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Case Report

Generalized epilepsy in Baraitser–Winter cerebrofrontofacial syndrome☆

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1. Introduction

The syndrome of iris coloboma, ptosis, hypertelorism, and mental retardation was first described by M. Baraitser and R. M. Winter when they published a series of three children with similar phenotypes [1]. By 2012, mutations in the actin genes ACTB, beta-actin, and ACTG1, gamma-actin, were identified as the cause of this syndrome [2] and in 2016 it was reported that genetic defects in beta- versus gamma-actin cause subtle differences in clinical manifestations [3]. The syndrome is now known as Baraitser–Winter cerebrofrontofacial syndrome (BWCS). Important features of BWCS include congenital heart disease and genitourinary tract malformations, both of which require imaging surveillance [4]. There is a wide spectrum of facial dysmorphisms and central nervous system involvement [4]. Approximately half of all patients with BWCS have epilepsy and the mean age of onset is 5–6 years old [4]. There has been no detailed description of the seizure characteristics or electroencephalographic features of BWCS. The purpose of this article is to briefly review the seizure semiology and electroencephalogram (EEG) features in one such patient.

2. Case report

The patient is a 27-year-old, left-hand-dominant woman, previously published by Rivière et al. as LP98–085 [2] and by Verloes et al. as B2 [4].

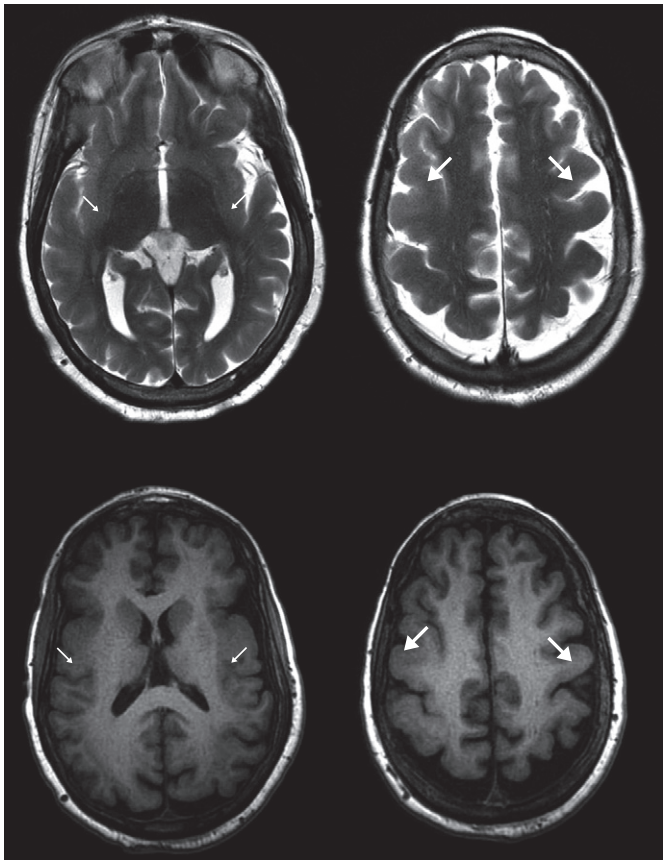

Fig. 1. Axial T2-weighted (top two slices) and T1-weighted (bottom two slices) MRI of the head shows bilateral cortical dysplasia with fairly symmetric thickening in both frontal lobes (large arrows), involving the middle and inferior frontal gyri particularly with some extension to the precentral gyri. There is cortical thickening seen in the parietal lobes and upper insula posteriorly (small arrows).

☆ Some of this work was previously presented at the 2015 Department of Clinical Neurological Sciences Epilepsy Research Day, London, Canada.

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She has a medical history significant for BWCS with associated intellectual delay, right cochlear agenesis causing hearing impairment, and bilateral colobomata causing visual impairment. She has behavioral issues with irritability, aggression, and defiance. She has an ACTB mutation of c.34A>G.

She was born at term, had a normal delivery without complications, but was hypotonic. She was delayed in gross and fine motor skills, as well as speech. She began having seizures at the age of two years. She has three seizure types. With the first type she has behavior arrest, staring, and unresponsiveness without preceding aura. These episodes last between a few seconds to a minute. She has post-ictal exhaustion and confusion. The second most frequent type of seizure involves a sudden tonic flexion of the head and neck with abduction of the arms; there is sometimes tonic extension of the lower limbs. There can be brief jerks of the upper limbs. She falls if she is standing when these seizures occur. These episodes last 5–20 s. She had clusters of up to 60 of these seizures per day. The last seizure type is generalized tonic–clonic. She has approximately one every five years with her last one in 2012.

