Epileptic Disord 2019; 21 (1): 108-11

Rasmussen syndrome: absence seizures may be induced by oxcarbazepine

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Received August 15, 2018; Accepted November 12, 2018

ABSTRACT – A female patient with electroclinical and neuroradiological features compatible with Rasmussen syndrome developed a particular clinical and EEG pattern. As the seizures were refractory to valproate at 750 mg/kg/day, oxcarbazepine (OXC) at 30 mg/kg/day was added. Seizures became more frequent and on neurological examination, no hemiparesis was detected. The interictal EEG showed focal spikes and diffuse paroxysms in the right fronto-temporal regions. Brain MRI revealed right hemiatrophy, mainly at the Sylvian fissure. After initiating OXC daily, brief absence seizures, lasting less than 20 seconds and associated with bilateral and synchronous 2.5-3-Hz spike-and-waves compatible with typical absences, were observed. OXC was discontinued and the typical absences disappeared. Treatment with intravenous gammaglobulin was started. At the last control visit, at nine years of age, no absence seizures were observed either by the parents or on the EEG recording. Our patient who met the diagnostic criteria for Rasmussen syndrome presented with absence seizures that may have been induced by OXC. The absence seizures disappeared after OXC was discontinued.

Key words: absences, epilepsia partialis continua, Rasmussen syndrome, oxcarbazepine

Rasmussen syndrome (RS) is a rare and severe immune-mediated brain disorder resulting in unilateral brain atrophy and leading to progressive neurological dysfunction and refractory seizures (Bien *et al.*, 2005). Different mechanisms have been suggested, however, the aetiopathogenesis is not fully understood (Bien *et al.*, 2005; Caraballo *et al*., 2013).

In the literature, patients with atypical features have been published (Granata *et al*., 2012). These patients may manifest with absence or delayed-onset seizures, unusual events such as epileptic spasms and hemidystonic episodes, headache as the initial manifestation, dual pathology, or bilateral brain involvement. A dual pathology is seen in 10% of patients and varies from low-grade tumour, cortical dysplasia, tuberous sclerosis, mesial temporal sclerosis, vascular abnormalities, to old ischaemic lesions (Bien *et al*., 2007; Granata *et al*., 2012).

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doi:10.1684/epd.2019.1035

The aim of this study was to describe the electroclinical pattern of absence seizures (AS) that may have been induced by oxcarbazepine (OXC) in a child with RS.

Case study

The patient was a seven-year-old girl, born to non-consanguineous parents with an unremarkable personal and family history, who consulted because of focal seizures with impaired consciousness, oroalimentary automatisms, and left-sided clonic movements with onset in the left leg, progressing to the ipsilateral arm. The episodes were preceded by a tingling sensation in the left leg. The interictal EEG recording showed focal theta activity in the right frontal region. Neurological examination as well as brain MRI were normal.

Valproic acid (VPA) was started at 750 mg/kg/day without response. The seizures increased in frequency and, in addition, continuous partial seizures were observed.

As the focal seizures were not controlled, at seven years and six months of age, OXC at 30 mg/kg/day was added. The seizures became more frequent, occurring daily and associated with loss of consciousness. The girl's school performance was good with a mild attention deficit and reading and writing difficulties for which she received educational therapy. On neurological examination, no hemiparesis was detected. The interictal EEG showed focal spikes and diffuse paroxysms in the right fronto-temporal regions. Brain MRI revealed right hemiatrophy, mainly at the Sylvian fissure (*figure 1*). Oligoclonal bands were found in the CSF. The electroclinical features, CSF findings, and MRI abnormalities met the criteria for RS, according to Bien *et al*. (2005).

Other immune-mediated epileptic encephalopathies, *i.e*. cerebral vasculitis including lupus erythematosus, subacute measles encephalitis with or without immunodeficiency, hemiconvulsion-hemiplegia-epilepsy syndrome, focal cortical dysplasia including hemimegalencephaly, tumour, stroke, Sturge-Weber syndrome, and neurometabolic diseases, particularly mitochondriopathies, were ruled out.

