

Biotinidase Deficiency by Variant c.281G>T p. (Gly94Val): Report of a Case

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Abstract: *Biotinidase deficiency (BTD) is a rare autosomal recessive disease associated with a mutation in the BTD gene. Clinically it manifests as a neurocutaneous syndrome, sometimes associated with respiratory and immunological disorders. Timely identification of this inborn error of metabolism (IEM) remains a major challenge due to its variable clinical presentation. Early diagnosis can improve the patient's prognosis and decrease morbidity and mortality. We describe the case of a patient with BTD with partial enzyme deficiency, with severe clinical manifestations.*

Keywords: BTD Deficiency; Múltiple Carboxylase Deficiency; Biotinidase Deficiency; Biotinidase; Biotin

1. Introduction

Biotinidase deficiency (BTD) is a rare, autosomal recessive, metabolic disorder with an incidence that varies by region, being higher in countries with high inbreeding rates (1, 2).

It is caused by a variant in the BTD gene, which generates a biotinidase deficiency, interfering with biotin recycling and the functioning of biotin-dependent carboxylases (3).

Clinically, it manifests as a neurocutaneous syndrome, with neurological (epileptic seizures, hypotonia, developmental delay, hearing loss, ataxia due to optic atrophy) and dermatological (eczematous erythema and alopecia) signs and symptoms of variable expression (1), which do not correlate with the degree of enzyme activity deficiency, but in patients with partial DBT the manifestations are usually milder.

Due to the low prevalence of the disease and clinical variability, diagnosis is often delayed, increasing neurological and auditory sequelae (4). The purpose of this article is to report the case of a female patient diagnosed with partial biotinidase deficiency, who debuted with severe clinical manifestations.

2. Clinical Case

Patient resulting from a fourth pregnancy, controlled, without complications, daughter of healthy parents with a history of consanguinity (distant cousins), born vaginally at 38 weeks' gestation, good neonatal adaptation, weight,

height and head circumference appropriate for gestational age.

At 2 months of age, he began episodes of epileptic spasms in flexion and extension of the trunk, with fixed gaze, disconnection from the environment, followed by inconsolable crying and nystagmus; physical examination revealed drowsiness, generalised hypotonia, absence of primitive moro and grasping reflexes; in-hospital therapy was started with phenobarbital and vigabatrin, with a diagnosis of West syndrome. A haemogram, ionogram, normal liver and renal function, CT scan and brain magnetic resonance imaging (MRI) without alterations, electroencephalogram (EEG) with slow and poorly organised activity, without hypsarrhythmias were performed. At the onset of the clinical picture the patient was suffering from acute bronchiolitis.

In the following two months, there was a decrease in the frequency of seizures, but with worsening drowsiness, hypoactivity and hypotonia, now associated with ciliary and supraciliary madarosis, alopecia, erythema and sphacelation predominantly in the head and neck. He was re-admitted to hospital in critical condition, in stupor, with generalised hypotonia, extensive skin involvement, imminent ventilatory failure, invasive mechanical ventilation, antibiotic and systemic antifungal coverage. The paraclinical findings summarised in table 1 highlight a significant metabolic acidosis, associated with lactic acidosis and hyperammonaemia. New brain MRI shows changes of the corpus callosum (Figure 1).

Table 1: Laboratories

Laboratory	Lab Results	
	Pre-Treatment	Post-Treatment
Blood count	Hg 7gr/dl, Leucocytes 12.140 x mm ³ , Platelets 265.000 x mm ³ .	Hg 9.1 g/dl, Leukocytes 9, 670 x mm ³ , Platelets 247, 000 x mm ³ .
Biochemical tests	Total Bilirubin 0.4 Indirect bilirubin 0.1 Urea Nitrogen 8.3mg/dl, Creatinine 0.16 mg/dl, Calcium: 1.3mEq/L, Chlorine: 116 mEq/L, Sodium: 142 mEq/L, Potassium: 3.8 mEq/L, Magnesium: 2 mEq/L. CRP 3.2 mg/L	GOT 15 Units, GPT 8 Units, Urea Nitrogen 4.7mg/dl, Creatinine 0.17 mg/dl, Calcium: 1.4mEq/L, Chlorine: 111 mEq/L, Sodium: 145 mEq/L, Potassium: 4 mEq/L, Magnesium: 1.46 mEq/L.
Venous gases	pH 7.2, Bicarbonate 3.7mmol/L, pCO ₂ 9.6	-
Lactic acid	14 mmol/l (VR< 2.2 mmol/L)	3.9 mmol/l (VR< 2.2 mmol/L)
Pyruvate	-	0.23 mmol/l (VR < 0.12 mmol/l)
Lactate/pyruvate ratio	-	16.9 (VR < 25)
Ammonium	77 mmol/L (VR< 50 mmol/L)	51.3 mmol/L (VR< 50 mmol/L)
Amino acids (urine and plasma)	Normal	-
Serumorganic acids	-	Normal