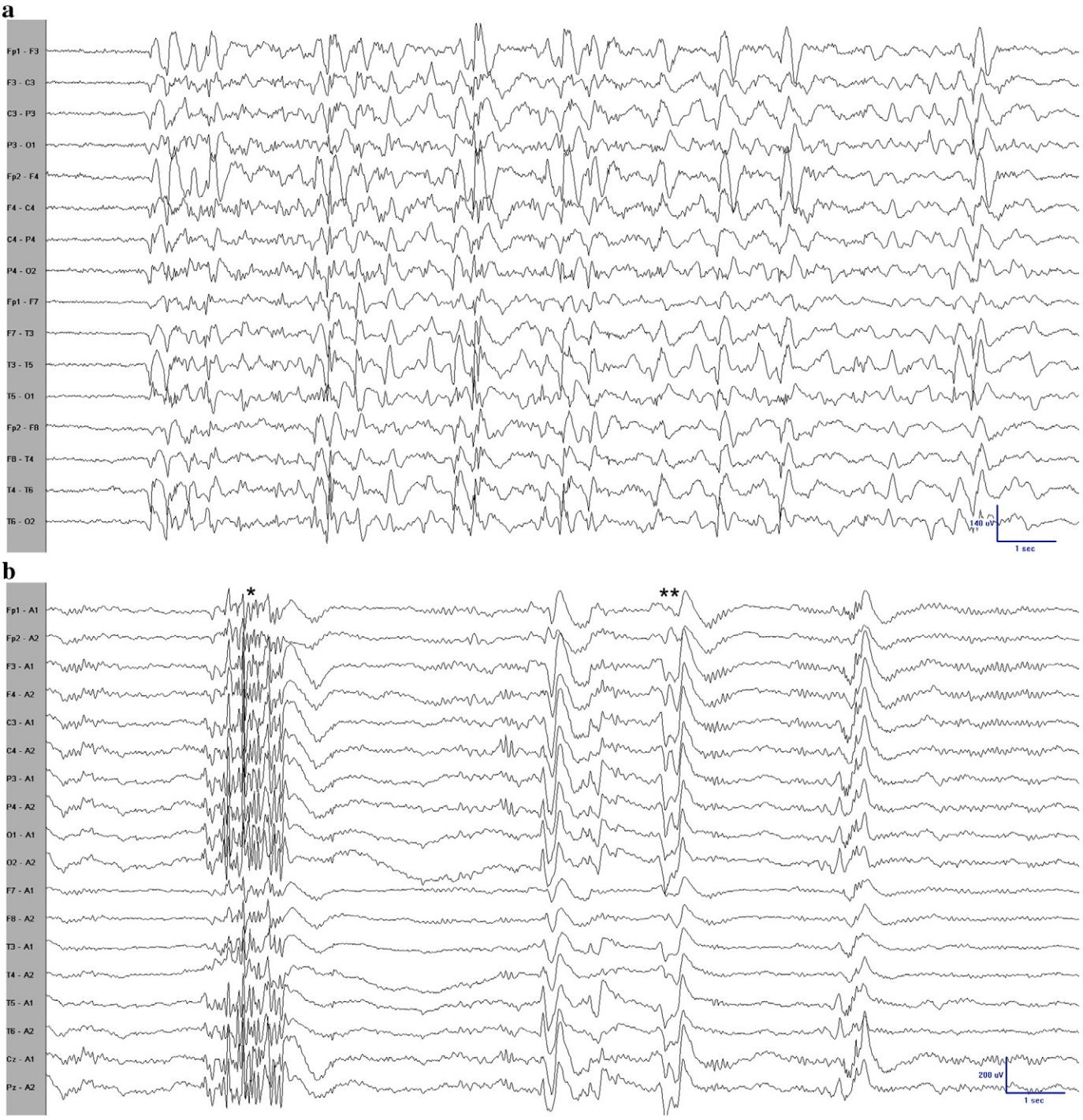

Fig. 2. Inter-ictal EEG recordings during wakefulness (top) and sleep (bottom). The top EEG is displayed in a longitudinal bipolar montage and the bottom in a referential montage. The awake EEG shows multiple generalized spikes, polyspikes, and polyspikes-and-waves. The asleep EEG shows polyspikes (*) and polyspikes-and-wave complexes (**). All EEG electrodes were placed using the international 10–20 system of electrode placement. Technical parameters; low frequency filter 1 Hz, high frequency filter 70 Hz, notch off, sensitivity 7 μV/mm, time base 30 mm/s, sampling rate 500 Hz.

Table 1
Comparing clinical, MRI, and EEG features in previously-reported cases of BWCS.

