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Case Report

Dopaminergic Agonists as a Treatment for Dystonia in a Pediatric Patient with RHOBTB2 Epileptic Encephalopathy

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Abstract

We present the case of a 22-month-old patient with a heterogenous de novo RHOBTB2 missense variant causing early infantile epileptic encephalopathy (EE) type 64. The patient presented at age 6 months with focal seizures followed by generalized status epilepticus, and he has missed several developmental milestones since infancy. He has also displayed significant intellectual disability, dystonia, microcephaly, and central and peripheral hypotonia. He has had good seizure control. This mutation has previously been identified in 16 EE patients in the literature, but this is the first such diagnosis in Lebanon and the Middle East. The management of infantile EE patients is multifaceted as they present with psychomotor, developmental, and intellectual deficits. One aspect that is particularly challenging to manage is muscle dystonia, and our patient is the first to show significant improvement here with dopaminergic treatment using carbidopa-levodopa..

Keywords: RHOBTB2; Epileptic Encephalopathy; Infantile Encephalopathy; Dystonia; Carbidopa-levodopa

Introduction

Epileptic encephalopathies (EE) are a group of diverse disorders where epileptic activity causes progressive cerebral dysfunction which is unaccounted for by the underlying condition. There have been a number of unique diagnoses classified under this definition. These include the Ohtahara, Lennox-Gastaut, West, Dravet, and Landau-Kleffner syndromes, and an increasing classification of epileptic conditions defined by their clinical conditions and their electroencephalographic features [5]. Studies have described debilitating presentations of these disorders including microcephaly, atonia, and severe intellectual disability [12].

These disorders commonly appear in childhood and are heavily and continuously associated with genetic predisposition. A caveat of this is that heterogenous de novo mutations seem to be the primary genetic cause of these disorders [1]. A prominent site of mutation causing EE is the tumor suppressor protein Rho-related BTB domain-containing protein 2 (RHOBTB2 MIM# 607352), which is a member of an atypical Rho GTPase family previously identified with mutations in 16 EE patients [1,8,12,13]. At the time of writing, no such cases have been described in Lebanon or the Middle East.

Case Report

In this study, we present the case of a 22-month-old male patient who initially presented to our clinic at the age of 6 months for focal seizures manifested as right eye deviation and right side tonic-clonic movements that lasted for ten minutes. The patient is a full-term male infant born to non-consanguineous parents who also have

a healthy 2-year-old male child. He was delivered at the hospital via spontaneous vaginal delivery with a birth weight of 3450g and head circumference of 35 cm. There were no complications during pregnancy or delivery. His developmental history is significant for delays in achieving motor milestones as well as a history of more than two consecutive months at the age of 4-6 months of frequent and persistent low grade fever of 38°C of unknown origin with negative workup.

The patient was hospitalized at the age of 6 months for fever and focal status epilepticus, at the age of 12 months for bronchiolitis, and at the ages of 16 months and 20 months for generalized status epilepticus. Since infancy, the patient consistently did not achieve normal developmental milestones. He could roll over at 9 months and he could sit unsupported at 17 months of age. He has not yet been able to crawl or walk, and he also has significant speech delay. Routine metabolic panels, ammonia, lactic acid, pyruvate, serum amino acids, and urine organic acids were all negative.

For better evaluation, whole exome genetic testing was performed and showed the patient to be heterozygous in the RHOBTB2 gene located on the chromosome 8p21.3 (mutation 1465 C>T,Arg489Trp), leading to a diagnosis of an autosomal dominant early infantile epileptic encephalopathy type 64. This is a new de novo missense variant in the gene that has not been previously reported.

On physical examination at 6 months, the patient looks alert, his pupils are symmetric and reactive to light, and his head circumference is 44 cm which is <3rd percentile for age and meets the diagnostic criteria for microcephaly. He displays central and peripheral hypotonia, dystonic posturing of his upper extremities, and symmetric deep tendon reflexes.

An electroencephalogram (EEG) was performed and showed left side slowing and frequent central and temporal sharp waves; the magnetic resonance imaging (MRI) of the brain was within normal limits.

Treatment was started at 6 months of age following his admission with status epilepticus. He was initially prescribed 60 mg/kg/day of levetiracetam, and 8mg /kg/day of topiramate was added 4 days later because his focal seizures were still present. 2 months later, he was shifted to oxcarbazepine (60 mg/kg/day) due to its fewer side effects as it was previously unavailable in the area where the patient was hospitalized, and his seizures were controlled for 10 months. However, he presented at 17 months of age with breakthrough status epilepticus associated with low grade fevers of 38C, so valproic acid (35 mg/kg/day) was added with good seizure control until now.