Source: own elaboration.

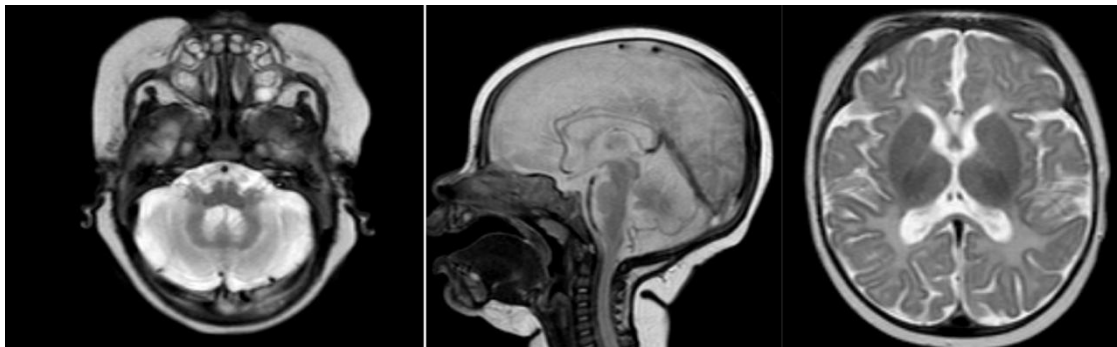


Figure 1: Brain MRI with decreased volume of the intermediate commissure with changes suggesting delayed myelination of the corpus callosum

Given the presence of epilepsy, associated with metabolic acidosis, with an elevated anion gap (32 mEq/l), increased serum lactic acid and skin involvement, an inborn error of metabolism (IEM) is suspected. Treatment was started with a diet restricted in proteins, lipids and carbohydrates and therapy with amino acids (carnitine) and multivitamin cofactors (biotin, hydroxocobalamin, pyridoxine, riboflavin, thiamine); extension studies were performed (see table 1).

Five days after the start of treatment, the patient was alert, more active, with no new crises, improved respiratory mechanics, no need for ventilatory support, progressive resolution of the dermatosis, normal 12-hour video telemetry. Control studies were performed (see table 1), with improvement in lactic acidosis.

Due to the patient's symptoms and evolution, a study of (a) biotinidase activity by colorimetry was requested: 5.4 nmol/min/mL (VR 7.8-13.1), and (b) analysis of the BTG gene, which identified the presence in homozygosity of the pathogenic variant NM_001370658.1: c.281G>Tp. (Gly94Val), confirming biotinidase deficiency. The molecular study was extended to the siblings, demonstrating genotypic alteration in one of them, with heterozygous presence of the same pathogenic variant.

She is currently 4 years old and continues to be treated with biotin and oxcarbazepine, remains free of seizures, alert and active, without alterations in muscle tone, with an increase in the polygon of support for walking, has a language delay and bilateral sensorineural hearing loss. Last cerebral MRI

with signs of cerebellar and mild cortical atrophy, with normal electroencephalogram for age.

3. Discussion

Biotin is a water-soluble B-group vitamin that acts as a cofactor for four mitochondrial and cytosolic enzymes, pyruvate carboxylase, propionyl CoAc carboxylase, B-methylcrotonyl-CoAc carboxylase and acetyl-CoA carboxylase (5); requires the action of biotinidase, an enzyme that allows its recycling for the formation of new active carboxylases (1, 2), a process important for the metabolism of fatty acids, amino acids and carbohydrates (5, 6).