Reference	Clinical	MRI	EEG
Ramer et al. [9]	• Unclear age of seizure onset • Focal seizures with loss of awareness	Diffuse pachygyria or mixed pachygyria and polymicrogyria, most evident in the frontal lobes	"[C]hanges often seen in lissencephaly"
Fryns and Aftimos [7]	• Seizures since three years old • Generalized tonic–clonic, absence, and myoclonic seizures	Diffuse pachygyria most evident in the frontal lobes	"EEG was diffusely disturbed with generalization from a right frontotemporal focus"
Shiihara et al. [10]	• Seizures since eight days old • Unclear seizure type(s)	Pachygyria, subcortical-band heterotopia, and periventricular heterotopia	"[C]entroparietal dominant theta background activity, intermittent occipital dominant alpha–beta activities, 14-Hz sleep spindles, relatively poor interhemispheric synchronization, and no distinctive epileptic discharges"
Current case report	• Seizures since two years old • Generalized tonic–clonic, absence, and generalized tonic	Diffuse pachygyria most evident in the frontal lobes	Interictal and ictal EEG revealed a normal background, mild diffuse generalized slowing, generalized spikes and polyspikes, and polyspikes-and-waves with an epileptic recruiting rhythm

She currently takes the following antiseizure drugs, which do not completely control her seizures: clobazam 20 mg total daily, lamotrigine 350 mg total daily, perampanel 6 mg daily, phenytoin 300 mg total daily, rufinamide 1600 mg total daily, and valproate 1000 mg total daily. She had three months of seizure freedom after starting rufinamide.

On physical examination she had slow and deliberate speech. She had bilateral ptosis, bilateral epicanthal folds, triangular irides, a coloboma on the right, and an elliptical left pupil. Her visual acuity was 20/200 in both eyes. She had roving eye movements. There was decreased bulk in her hand intrinsic muscles bilaterally. She had bilateral lower limb spasticity. Her muscle strength was normal. Her reflexes were brisk in the lower extremities with no clonus. Coordination testing was normal.

An MRI of the brain showed bilateral cortical dysplasia with fairly symmetric thickening seen in her frontal lobes, precentral gyri, insulae, and parietal lobes (Fig. 1).

She was admitted to our epilepsy monitoring unit for continuous video-EEG. Her EEGs revealed normal background activity at 9–10 Hz with well developed and normal sleep potentials. She had frequent generalized spikes, polyspikes, polyspikes-and-waves, and frequent electrographic seizures during wakefulness without apparent clinical findings (Fig. 2). Her generalized spikes, polyspikes, and polyspikes-and-waves were augmented during sleep (Fig. 2). On continuous monitoring two of her stereotyped, typical generalized tonic seizures were captured. There were also multiple electrographic generalized seizures with generalized ictal recruiting rhythms. Some of these may have represented absence seizures. In a video-EEG of her typical seizure she can be seen to display sudden tonic bilateral abduction of her arms then elevation of her arms (Video 1).

3. Discussion

We have herein described the seizure semiology, EEG characteristics, and MRI findings of one patient with BWCS who has epilepsy. Seizures in BWCS can be drug-resistant. Epilepsy treatment can be challenging when there also exist developmental delays and behavioral issues. Some patients with BWCS have a form of generalized epilepsy with a known genetic cause. It is difficult to classify BWCS-associated seizures [5] system. One option is to classify the seizures in the structural or metabolic category; alternatively, the category of genetic epilepsy may be more apt.

A recent review of BWCS revealed that epilepsy was present in approximately half of patients with BWCS [4]. In this review, all patients with epilepsy had MRI abnormalities, but not every patient with MRI abnormalities had epilepsy. In some patients with BWCS, the epilepsy was drug-resistant [6–8]. In one case a patient had BWCS and Lennox–Gastaut syndrome with refractory atonic seizures, atypical absence seizures, and tonic seizures. EEGs have been described for three patients. They are outlined in Table 1 and compared to our patient. Prior reports of generalized tonic–clonic, absence, and tonic seizures already exist in the literature but none of these reports include comprehensive EEG findings.

4. Conclusion

We described the case of a young woman BWCS who had absence, generalized tonic, and generalized tonic–clonic seizures. Her MRI revealed bilateral cortical dysplasia. Continuous video-EEG captured tonic seizures associated with bursts of generalized spikes, polyspikes, and polyspikes-and-waves.

Neurologists should suspect BWCS in patients with dysmorphic features, iris coloboma, developmental delay, and generalized epilepsy from childhood. It is a rare condition. Patients with BWCS can have structural brain abnormalities that make it difficult to know whether their epilepsy etiology is structural-metabolic or genetic.

Acknowledgements and disclosures

The authors have no conflicts of interest to declare. The patient assented to publication of this manuscript which includes potentially identifying information. Informed consent was obtained from the patient's caregiver.

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