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Possible induction of West syndrome by oxcarbazepine therapy in a patient with complex partial seizures

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ABSTRACT – Oxcarbazepine has been reported to precipitate myoclonic, generalised tonic-clonic, absence, and complex partial seizures, and carbamazepine to precipitate absences, myoclonic seizures and spasms. Here, we report a one-year, six-month-old girl with complex partial seizures who developed infantile spasms, developmental regression, and hypsarrhythmia during the two weeks directly following initiation of oxcarbazepine (14 mg/kg/day). All of these resolved within a few days after discontinuation of this medication. Although we cannot rule out that the above association may have been coincidental, or that the improvement may have been due to concurrent therapy, this case raises the possibility that oxcarbazepine, like carbamazepine, may precipitate infantile spasms and West syndrome.

Key words: carbamazepine, AED, seizure, infantile spasm, epilepsy, hypsarrhythmia

Oxcarbazepine (OXC), a keto-analog of carbamazepine (CBZ) (Kalis and Huff, 2001), has been known to aggravate some types of pre-existing seizures, to precipitate new seizure types, and to worsen electroencephalographic (EEG) changes in certain epilepsy syndromes (Chapman *et al*., 2003; Gelisse *et al*., 2004; Grosso *et al*., 2006; Vendrame *et al*., 2007; Menon *et al*., 2011). Seizure types so far reported to be induced by OXC include myoclonic, generalised tonic-clonic, absence, and even complex partial seizures (Gelisse *et al*., 2004; Vendrame *et al*., 2007). Here, we report a patient with complex partial seizures who developed infantile spasms and West syndrome, apparently secondary to OXC therapy.

Case Report

The girl, born after a full-term pregnancy and normal vaginal delivery, was healthy until the age of 17 months when she presented to an outside neurologist with a history of three complex partial seizures in the preceding three days. These consisted of staring, unresponsiveness, unilateral clonic activity, and nystagmus with occasional generalisation leading to tonic body stiffening, each lasting for 10-20 seconds and

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followed by about 15 minutes of postictal sleepiness. Developmentally, the patient was normal. She sat at six months of age, crawled at nine months, walked and said her first words at one year, and had a vocabulary of 30 to 50 words at 17 months of age. Medical history was otherwise unremarkable. Family history of epilepsy or developmental delay was negative. She lived with both of her parents who were very devoted carers. Her treatment was started with levetiracetam (25 mg/kg/day), but her seizures did not respond and continued to increase up to an average of 10 seizures a day. She was admitted by her neurologist 12 days later because she was having up to 10 partial seizures per day with occasional secondary generalisation. Interictal EEG revealed frequent right posterior quadrant delta slowing with C4-P4 focal sharp waves and spikes. There were much less frequent left frontal focal sharp waves and spikes (*figure 1A*). Ictal recordings showed electrographic seizures with focal onset from T6. This consisted of focal (T6) sharp rhythmic theta activity that built up over several seconds into high-voltage sharp delta involving the entire right hemisphere, then both hemispheres, with maximal amplitude over the right posterior quadrant. Brain MRI was normal. She was discharged with 14 mg/kg/day of OXC and levetiracetam was tapered. Over the next two weeks, she developed spasms (multiple per day) consisting of repetitive episodes of sudden flexion of torso with extension of extremities that clustered around the time she would go to sleep, usually in the evenings. In addition, there was persistence of her complex partial seizures which were also occasionally associated with left-sided Todd's paralysis. Gradually, during these two weeks, the spasms became the predominant, and then the only, seizure type. During the same two-week period, she also had severe regression in all developmental domains; she lost her ability to walk, lost all speech, could not follow even simple commands, could not feed herself, and she became very irritable and hypotonic. She was seen by her referring neurologist three days before she presented to us because of the above regression and because she was having an average of 10 spasms per day. Treatment was started at that time with 3 mg/kg/day of topiramate. However, when she presented to us three days later, by then at the age of 18 months, she had not experienced any significant improvement. She was hospitalised on the same day for video-EEG monitoring. Interictal EEG over the next 48 hours revealed continuous hypsarrhythmia throughout all her awake and asleep recordings (*figure 1B, figure 1C*). Ictal recording demonstrated frequent spasms as described above with corresponding delta wave activity lasting 1.5 to 2 seconds. Other spasms were associated with desynchronisation of the background, consisting of one-second periods of low-voltage, fast, beta activity superimposed on low-voltage delta activity during these spasms.

