Biotin-Responsive Basal Ganglia Disease: EEG Characteristics and Seizure Phenotypes

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Abstract

Objective: To discuss EEG findings and seizure phenotypes in "biotin-responsive basal ganglia disease" (BRBGD), a rare, autosomal recessive, life-threatening, but potentially reversible encephalopathy with characteristic MRI findings.

Methods: We report on two patients with BRBGD in whom we correlated the EEG findings with MRI abnormalities. We also review the literature on EEG and seizure types in this syndrome.

Results: Our patient 1 had a focal electrographic seizure corresponding to a homotopic focal MRI pathology. Patient 2 had a normal EEG. The literature review showed both partial and generalized convulsive seizures with occasional occurrence of infantile spasms.

Conclusion: 1- The data suggest both electro-clinical and electro-anatomical dissociation in BRBGD. 2-Seizures in BRBGD are primarily caused by the underlying metabolic encephalopathy, although focal epileptiform discharges may signify a homotopic focal cerebral pathology caused by BRBGD.

Keywords: *Biotin, Thiamine, Seizure, Electroencephalography.*

Introduction

In 1998, Ozand et al.[1] described 10 patients, mostly from the Arabian Peninsula, who presented with episodic subacute encephalopathy manifested by confusion, bulbar symptoms, quadriparesis or quadriplegia, extrapyramidal symptoms, and occasional central facial weakness, external ophthalmoplegia, and seizures. The patients rapidly responded to biotin, hence, biotin-responsive basal ganglia disease (BRBGD). It was hypothesized that the pathogenesis of this autosomal recessive syndrome was "a defect in the transportation of biotin across the blood-brain barrier". Later, it was discovered that availability of biotin is a sine qua non in the expression of the gene SLC19A3[2-4]. Accordingly, the mutation of this gene (due to biotin deficiency) is primarily responsible for the symptomatology described above. The diagnosis of this syndrome is underpinned by the characteristic MRI findings[5-7].

Various investigators have reported seizures and EEG abnormalities in BRBGD, which we will review in this paper. Moreover, we report, for the first time, on a patient with BRBGD whose EEG showed focal

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electrographic seizures during sleep, corresponding to a focal, homotopic subcortical MRI pathology. We will also discuss a second case with a normal EEG.

Case 1

The patient was a 9-year-old Saudi male who was admitted to the hospital with a rapid onset of difficulty speaking and difficulty walking without antecedents. Two years earlier, the patient had a similar episode along with a seizure episode prompting his evaluation at a local clinic where he was placed on levetiracetam. Within 2 months the patient completely recovered from his symptoms. His family then discontinued seizure therapy.

The patient's birth history and developmental milestones were unremarkable. His family history was significant in that the parents were consanguineous.

The neurological examination showed the patient to be awake and alert. He had severe dysarthria, but a full comprehension of the spoken language. Cranial nerves were intact. There was weakness and increased tone in all extremities. A conspicuous feature was a marked orofacial dyskinesia and dystonia of the extremities. There was moderate generalized hyperreflexia. No Hoffmann's or Babinski's. Sensation and cerebellar functions were normal. There were no meningeal signs.

General physical examination and vital signs were normal. CBC and routine chemistry profile were normal. A CSF study was also normal.

The EEG showed an electrographic seizure in the right temporal region during sleep (Fig. 1), which corresponded to an isolated MRI lesion in the deep white matter of the right temporal region (Fig. 2). In addition, the MRI showed abnormalities consistent with BRBGD (Fig.2).

Based on the available data, we made the diagnosis of BRBGD and successfully treated the patient with a combination of biotin and thiamine.

Case 2

The patient is a 3-year-old Saudi male who was admitted to the hospital with a rapid onset of weakness of the lower extremities followed by weakness of the upper extremities. The symptoms started 3 days prior to admission following a mild back injury. There was no sphincter dysfunction. The patient had a history of non-progressive speech delay.

Family history was significant in that the parents were consanguineous. The neurological examination showed normal cognitive development for age except for a mild speech delay. Cranial nerves were intact. Initially, he had weakness, hypotonia, and hyporeflexia in all extremities, and which in a few days evolved into increased weakness and tone along with hyperreflexia. General physical examination and vital signs were normal. Systemic metabolic work up and CBC were normal. An EEG (awake and sleep) was within the range of normal variation for the patient's age. An MRI study was consistent with BRBGD (Fig.3).

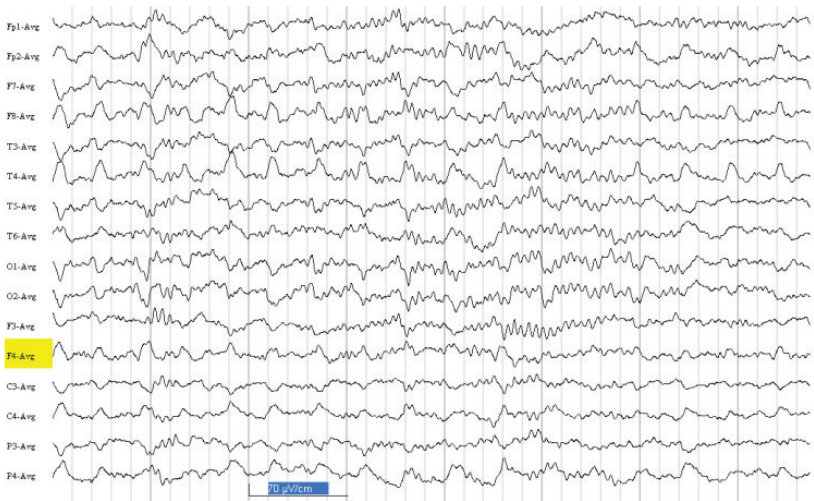

Figure 1: The EEG showed an electrographic seizure in the right temporal region during sleep.

