

CASO CLÍNICO/CASE REPORT

Association between Rhabdomyolysis and *RHOBTB2* Encephalopathy

Associação entre Rabdomiólise e Encefalopatia *RHOBTB2*

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Abstract

First described in 2018, heterozygous variants of the *RHOBTB2* gene, affect the translation of a Rho GTPase protein, essential in neuronal development and synaptic plasticity. The few cases described are characterized by a clinical spectrum of epileptic encephalopathy, psychomotor and cognitive delay, microcephaly, nonspecific facial dysmorphism and movement disorder.

We report a case of a female child, who had two seizures at 28 days of age. She exhibited a normal psychomotor development, until she had another seizure at 6 months, after which she started showing a movement disorder, followed by impairment of psychomotor development. Amongst the multiple hospitalizations, one of them was due to status epilepticus with severe rhabdomyolysis. At the age of 7, by exome sequencing, a de novo pathogenic variant was identified in the *RHOBTB2* gene.

Although the main characteristics of this syndrome have been described in previous studies, its possible relation with rhabdomyolysis has never been reported.

Resumo

Primeiramente descritas em 2018, variantes em heterozigotia do gene *RHOBTB2*, afetam a tradução duma proteína Rho GTPase, essencial no desenvolvimento neuronal e plasticidade sináptica. Os poucos casos descritos caracterizam-se por um espectro clínico com encefalopatia epilética, atraso do desenvolvimento psicomotor, microcefalia, dismorfismo facial inespecífico e perturbação do movimento.

Apresentamos o caso de uma criança, sexo feminino, que apresentou dois episódios convulsivos aos 28 dias de vida. Exibia um normal desenvolvimento psicomotor, até apresentar um novo episódio convulsivo aos 6 meses, após o qual iniciou perturbação do movimento, e subsequente compromisso do desenvolvimento psicomotor. De entre os múltiplos internamentos, um deles deveu-se a estado de mal epilético com rabdomiólise grave. Aos 7 anos, através da sequenciação do exoma, identificou-se uma variante patogénica de novo no gene *RHOBTB2*.

Embora as principais características desta síndrome tenham sido descritas em estudos anteriores, a sua possível relação com rabdomiólise nunca foi relatada.

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Introduction

RHOBTB2 encephalopathy is a rare autosomal dominant syndrome, caused by a variant in a gene located on the short arm of chromosome 8 (8p21.2), that affects the translation of a protein from the atypical Rho GTPase family, important in the process of neuronal development and synaptic plasticity.¹ The altered *RHOBTB2* gene increases the overexpression of the codified protein which, most likely, leads to an impaired degradation in the proteasome.²

It was first described in 2018 by Straub *et al*, with the identification of 5 de novo heterozygous missense variants in the *RHOBTB2* gene, in 10 unrelated patients, aged between 2 to 17, with developmental and epileptic encephalopathy-64.¹⁻³ These variants were found due to recent genetic advances, by exome sequencing. Since then, its identification has grown, which makes the characterization of this syndrome increasingly important. Currently, there are less than 100 cases described worldwide.^{1,4}

So far, this syndrome has presented with early-onset epilepsy, movement disorder, including dystonic and paroxysmal movements, psychomotor developmental delay, cognitive impairment, postnatal microcephaly and nonspecific facial dysmorphism (including micrognathia, low nasal bridge, deep-set eyes and epicanthal folds).¹ Some of the reported cases also reveal alterations in imaging tests, in particular in brain magnetic resonance imaging (MRI), with cerebral edema, myelination alterations and diffuse reduction of several brain regions.⁵ Most of the *RHOBTB2* clinical manifestations appear during the infantile period, though the order and severity of the symptomatology is variable, making this syndrome similar to other pathologies, hindering differential diagnosis.

In this paper, we report a severe case of rhabdomyolysis diagnosed in a child with *RHOBTB2* syndrome, which has not been previously described.

Case Report

We report a female child, currently 9 years old, second daughter of healthy, non-consanguineous parents, with no relevant family history. She was transported to the emergency room (ER) at 28 days of age, due to 2 short-term seizures with eye deviation. After an electroencephalogram (EEG) and transfontanelar ultrasound were performed, no changes were identified.

She maintained a good evolution and psychomotor development until 6 months of age, when she exhibited a new left focal clonic seizure, with subsequent secondary generalization, lasting about 20 minutes. The EEG did not reveal paroxysmal epileptiform activity or any other anomalies, and the computed tomography (CT)-scan was normal. Since that episode, a progressive regression of psychomotor and cognitive development began, with axial hypotonia and progressive acquired microcephaly. An extensive neuro-metabolic study, brain MRI with spectrometry, and genetics studies, which included a karyotype and whole exome sequencing (WES), were performed with no changes justifying the clinical picture. At the age of 2, a brain MRI showed a nonspecific delayed myelination with poor contrast between cortical and subcortical white matter.