Her work-up during the hospital stay was normal and included the following: blood/plasma/serum (complete and differential blood count, lactic acid, enzyme assay for lysosomal storage disorders [β-galactosidase, β-mannosidase, β-hexaminidase A, arylsulfatase A, and galactocerebrosidase], amino acids, pipecolic acid, acyl carnitine profile, coenzyme-Q10, and biotinidase), urine (organic acids, orotic acid, creatine, guanidinoacetate, s-sulfocysteine), CSF (neurotransmitter metabolites, tetrahydrobiopterin, neopterin, 5-methyltetrahydrofolate, and pyridoxal 5'-phosphate), genetic testing (PNPO gene sequencing), and white blood cell enzyme assay for neuronal ceroid lipofuscinosis (palmitoyl-protein thioesterase 1 and tripeptidyl peptidase 1). Repeat brain MRI (epilepsy protocol) was also normal. Serum OXC metabolite level was 11 μg/mL (ref: <40 μg/mL) and topiramate level was 2.9 μg/mL (ref: 2-4 μg/mL).

OXC was discontinued as of the third day of hospitalisation. This resulted in a prompt and remarkable improvement developmentally and of her spasms. Compared to about 10 spasms per day during the first two days of hospitalisation when she was taking OXC, she only had five spasms on the first day without OXC, one on the second day without OXC, and none after that. In addition, by the second day without OXC, she also had already regained her ability to talk, eat independently, and walk. The following day (third day without OXC), her topiramate dose was increased to 6 mg/kg/day. EEG on the following day (fourth day without OXC) showed a markedly milder hypsarrhythmia that covered only 30% of the sleep and awake EEG, compared to a previous continuous presence (100% of sleep and awake EEG). The background in between showed mixed theta and delta waves with occasional spike-wave activity from the right parasagittal region. EEG a day later (fifth day without OXC) showed complete resolution of the hypsarrhythmia with an awake background of intermixed theta and delta activity and rare multifocal spikes. Sleep background was normal (*figure 2*). She was discharged with topiramate monotherapy (9 mg/kg/day). EEG performed one week after discharge revealed diffuse slowing with intermittent spike-and-slow wave activity from the right parasagittal region, and follow-up four months later revealed that she continued to be seizure-free without any further episodes of spasms. Also, her development was normal. She was regularly using two and occasionally three-word sentences, her comprehension was excellent, and cognitively, she was judged to be at least age-appropriate. Motor development was within normal range and her neurological examination was also normal.