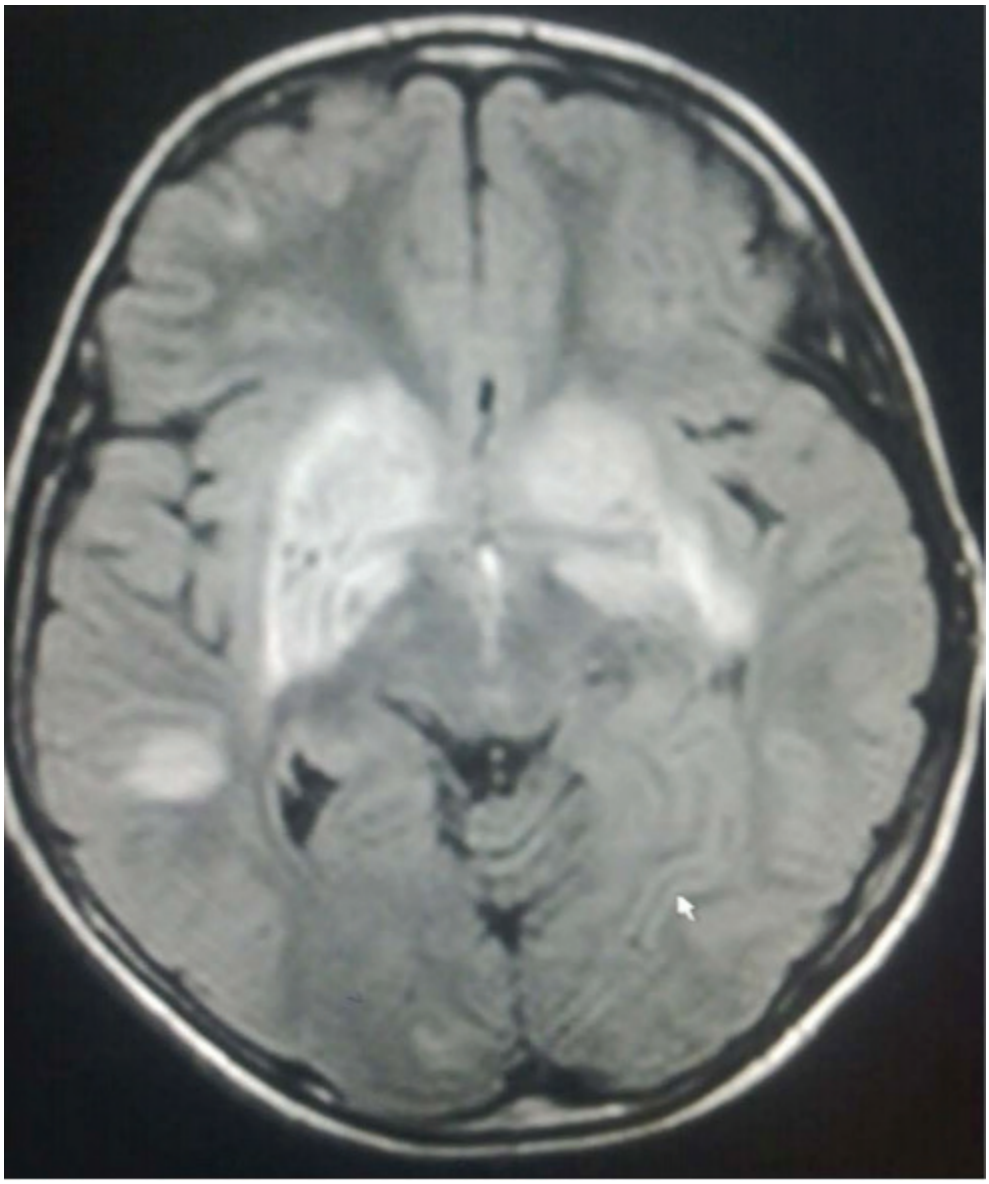

Figure 2: MRI T2 image: Bilateral hyper-intense signals involving the basal ganglia and the thalamus. Additionally, multiple cortical-sub-cortical hyper-intense lesions are present in the frontal and parietal lobes bilaterally. Note the focal hyper-intense

Table 1: EEG findings and seizure types in BRBGD (literature review)

Author	Patient	EEG	Seizure Type
Ozand et al. 1998	*12*	Normal background (2 patients) Diffuse background slowing (1 patient) Regional (anterior) slowing (1 patient)	Generalized convulsive (4 patients)
Debs et al. 2009	2	Diffuse background slowing (1 patient)	Simple partial with secondary generalization (1 patient) Generalized convulsive (1 patient)