Carbidopa-levodopa treatment was started at a dose of 25 mg of carbidopa per day divided 3 times at age 12 months with a well-marked improvement in his dystonia. Our patient has also started early intervention therapies at 6 months of age including physical, psychomotor, and occupational therapies which have resulted in good improvement.

Our plan for future treatment is to monitor his seizures and to reduce his antiepileptic drugs when appropriate. He will also continue with physical therapy, speech therapy, and psychomotor therapies.

Discussion

It has been important to classify conditions of epileptic encephalopathy as they are refractory to many of the typical anti-epileptic drugs and can present as challenging cases to professionals in the field. This is especially concerning when we consider the deteriorative effects of these conditions on the pediatric brain, which can be mitigated with specialized treatment including immunomodulatory therapies, more aggressive drug treatments, ketogenic diets, and surgical treatments [7]. However, many of these patients' symptoms, including deficits in motor function, remain undertreated with the current protocols.

RHOBTB proteins first attracted interested due to their potential role in tumor suppression [3,6]. Similar to the function of the well-established Cul2-pVHL complex in downregulating transcription factors, RHOBTB proteins seem to function as adaptor proteins for the Cullin-3 ubiquitin ligase complex that targets specific substrates for degradation [2,9,10]. RHOBTB2 in particular has been identified as a homozygously deleted gene in some breast cancer samples, thereby dubbed DBC2 (deleted in breast cancer 2) [4].

RHOBTB2 has also been shown to be mostly expressed in human neural tissues, which indicates potential importance to nervous system functioning [11]. Straub., *et al*. (2018) identified 10 patients with de novo missense mutations in RHOBTB2 and very similar phenotypes consistent with EE [13]. Spagnoli., *et al*. (2020) and Belal., *et al*. (2018) also identified 1 and 3 patients respective-

ly with de novo missense mutations in RHOBTB2 who presented with EE, while Knijnenburg., *et al*. (2020) identified two patients with underlying RHOBTB2 mutations who had episodes of EE precipitated by trauma and fever [1,8,12]. Across studies, symptoms included early onset epilepsy, postnatal microcephaly, varying degrees of intellectual disability and developmental delay, and movement disorders. Belal., *et al*. (2018) performed electroencephalograms that showed spikes or polyspikes in all 3 patients, which are well-recognized as hallmarks of epilepsy [1]. Seizure types varied between patients and included focal, tonic, myoclonic, and generalized tonic-clonic seizures, but there was notably a recurrence of status epilepticus in at least 9 patients across these four studies, which tended to be febrile and occasionally focal. Please refer to table 1 for a comparison of all 17 cases of EE with a known RHOBTB2 mutation.

	Our patient	**Straub., *et al*. [13]**	**Belal., *et al*. [1]**	**Spagnoli., *et al*. [12]**	**Knijnenburg., *et al*. [8]**
Gender	Male.	4 males, 6 females.	1 male, 2 females.	Female.	1 male (index patient), 1 female. Findings summarized for index patient.
Age	22 months.	23 months to 17 years.	7 years, 9 years, 20 years.	9 years.	5 years, 14 years.
Genetic Variant	c.1465C>T (Arg489Trp)	p.(Ala474Gly) x1 p.Arg483His) x4 p.(Asn510Asp) x1 p.(Arg511Trp) x2 p.(Arg511Gln) x2	p.(Arg511Gln) x1 p.(Arg483His) x1 p.(Arg507Cys) x1	c.1532G>A (Arg511Gln)	p.(Arg483His) x1 p.(Arg551Gln) x1
Weight	Birth: 3450g. Current: 13 Kg	All normal birth weight. 3/9 develop weight < -2SD.	2/3 normal birth weight. 1/3 birth weight < -2SD. 2/3 develop weight <-2SD.	N/A	N/A
Height	Current: 84 cm	4/9 develop weight <-2SD	N/A	N/A	N/A
Head Circumference	Birth: 35 cm. Current: 44 cm (<3rd percentile).	6/6 normal head circumference at birth. 6/10 develop head circumference < -2SD.	3/3 normal head circumference at birth. 2/3 develop head circumference < -2SD.	Birth: 31cm.	N/A
Seizure Type and Onset	Focal status epilepticus (6 months). Generalized status epilepticus (6 and 12 months).	Status epilepticus, generalized tonic clonic, focal, complex partial, febrile. 9/10 had seizure onset within 9 months of age. 1/10 had seizure onset at 3 years.	Febrile status epilepticus, tonic seizure, complex focal seizure evoked by visual pattern, myoclonic seizure. 2/3 have seizure onset at 3 months, 1/3 at 15 months.	Afebrile focal epileptic status and epileptic seizures (first years of life). Paroxysmal non-epileptic seizures (emerged at 1 year).	Multiple seizure types, including status epilepticus. First seizure activity noted at 4 days. Status epilepticus precipitated by trauma at 5 years.
Intellectual Disability	Mild to Moderate	9/10 severe 1/10 moderate	2/3 severe 1/3 moderate	Significant	N/A
Motor Abilities	Roll over at 9 months. Sit unsupported at 17 months. No crawling or walking.	5/10 cannot walk. 2/10 can walk. 1/10 can walk with support. 2/10 can walk short distances.	1/3 wheelchair bound. 1/3 stands with support. 1/3 unsteady gait.	Head control at 9 months. Sit unsupported at 2 years. Walking independently at 7 years.	Severe global psychomotor impairment.