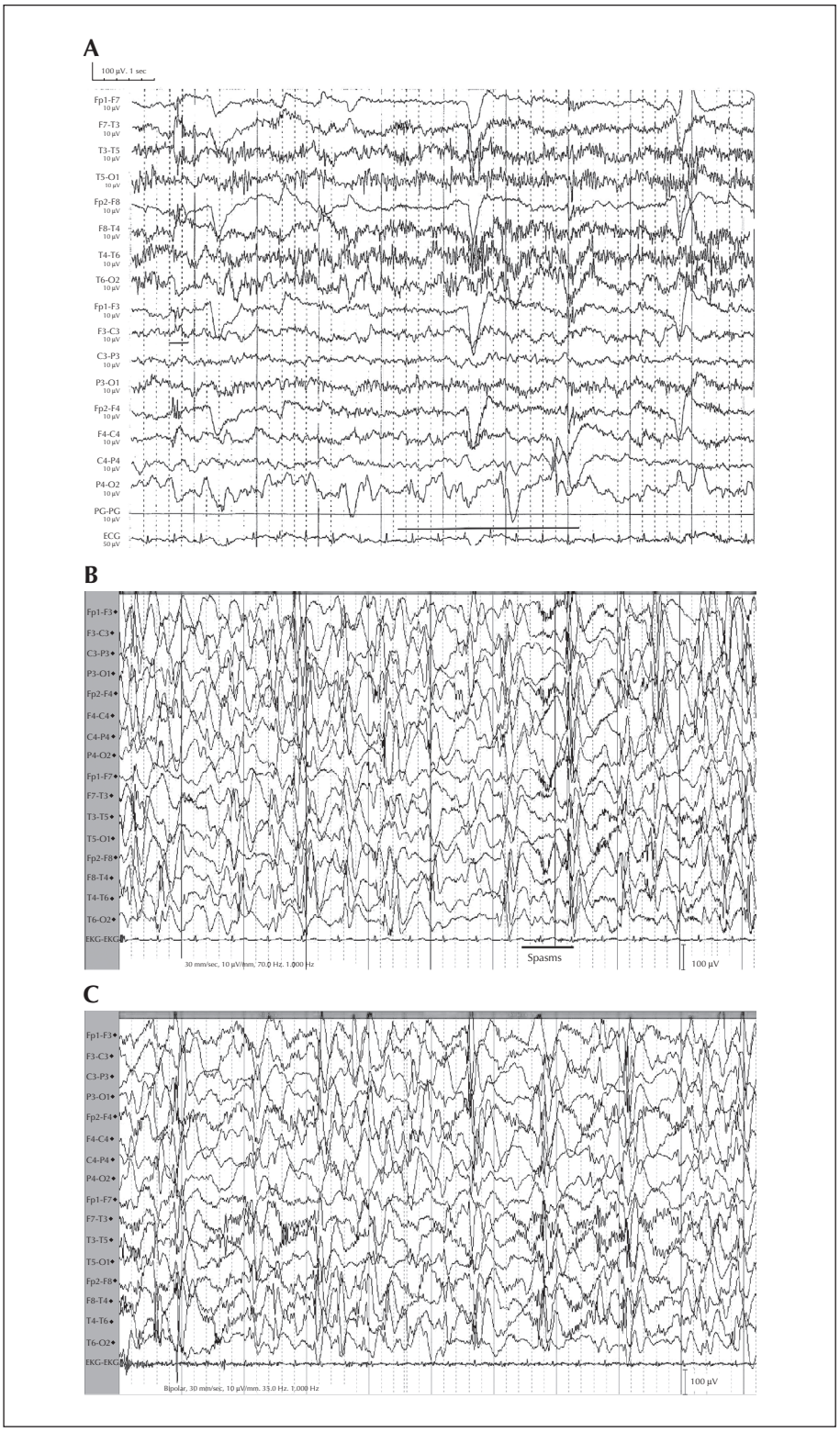

Figure 1. (**A**) EEG at the age of 17 months before the onset of infantile spasms revealing right posterior quadrant delta slowing with C4-P4 focal sharp waves and spikes (lower bar), and less frequent left frontal focal sharp waves and spikes (upper bar). (**B**) EEG at 18 months of age while awake showing diffuse hypsarrhythmia. The patient had approximately 800-millisecond flexor spasms with evident muscle artefact and some voltage attenuation (bar). (**C**) Hypsarrhythmia pattern in sleep on the same day.

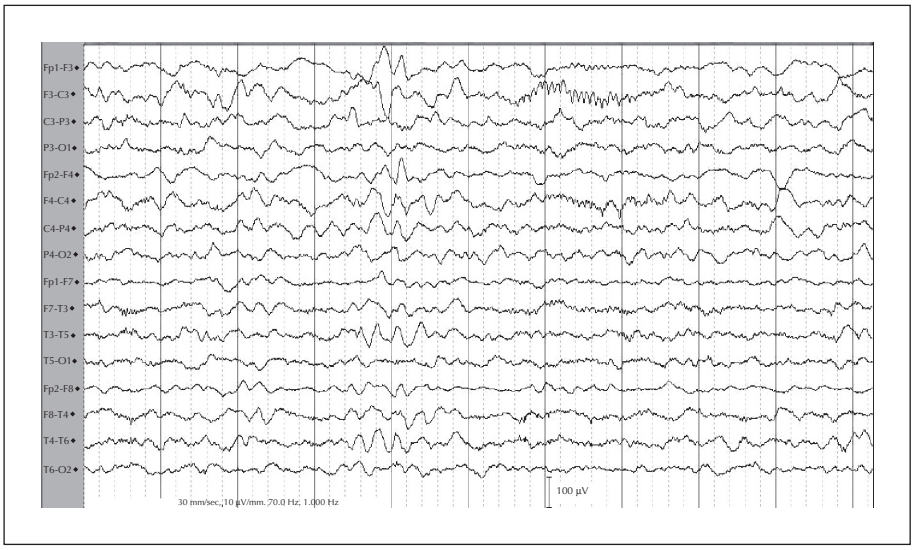

Figure 2. EEG during sleep on the third day after the cessation of oxcarbazepine revealing normal sleep background with sleep spindles.