Cont... **Table 1: EEG findings and seizure types in BRBGD (literature review)**

Yamada et al. 2010	4	Anterior-dominant spike-wave and polyspike-wave complexes (1patient) Multifocal spikes (1 patient)	Atypical infantile spasms
Alfadhel et al.2013	18	Not available	Partial or generalized (13 patients)
Stremba et al.2014	1	Burst-suppression + multifocalepileptiform discharges (1 patient); evolved into hypsarrhythmia with further evolution into LGS	Atypical infantile spasms

Discussion

In this article, we describe two children who presented with a sub-acute onset of weakness of extremities, dysarthria, and in one case extra-pyramidal symptomatology. The MRI of the brain was consistent with BRBGD. Although, we have no genetic confirmation of this diagnosis, we excluded BRBGD mimics. Among those, Leigh syndrome, a mitochondrial disorder primarily affecting infants, which is a progressive and eventually fatal disease. Similarly, organic acid disorders occur in infancy, and not in older children. Toxic encephalopathy was ruled out by the absence of a history of exposure to environmental hazards. Moreover, urine screening for heavy metals was negative. We ruled out CNS vasculitis by the absence of fever and headaches, unremarkable systemic examination, a normal ESR, a negative CRP, and a non-focal MRI. The mode of onset and the course of illness were inconsistent with Wilson's disease. Intact sensorium and normal extra-ocular muscles are incompatible with Wernicke's encephalopathy. Acute demyelinating encephalomyelitis (ADEM) was deemed unlikely because of a lack of antecedents (I.e. infections), and a paucity of white matter abnormalities on the MRI along with a preponderance of gray matter involvement. Finally, the MRI was inconsistent with childhood multiple sclerosis. The dramatic and sustained response of our patients to a combination of biotin and thiamin is the best evidence that the diagnosis was indeed BRBGD.

Since the original description of BRBGD by Ozand et al.[1], there have been several studies of this syndrome, some of which reported EEG findings and seizure types in their cohorts (Table1). The EEG background activity has reportedly ranged from normal to diffusely slow, with occasional regional slowing or suppression-burst pattern. The reason for such variations is not immediately apparent, although it is conceivable that each variation may represent a specific phase of cerebral involvement within the spectrum of BRBGD. Similar "variations" have been reported in other encephalopathies, and where they have served as the cornerstone of EEG classification systems designed for therapeutic monitoring and prognostication[8-9]. Our patient 2 had a normal background activity despite severe neurological and MRI abnormalities, indicating a lack of concordance between the EEG and MRI in this syndrome (electro-anatomical dissociation).

Similar to some unrelated encephalopathies[10], an "electro-clinical" dissociation exists in BRBGD, including in the group with seizures. For example, the EEG of our patient 1 showed a focal electrographic seizure in the right temporal region (corresponding to a deep right temporal lobe lesion on the MRI) without discernible peripheral manifestations. Conversely, some of the patients reported in the literature had clinical seizures without documented epileptiform discharges in the EEG, with the exception of patients with BRBGD-induced infantile spasms. It is notable that in one previous case report[4], the patient developed infantile spasms, which later evolved into Lennox-Gastaut syndrome. Thus, BRBGD should be considered as a potential etiology for West's syndrome and Lennox-Gastaut syndrome.

The electrographic seizure in patient 1 occurred only during sleep, signifying the importance of sleep EEG in patients with BRBGD. A review of the literature reveals the occurrence of several seizure types in BRBGD including focal and generalized convulsive seizures. In the patients with infantile spasms (4, 7) myoclonic seizures as well as axial tonic spasms were described. By-and-large, seizures are triggered by the underlying metabolic disease, however, when associated with focal EEG discharges (vide supra), they may raise the possibility of focal pathology.

At this time, it is not clear whether in the event of a seizure activity complicating BRBGD, anticonvulsants (AEDs) should be prescribed and if so, for how long. Is it necessary to prescribe AEDs prophylactically in cases where focal or generalized epileptiform discharges persist in the EEG? Importantly, these issues are confounded by the fact that pathological findings on the MRI usually persist well beyond clinical recovery. These questions remain to be answered until more data become available.

It should be noted that we did not obtain serial EEGs in our patients to assess the evolution of the encephalopathy, primarily because of the patients' rapid response to vitamin therapy.

In summary, further investigations are necessary to determine the significance of the EEG, in particular, serial EEGs in the diagnosis and prognostication of BRBGD. Perhaps, on a larger scale an EEG classification system could be developed to optimize care in this rare, life-threatening, yet reversible condition. Such a study would, of course, require an international, multi-center, collaborative effort to address this manifold topic.

Conclusion

1- The data suggest both electro-clinical and electro-anatomical dissociation in BRBGD. 2-Seizures in BRBGD are primarily caused by the underlying metabolic encephalopathy, although focal epileptiform discharges may signify a homotopic focal cerebral pathology caused by BRBGD.

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Conflict of Interest: Nil

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