At eight years of age, in addition to the focal seizures, the patient developed brief absence seizures (AS) lasting less than 20 seconds and occurring many times daily, associated with bilateral, synchronous and asymmetric 3-Hz spike-and-waves, compatible with typical absences (*figure 2*). The AS were induced by hyperventilation. OXC was discontinued and subsequently clobazam was started. The typical AS disappeared while the focal motor seizures persisted with occasional secondary generalization.

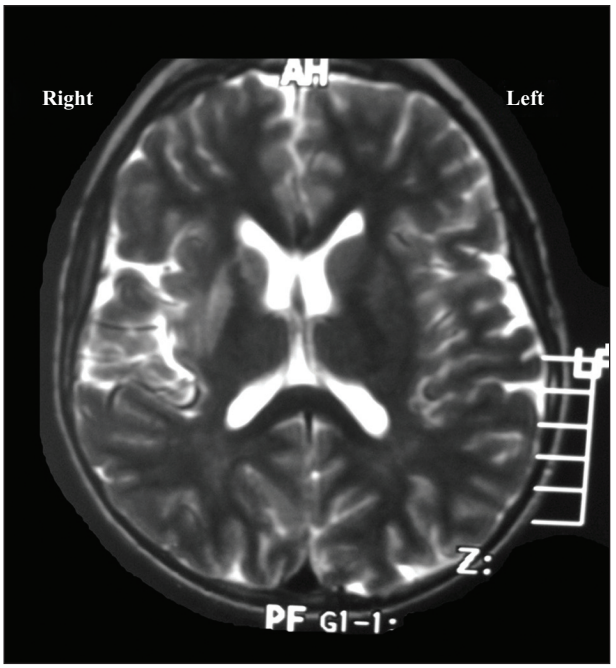

Figure 1. T2-weighted axial section shows right cerebral hemiatrophy predominantly in the perisylvian region; hyperintense lesions are also observed in this region.

Treatment with intravenous gammaglobulin was started every 30 days and gradual improvement of the seizures was observed. The seizures were short, lasting no more than three minutes, and occurred with a frequency of seven to 15 a month. At the last control visit, at nine years of age, no new neurological signs were detected. No further AS were observed either by the parents or on the EEG recording. The focal motor seizures persisted while the patient was receiving VPA at 1,250 mg/day, clobazam at 22.5 mg/day, and monthly intravenous gammaglobulin.

Discussion

Here, we present a patient who met the diagnostic criteria for RS with a particular type of seizure and electroclinical features of typical AS.

Typical AS are characterized by absences that last 5-25 seconds with abrupt and clear impairment or loss of consciousness, occurring several times a day. The ictal EEG shows discharges of generalized high-amplitude spikes and slow-wave complexes with rhythmic spike-waves at around 3 Hz.

Considering that, in our patient, the typical AS disappeared after withdrawing OXC, we may hypothesize that OXC was the culprit drug.

Differentiating between typical AS and complex focal seizures should be easy, although automatisms may be