Discussion

OXC has been reported to: (i) aggravate myoclonic jerks and absence seizures in patients with juvenile idiopathic generalised epilepsies (Gelisse *et al*., 2004); (ii) induce absences and aggravate partial seizures in children with benign epilepsy with centrotemporal spikes (Chapman *et al*., 2003; Grosso *et al*., 2006); (iii) induce generalised tonic-clonic seizures, myoclonic seizures, and absence seizures in children with complex partial seizures (Vendrame *et al*., 2007); (iv) aggravate the frequency of seizures in children with generalised tonic-clonic seizures (Vendrame *et al*., 2007); and (v) worsen seizures in juvenile myoclonic epilepsy (Menon *et al*., 2011). In addition, OXC has also been reported to worsen EEG features in children with idiopathic generalised epilepsies and complex partial seizures (Grosso *et al*., 2006; Vendrame *et al*., 2007). However, to our knowledge, induction of West syndrome by OXC has not been reported.

The very close temporal relationship between initiation of OXC treatment and onset of infantile spasms, developmental regression, and hypsarrhythmia raises the possibility that these changes were induced by OXC. The rapid clinical improvement after OXC cessation may also suggest this. However, the patient had been taking topiramate (3 mg/kg/day) for five days beforehand, and one cannot rule out a response to this medication. On the other hand, a response of West syndrome to such a low dose of topiramate (3 mg/kg/day) over five days is not what one would have normally expected based on the literature. Glauser *et al*. (1998) reported that two of their 11 patients with infantile spasms treated with topiramate became spasm-free on days six and 11 of topiramate therapy at doses ranging from 6.7 to 8.8 mg/kg/day, and that three other patients became seizure-free on days 32, 36, and 90 after their first topiramate dose, at doses ranging from 19.2 to 29.9 mg/kg/day. Thus, the dose that our patient was taking when she experienced the initial quick and remarkable improvement (3 mg/kg/day) was significantly lower than the doses that the above authors reported response to.It is also possible that the occurrence of infantile spasms, hypsarrhythmia, and developmental regression within two weeks of start of OXC treatment could have been purely coincidental. However, the age at onset of West syndrome in our patient (17 months) is unusual, and thus raises the possibility of an inducing factor. It is very uncommon for West syndrome to start after the first year of life (Pellock *et al*., 2010). Based on prior studies, as few as 1/117 patients with cryptogenic infantile spasms had onset between 12-18 months of life (Lombroso, 1983). Late-onset spasms at or after the age of one year, with clinical features consistent with an epileptic encephalopathy, have been reported (Eisermann *et al*., 2006; Auvin *et al*., 2010). However, unlike our patient, these patients had slow waves, slow spikes or spike-waves, but not hypsarrhythmia on their ictal-EEG. Thus, our case raises the possibility that OXC may induce infantile spasms, and clinicians treating infants who develop spasms while on OXC should be aware of this possibility.

The related antiepileptic drug CBZ was also reported to induce spasms in two cases from Japan (Mutoh *et al*., 1993). The first case was a two-year-old girl

with partial seizures and secondary generalisation who developed tonic spasms and burst-suppression pattern on EEG at the age of four months when she was treated with CBZ. These spasms increased when the dose of CBZ was increased. The second case was a 14-month-old boy with partial seizures since the age of two months, who developed clusters of tonic spasms and burst-suppression on EEG, two weeks after treatment with CBZ. In both cases, tonic spasms and burst-suppression resolved within two days after withdrawal of CBZ, and in one of these two cases (the first case), reintroduction of CBZ re-induced the spasms. We did not reintroduce treatment with OXC as we considered that this was not in the patient's best interest.

