; Vendrame et al., 2007). Neuropsychological deterioration and exaggeration of EEG epileptic discharges during sleep, as seen in ESES, have been described following the introduction of OXC in only two children with atypical IFEC (Grosso et al., 2006). In this report we describe an additional patient in whom treatment with OXC induced ESES.

## Case report

A male aged 7 years and 1 month, with an unremarkable perinatal and family history and normal psychomotor development, started to present at the age of 6 years and 10 months seizures characterized by smacking sounds, perioral twitching, eye deviation to the right evolving to jerks in the right limbs, and hyper-tonus. Seizures occurred several times per week exclusively during nocturnal sleep. Interictal EEG

showed a spike-wave focus in the left central region (Fig.1a). Brain magnetic resonance imaging was normal. A diagnosis of BECTS was made. After two months, due to the persistence of frequent seizures, treatment with OXC was started; this was followed initially by seizure decrement. However, one month later, an abrupt cognitive deterioration appeared, consisting of severe language problems, difficulties in remembering words and numbers, and behavioral and attention disorders. Following the appearance of absence-like seizures, OXC was withdrawn, and valproate and clobazam were introduced. At the same time, a 24-hour EEG recording showing left hemispheric spike waves for 85% of NREM sleep (Fig. 1b) and a neuropsychological evaluation (subsets of the TEA-Ch, NEPSY and WPPSI – the patient was not able to complete these tests) demonstrating severe cognitive decline, with prominent language and attention deficits, were consistent with ESES. Sulthiame was added and a cycle of prednisolone was also performed. One month after OXC discontinuation and introduction of the AEDs and steroid treatment, the patient's language improved, whereas the inattentiveness and hyperactivity persisted. At the first neurophysiological follow-up, five months after ESES onset, a 24-hour EEG recording showed the disappearance of spike-wave activity during sleep (Fig.1c) and the neuropsychological evaluation showed an age-appropriate cognitive level, with further improvement of language; however, inattentiveness and moderate behavioral problems were still present (RIAS: verbal IQ = 96, 40<sup>th</sup> percentile; performance IQ = 88, 21<sup>st</sup> percentile; overall IQ = 92, 30<sup>th</sup> percentile). Clinical follow-up and yearly 24-hour EEG recordings through to present – the patient is now aged 10 years and 2 months – have not shown electroclinical relapses, and normal school performances and behavior have consistently been reported. The most recent neuropsychological evaluation (WISC IV, TEA-Ch, RIAS, D-KEFS and a subset of the NEPSY), performed 2 years and 5 months after ESES resolution, showed an age-appropriate overall IQ with persistence of moderate language and attention disturbances (RIAS: verbal IQ = 96, 40<sup>th</sup> percentile; performance IQ = 101, 52<sup>nd</sup> percentile; overall IQ = 98, 45<sup>th</sup> percentile).

## Discussion

Antiepileptic drug-induced worsening of seizures is a clinical problem that can be unrecognized or overlooked by the treating physician. In ESES, worsening of the clinical and EEG picture has been observed with several AEDs, particularly carbamazepine (Tassinari et al., 2012). In addition, *de novo* induction of ESES in children with IFEC has been observed with carbamazepine, valproate and phenobarbital (Tassinari et al., 2012). In this report we describe a child who developed ESES after the introduction of OXC for the treatment of BECTS. OXC is a new AED that has been developed through structural variation of carbamazepine, with the aim of avoiding the side effects caused by carbamazepine metabolites. However, significant differences in the OXC mechanism of action and metabolism, as well as various clinical evidence (fewer side effects and interactions with other drugs, better tolerability) show that OXC and carbamazepine have distinctly different characteristics and properties (Schmidt and Elger, 2004).

In our patient, OXC initially reduced the seizure frequency, but then caused the appearance of cognitive and behavioral deterioration, the appearance of new seizure types, and a marked increase of EEG spike activity during sleep (85% of NREM sleep), features consistent with a diagnosis of ESES. Withdrawal of OXC and introduction of the drugs used for ESES (valproate, clobazam, sulthiame, and later a cycle of steroids) led to a rapid clinical improvement.

Although OXC has been demonstrated to be an effective drug for the treatment of IFEC, some papers have also shown, in the same group of epilepsies, the possibility of seizure and EEG aggravation (Chapman et al., 2003; Vendrame et al., 2007). In addition, worsening of an ongoing ESES has also been reported (Caraballo et al., 2013). *De novo* appearance of ESES following the introduction of OXC was observed by Grosso et al. (2006) in two out of three children with atypical BECTS. In these two children, OXC provoked an increase in seizure frequency, the appearance of new seizure types, and the extreme activation of EEG epileptic abnormalities during sleep, as in ESES. ESES disappeared after OXC withdrawal and treatment with valproate. At variance with the cases reported by Grosso et al. (2006), our patient was

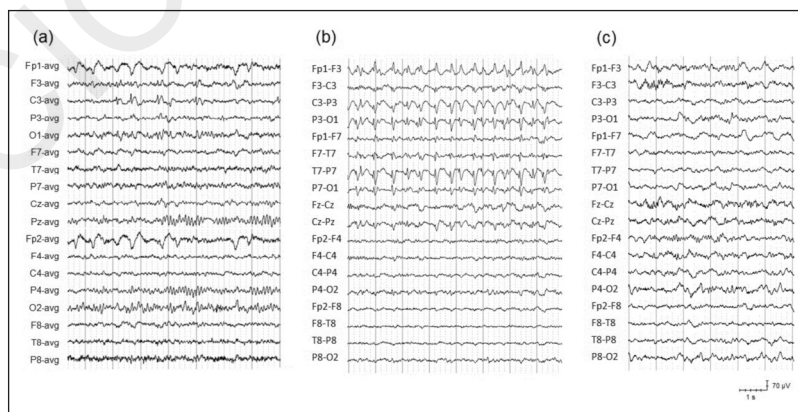


Figure 1 - Sleep EEG recordings in a child with idiopathic focal epilepsy and ESES induced by oxcarbazepine.

(a) EEG before ESES onset (7 years). Moderate active spike-and-wave focus in the left central region. (b) After the introduction of OXC therapy (age 7 years and 3 months). Spike-and-wave discharges in the left fronto-centrotemporal region almost continuous during NREM sleep (Spike and Wave Index: 85%). (c) About 3 months after OXC discontinuation, epileptiform abnormalities during sleep have disappeared.

Recording parameters: speed=20 mm/s; sensitivity=150  $\mu$ V/cm; filter=70-1.6 Hz; electrode positions according to Nuwer MR et al (1998).

diagnosed with typical BECTS and the appearance of ESES was preceded by an initial transitory reduction in the frequency of the seizures.

In conclusion, in our case, the rapid appearance of ESES after introduction of OXC, its brief duration and its prompt resolution without relapses suggest that OXC acted as a precipitating factor for ESES, and that its discontinuation may have contributed to ESES disappearance. Although OXC has been demonstrated to be an effective and well tolerated treatment in IFEC, our report adds to the existing evidence, reported in a few studies, of ESES induced by OXC in IFEC. Clinicians should be aware of the possibility of drug-induced ESES when children with IFEC, treated with OXC, start to present clinical and EEG deterioration.

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