Movement Disorders	Dystonic posturing of upper extremities.	8/10 yes, including paroxysmal, dystonic, and chorea-like.	2/3 dyskinesia. 1/3 athetoid movements.	Dystonic posturing (1 year). Ataxia (9 years).	Dystonic posturing. Periodic kinesigenic dyskinesia.
Speech Abilities	Significant delay.	7/10 nonverbal. 2/10 can speak a few short words. 1/10 has rare two-word combination.	N/A	Limited to vocalizations and single words (1 year).	N/A
Hypotonia	Central and peripheral hypotonia.	4/10 hypotonia. 4/10 truncal hypotonia. 1/10 axial hypotonia.	N/A	Yes	Mild axial hypotonia at 3.5 months.
EEG	Left side slowing with frequent central and temporal sharp waves.	N/A	3/3 spikes or polyspikes.	Background asymmetry and sharp waves (3 months). Abnormal centro-temporal monomorphous theta waves (1 year).	Severe slowing.
MRI Abnormalities	Normal.	5/10 none. 5/10 include thin corpus callosum, delayed myelination, cortical atrophy, ventriculomegaly, diffusion anomalies, cerebellar hypoplasia.	2/3 brain atrophy. 3/3 reduced diffusion during acute encephalopathy.	Increased subarachnoid spaces in fronto-temporal areas (3 mo), cortical atrophy, corpus callosum hypoplasia and diffuse hypomyelination (8 years).	Diffusion restriction in hippocampal area with subsequent hippocampal atrophy (index patient). Focal periventricular atrophy (second patient).
Treatment	Levetiracetam, topiramate, oxcarbazepine, and valproate for seizures. Carbidopa-levodopa for dystonia.	1/10 none. 5/10 levetiracetam 3/10 carbamazepine 4/10 phenobarbital 2/10 valproic acid 2/10 topiramate. Others: zonisamide, lacosamide, clobazam, and memantine.	1/3 phenytoin 1/3 phenobarbital, potassium bromide, oxcarbazepine, clonazepam 1/3 valproic acid	Valproate for seizures Topiramate and levetiracetam discontinued due to side effects. Carbamazepine for paroxysmal movement disorder.	Phenobarbital Valproic acid Levetiracetam Carbamazepine for dyskinesia Midazolam, levetiracetam, and carbamazepine for post-traumatic status epilepticus.
Response to Treatment-Seizures	Good seizure control on valproic acid until now	7/10 successfully controlled. 1/10 ceased spontaneously without treatment. 2/10 refractory to treatment.	1/3 successfully controlled (phenobarbital) 2/3 refractory to treatment	Good seizure control on valproate until now	Relatively stable until trauma. Gradual recovery from post-traumatic status epilepticus. Increase in hyperkinetic movements after discharge.
Response to Treatment-Dystonia	Marked improvement in dystonia on carbidopa-levodopa	1/10 partial improvement	N/A	Carbamazepine completely resolved the movement disorder with no recurrence at 14mo	N/A

Table 1

We presented the case of a 22-month-old patient receiving treatment for autosomal dominant early infantile epileptic encephalopathy type 64. We note that this is the first recorded case of genetic RHOBTB2 epileptic encephalopathy that has shown an improvement in dystonia with carbidopa-levodopa treatment. Crucially, only one of the previously reported cases did not display symptoms of motor dysfunction, and this has been an area of focus for treatment in this population. This suggests there may be a therapeutic benefit to using dopamine agonists in encephalopathic patients with dystonia as an adjunct to current drug and interventional therapies.

Conclusion

In conclusion, our study adds to the growing body of literature that identifies de novo RHOBTB2 missense mutations as causes of EE. We presented the case of a 22-month-old patient with epileptic encephalopathy attributed to an underlying RHOBTB2 mutation. Carbidopa-levodopa treatment was initiated to improve his muscle dystonia, and this has shown promising results. We suggest further exploring the use of dopaminergic agents for the management of dystonia and other psychomotor symptoms in patients with EE.

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