The mechanisms by which OXC may induce infantile spasms are not clear. The mechanism of action of OXC is thought to be similar to that of CBZ, namely, blockade of voltage-gated sodium channels (Kalis and Huff, 2001). It has been speculated that the paradoxical effects of antiepileptic drugs may be due to alterations in the inhibitory-excitatory balance by over-inhibiting inhibitory neurons (Gayatri and Livingston, 2006; Vendrame *et al*., 2007). In addition, in a recently developed animal model of infantile spasms, it has been demonstrated that infusion of tetrodotoxin, a sodium channel blocker, induced infantile spasms in P10-P12 rats by inhibiting neuronal activity (Lee *et al*., 2008). Neuronal activity is critical in the organisation of cortex, growth of dendrites, formation of synapses, and expression of neurotransmitter receptors. It has been hypothesized that sodium channel blockade by tetrodotoxin could inhibit this activity resulting in desynchronization of developmental processes that normally takes place in the developing brain (Lee *et al*., 2008). Similar mechanisms might be implicated in the induction of spasms by sodium channel blocking drugs, such as CBZ and OXC. However, to the best of our knowledge, there have not been any experimental studies that have specifically investigated the mechanisms of these paradoxical effects of OXC or CBZ. Further studies, perhaps using one or more of the recently developed animal models of infantile spasms, may be needed to elucidate the mechanisms underlying such potential paradoxical effects (Chudomelova *et al*., 2010). □

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References

Auvin S, Lamblin MD, Pandit F, Vallee L, Bouvet-Mourcia A. Infantile epileptic encephalopathy with late-onset spasms: report of 19 patients. *Epilepsia* 2010; 51: 1290-6.

Chapman K, Holland K, Erenberg G. Seizure exacerbation associated with oxcarbazepine in idiopathic focal epilepsy of childhood. *Neurology* 2003; 61: 1012-3.

Chudomelova L, Scantlebury MH, Raffo E, Coppola A, Betancourth D, Galanopoulou AS. Modeling new therapies for infantile spasms. *Epilepsia* 2010; 51: 27-33.

Eisermann MM, Ville D, Soufflet C, *et al*. Cryptogenic late-onset epileptic spasms: an overlooked syndrome of early childhood? *Epilepsia* 2006; 47: 1035-42.

Gayatri NA, Livingston JH. Aggravation of epilepsy by antiepileptic drugs. *Dev Med Child Neurol* 2006; 48: 394-8.

Gelisse P, Genton P, Kuate C, Pesenti A, Baldy-Moulinier M, Crespel A. Worsening of seizures by oxcarbazepine in juvenile idiopathic generalized epilepsies. *Epilepsia* 2004; 45: 1282-6.

Glauser TA, Clark PO, Strawsburg R. A pilot study of topiramate in the treatment of infantile spasms. *Epilepsia* 1998; 39: 1324-8.

Grosso S, Balestri M, Di Bartolo RM, *et al*. Oxcarbazepine and atypical evolution of benign idiopathic focal epilepsy of childhood. *Eur J Neurol* 2006; 13: 1142-5.

Kalis MM, Huff NA. Oxcarbazepine, an antiepileptic agent. *Clin Ther* 2001; 23: 680-700; discussion: 645.

Lee CL, Frost JD Jr, Swann JW, Hrachovy RA. A new animal model of infantile spasms with unprovoked persistent seizures. *Epilepsia* 2008; 49: 298-307.

Lombroso CT. A prospective study of infantile spasms: clinical and therapeutic correlations. *Epilepsia* 1983; 24: 135-58.

Menon R, Baheti NN, Cherian A, Iyer RS. Oxcarbazepine induced worsening of seizures in Jeavons syndrome: lessons learnt from an interesting presentation. *Neurol India* 2011; 59: 70-2.

Mutoh K, Okuno T, Mitsuyoshi I, Hayakawa T, Hamada Y, Mikawa H. Induction of tonic spasms by carbamazepine: observations on 2 infants. *Jpn J Psychiatry Neurol* 1993; 47: 304-5.

Pellock JM, Hrachovy R, Shinnar S, *et al*. Infantile spasms: a U.S. consensus report. *Epilepsia* 2010; 51: 2175-89.

Vendrame M, Khurana DS, Cruz M, *et al*. Aggravation of seizures and/or EEG features in children treated with oxcarbazepine monotherapy. *Epilepsia* 2007; 48: 2116-20.