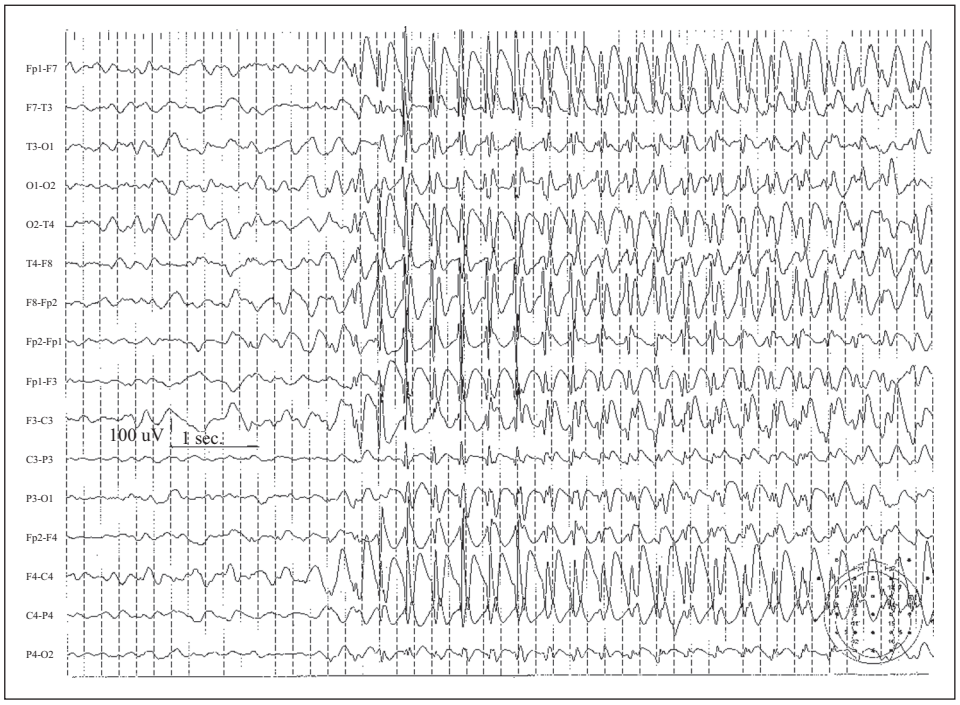

Figure 2. The ictal EEG recording shows bilateral, synchronous and asymmetric spike-waves at 3 Hz, associated with an absence seizure.

common in both. One of the main problems involves typical AS of frontopolar lobe origin that may also exhibit concomitant, more or less, regular bilateral 3-Hz spike-wave discharges (Medina *et al*., 2012). Focal motor components, asymmetric ictal discharges, or stable interictal frontal foci on the EEG may help to distinguish them. MRI may show frontal abnormalities. Ferrie *et al*. (1995) listed diffuse and focal brain disorders in which AS have been reported.

Typical AS should be distinguished from atypical AS that occur in children with epileptic encephalopathies, mainly Lennox-Gastaut syndrome. These are distinct from typical absences in that onset and termination is slow, impairment of consciousness is mild, and they are often associated with loss of muscle tone. On the ictal EEG, the diffuse spikes and waves are slower than those observed in typical AS, usually between 1.5 and 2.5 Hz.

In our case, considering the presence of focal frontal spikes and the focal brain lesion in the insular region on brain MRI, the AS may have arisen from the right frontal lobe, triggering a thalamo-cortical system due to secondary bilateral synchrony (Medina *et al*., 2012). In our patient, the AS may have been induced by OXC, since upon discontinuation of this antiepileptic drug (AED), the AS disappeared. It is widely known that many AEDs, such as carbamazepine (CBZ), OXC, gabapentin, vigabatrine, and tiagabine, may aggravate absence epilepsies (Genton *et al*., 2012). Phenytoin (PHT) seems to be less aggravating for AS (Genton *et al*., 2012). Phenobarbital may have a dual effect by increasing absences at high doses and decreasing them at low doses (Genton *et al*., 2012). In one study, aggravation of AS was reported in eight cases within days of VPA introduction. All improved after VPA discontinuation. In five, VPA was reintroduced, resulting in new seizure aggravation (Lerman-Sagie *et al*., 2001). An aggravation of AS was reported in three adolescents with juvenile absence epilepsy by levetiracetam at a daily dose of more than 1,750 mg/day (Auvin *et al*., 2011).

In rat models of genetic absence epilepsy, certain AEDs, such as CBZ and PHT, have been found to worsen spiking (Depaulis and Van Luijteaar, 2006).

In our case, the AS may have resulted from the relationship between RS and the reaction to OXC or may have occurred as a coincidence. □

Disclosures.

None of the authors have any conflict of interest to declare.

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