By the time she was 6 years old, she was admitted to the ER with a generalized tonic-clonic seizure. This seizure started at home, and lasted about 90 minutes, despite appropriate medication. There was resolution of the status epilepticus after the infusion with sodium valproate for 15 minutes, and she was later transferred to the pediatric intensive care unit (PICU). At the admission, she had no fever or other symptomatology. During the first 24 hours of hospitalization, she presented sustained fever, around 40° Celsius, difficult in yielding with antipyretics. The diagnosis of malignant hyperthermia was considered, and therapy with dantrolene was initiated. A few hours later, she presented reddish-brown urine, her blood tests revealed an elevation of creatine kinase (CK) to 52560 U/L, of aspartate aminotransferase to 797 U/L, alanine aminotransferase to 259 U/L, lactate dehydrogenase of 1287 U/L and myoglobin to 1538 ng/mL. Diagnosed with severe rhabdomyolysis, she initiated fluid and electrolyte management and discontinued chloral hydrate, a drug that could potentiate this syndrome and its complications. Even with the treatment and careful monitoring, she developed acute renal failure and subsequently arterial hypertension, that was treated accordingly with intravenous (IV) fluids and loop diuretics (furosemide). During hospitalization, she presented worsening of movement abnormalities, with dystonia and athetosis. For that reason, therapy with tetrabenazine was initiated. She was in the PICU for 10 days, and was discharged from the hospital after 42 days with clinical resolution of the rhabdomyolysis, acute kidney failure and an improvement of her movement

disorder with tetrabenazine 12 mg per day, trihexyphe-
nidyl 0.1 mg/kg/day twice daily and levetiracetam 35
mg/kg/day twice daily. When she was 7, a new genetic
study by WES was performed, that identified a *de novo*
pathogenic variant in the *RHOBTB2* gene c.1532G>A
(p.Arg511Gln), not previously described.

Currently, almost 3 years later, she maintains multi-
disciplinary follow-up, and is medicated with trihexyphe-
nidyl, tetrabenazine, levomepromazine and anti-seizure
medication (levetiracetam, carbamazepine). Since then,
she has not presented any new seizures or hospitaliza-
tions, namely due to rhabdomyolysis.

The patient maintains mild hypotonia, with inde-
pendent walking. She still presents an important cog-
nitive delay, with language impairment, only stuttering
some words. She also maintains dyskinetic movements,
however, with ability to perform some daily activities,
particularly in terms of feeding.

Discussion

RHOBTB2 encephalopathy is a rare syndrome, with
a complex diagnosis and a poor prognosis. In previous
studies, patients identified with this syndrome had a de-
velopmental and epileptic encephalopathy-64 (DEE-64).
DEE-64 is a neurodevelopmental disorder, clinically pre-
sented by onset of seizures usually in the first year of life
and associated with intellectual disability, poor motor
development, and poor or absent speech.³ Also include
hypotonia, abnormal movements (including dystonic
and paroxysmal), microcephaly and nonspecific dysmor-
phic features (micrognathia, low nasal bridge, deep-set
eyes and epicanthal folds).³ The identification of the
RHOBTB2 gene in 2018 by Straub *et al* using trio exome
sequencing, was initially found in one individual, and af-
terwards identified by using matchmaking platforms and
collaborative efforts in a total of 10 individuals.² All of
the variants of RHOBTB2 encephalopathy reported so
far were located in the BTB domains that binds to GT-
Pase domain and ubiquitin ligase scaffold CUL3, which
promotes proteasomal degradation.^{1,2}

Most individuals with RHOBTB2 syndrome present
with various types of seizures in the first months of life,
that include focal, myoclonic and generalized tonic-clonic
seizures. In a study published in 2021, 65% of patients pre-
viously identified reported status epilepticus. Even though
some of the patients with *RHOBTB2* variant had status epi-
lepticus, none of them had ever reported rhabdomyolysis.¹

Rhabdomyolysis is a syndrome caused by severe
muscle necrosis and release of its constituents into
circulation, that can originate muscle pain, dark red to
brown urine due to myoglobinuria, elevations of muscle
enzymes, mainly creatine kinase. In severe cases, it can
be life-threatening with electrolyte imbalances and acute
kidney injury (AKI).^{6,7} This syndrome is mainly caused by
trauma, use of certain drugs, infection, congenital condi-
tions, as certain myopathies, and, in rare situations, as-
sociated with status epilepticus. There is no clear data
on the real morbidity of this syndrome associated with
status epilepticus, due to the limited cases reported.

Even though features of the syndrome have already been
described in previous studies, in none of them was there an
association of the RHOBTB2 syndrome with severe rabdo-
myolysis and, consequently, acute kidney injury.

In a previous study, based on the pharmacology of
statins, the association between GTPase family and myo-
toxicity has been described. Statins inhibit the enzyme
HMG-CoA reductase, subsequently blocking the synthe-
sis of mevalonate. The mevalonate pathway is vital for the
production of isoprenoids that are important for anchor-
ing GTPases to the membrane, that also includes Rho GT-
Pases. It has been shown, in this experimental study, that
the inactivation of these GTPases, were crucial for statin-
induced myotoxicity.⁸ Taking this study into account, the
authors hypothesize that since the *RHOBTB2* gene en-
codes a protein, from the atypical Rho GTPase family, it
may be possible that variants of this gene, might have an
important role in rhabdomyolysis, but further research is
necessary to establish causal relationship.

It is important to enhance that, given that the child
experienced status epilepticus for about 90 minutes,
there is a possibility that the prolonged seizure itself
could have directly caused the rhabdomyolysis.

With this case, we intend to highlight the possibility
of rhabdomyolysis being a manifestation of RHOBTB2
syndrome contributing to a better characterization of
this genetic syndrome. ■

Contributorship Statement / Declaração de Contribuição

FC and KF: Research and writing.
AF, CC and PRS: Review and contribution of professional clinical
experience.

All authors approved the final version to be approved.

FC e KF: Pesquisa e redação.
AF, CC e PRS: Revisão e contributo de experiência clínica
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Todos autores aprovaram a versão final a ser aprovada.

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