Biotinidase deficiency (BDD) is a rare disease, with a worldwide incidence of 1/60, 000 births, being higher in countries such as Turkey, Saudi Arabia and Brazil, where there are high rates of inbreeding, with incidences 5 to 8 times higher. Carrier status of the genetic variant is much more frequent, with data ranging from 1/123 individuals (1, 2, 6).

DBT is part of the so-called IEM, a group of diseases caused by genetic variants that cause defects in specific proteins. In DBT, of autosomal recessive inheritance, the mutation is found in the BTG gene, located in the locus of chromosome 3p25, around 200 variants have been identified, 150 of which are categorised as pathogenic (7, 8). In the patient, the homozygous c.281G>T p. (Gly94Val) mutation was identified, a rare variant that generates a missense-type

change that predicts the substitution of an amino acid Glycine for Valine at position 94 of the protein.

The clinical manifestations of DBT are variable, with symptoms similar to other inborn errors of metabolism (9). In profound enzyme deficiencies, corresponding to < 10% of normal activity, the disturbances usually appear between 2 and 5 months of age, less frequently later in childhood or adolescence, or even remain asymptomatic (8, 10). Manifestations are predominantly neurological, including hypotonia, lethargy, epileptic seizures, ataxia, optic atrophy, hearing loss, visual disturbances and developmental delay, eczematous rashes and alopecia (11), respiratory symptoms such as stridor, apnoea and episodes of hyperventilation secondary to metabolic alterations such as ketoacidosis, lactic acidosis or hyperammonaemia (12, 13); recurrent, predominantly fungal infections due to immune dysfunction are also common (1). Partial biotinidase deficiency, defined as enzyme activity 10-30% of normal, describes the development of symptoms under stress, often secondary to infectious or metabolic processes (8, 11, 13). This describes the case of the child, who had an early debut with a neurocutaneous syndrome, associated with metabolic disorder, with progressive deterioration, which ended in respiratory failure.

The diagnosis is made by determining biotinidase activity, the normal mean of which is 7.57 ± 1.41 nmol/min/ml (8), a value that varies according to the reference ranges adopted by the laboratory processing the sample. In many countries there are established policies for neonatal screening for IEM, including DBT (12); in Colombia, neonatal metabolic screening was established by tandem mass spectrometry with heel stick blood (14). When enzyme activity is inconclusive, as with the patient in the case report, in whom biotinidase measurement yielded decreased but non-diagnostic values, it is essential to perform a genetic study of variants for DBT. Other tests to be performed include measurement of ammonium, lactic acid, pyruvic acid, urine organic acids and arterial gases (1, 3).

Management consists of biotin supplementation at a dose of 5-20 mg/day, monitoring urinary organic acid values to guide dosage adjustments. Clinical manifestations improve on initiation of therapy, seizures resolve within hours to days, but skin changes take weeks to resolve (1), optic atrophy, hearing impairment and developmental delay improve, but are usually not completely reversible (6). The patient in the present case showed marked improvement after initiation of biotin therapy, with disappearance of epileptic seizures, decreased hypotonia and skin lesions within a few days of treatment. Unfortunately, the hearing impairment was irreversible, partial recovery of lost developmental milestones was achieved, but there is a delay in language development.

The prognosis for these patients is generally good, provided early diagnosis and treatment, ideally pre-symptomatic, avoids further sequelae. Patients should be included in a comprehensive care programme, ensuring regular monitoring by neuropaediatricians with developmental surveillance, annual auditory and ophthalmological

evaluation for patients with profound deficit and biannual for those with partial deficit (1).

4. Conclusions

DBT is a rare metabolic error resulting from a genetic mutation. Early diagnosis, especially presymptomatic, improves the survival and functional prognosis of those affected, and should be considered in patients with neurological and cutaneous symptoms, as well as the presence of metabolic acidosis and hyperammonaemia. Few cases have been reported in the literature, especially in Latin America, so we describe the clinical characteristics of this patient and highlight the importance of neonatal screening for early detection of this condition to avoid late diagnosis and long-term complications, as well as the genetic study of parents and family members.

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