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CASE REPORT

Propionic Acidemia and Optic Neuropathy: A Report of Two Cases

Carolina Arias • Erna Raimann • Pilar Peredo • Juan Francisco Cabello • Gabriela Castro • Alf Valiente • Alicia de la Parra • Paulina Bravo • Cecilia Okuma • Verónica Cornejo

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Abstract *Introduction:* Propionic acidemia is a metabolic disease produced by a deficiency of the enzyme propionyl-CoA carboxylase. It can lead to coma, with severe neurologic encephalopathy or present later in life with vomiting, hypotonia, and seizures. An early diagnosis with adequate treatment helps to prevent the sequelae. Among the described complications is optic neuropathy, although not commonly reported, it is very disabling. *Objectives:* To describe two patients with propionic acidemia and optic neuropathy. *Patients and Methods:* Patient 1: 16 years old, male, parents without consanguinity. He was diagnosed at 5 months of age because of hypotonia and seizures. Until the age of 9 years, he evolved satisfactorily; therefore, he stopped treatment. At 13 years, he presented bilateral optic neuropathy. Patient 2: 20 years, female, parents without consanguinity. She was diagnosed with PA at 11 months of age because of hypotonia and seizures. She evolved satisfactorily until the age of 9 years when she presented a metabolic decompensation followed by a bad metabolic control. At 18 years, she presented bilateral progressive optic neuropathy. *Results:* Both patients have psychometric scores with borderline IQ 84–75 (WISC-R) beside optic neuropathy. They were evaluated by an ophthalmologist and also by neuroimaging (MRI of optic pathway). *Conclusions:* Pathophysiology of optic neuropathy is not completely understood. There is evidence that the damage is due to an accumulation of neurotoxic compounds secondary to the metabolic block increasing the oxidative stress. We suggest an annual ophthalmologic evaluation in the long-term follow-up of organic acidurias with visual loss, in order to detect this disabling sequela at an earlier stage.

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C. Arias (✉) · E. Raimann · P. Peredo · J.F. Cabello · G. Castro · A. Valiente · A. de la Parra · P. Bravo · V. Cornejo
Laboratory of Genetics and Metabolic Diseases, Institute of Nutrition and Food Technology, (INTA) University of Chile, El Líbano 5524, Santiago 7830490, Chile
e-mail: carias@inta.uchile.cl

C. Okuma
Division of Neuroradiology, Institute of Neurosurgery (INCA)
Dr. Alfonso Asenjo, Santiago, Chile

Introduction

Propionic acidemia (PA) (OMIM 606054) is an organic aciduria (OA) due to propionyl CoA carboxylase enzyme deficit, composed by two subunits: α (PCCA, OMIM 232000), chromosome 13q32 and β (PCCB, OMIM 232050), chromosome 6p21. The incidence is 1:100.000 newborns.

There are two clinical presentations: an acute neonatal form, characterized by severe metabolic decompensation and a late chronic progressive form with hypotonia, failure to thrive, and developmental delay. The diagnosis is confirmed by enzyme or molecular analysis (Cornejo and Raimann 2010; Ogier de Baulny and Saudubray 2002).

The accumulation of organic acids, either transported through the blood-brain barrier (BBB) or synthesized in the central nervous system, leads to secondary metabolic alterations due to their toxicity (Schreiber et al. 2012). This causes brain damage and inhibition of mitochondrial metabolism explaining acidosis, hypoglycemia, and hyperammonemia. It has been suggested that there is an imbalance of amino acids transport through the BBB leading to a low protein synthesis and secondary carnitine deficit, which can generate less energy (Wajner and Goodman 2011). Recently, oxidative stress has been

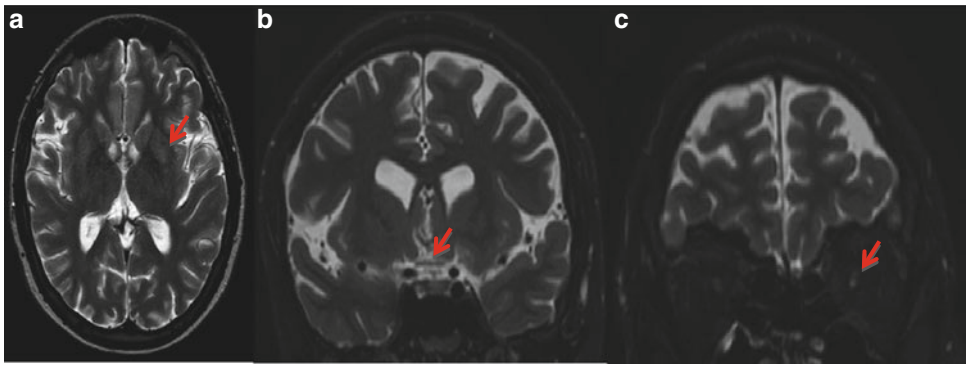

Fig. 1 MRI brain and orbits: Case 1 at 15 years old. (**a**) T2W-weighted axial image, *red arrow* shows discrete hyperintense signal in putaminal nucleus, there is also signs of brain atrophy. (**b**) T2W-weighted coronal image, *red arrow* shows decreased volume and increased signal of optic chiasm (chiasmal atrophy). (**c**) Coronal T2-weighted STIR, *red arrow* shows decreased volume and increased signal in intraorbital portions of both optic nerves (severe bilateral optic atrophy)

reported in OA due to decreased antioxidant capacity (Ianchulev et al. 2003; Wajner and Goodman 2011). These pathophysiological effects explain the multisystemic complications in OA, most frequently neurologic (symmetrical necrosis of globus pallidus), renal, dermatologic, pancreatic, and cardiac. Optic nerve atrophy has been reported in organic acidemias, mainly, propionic acidemia and methylmalonic acidemia (Ianchulev et al. 2003; Williams et al. 2009; Patton et al. 2000; Gerth et al. 2008; Grünert et al. 2013); however, it is very disabling.

Case Reports

The first case: Male, 16 years old, parents without consanguinity. His brother died at 27 weeks of gestational age (GA) of undetermined cause. He was born at 34 weeks GA, birth weight 2,160 g, length 46 cm, Apgar 9–9.

Diagnosis was suspected at 5 months of age by developmental delay, hypotonic syndrome and focal seizures. Increased glycine and propionylcarnitine were found. Nutritional treatment was started with natural protein restriction (1.2 g/kg/day), L-carnitine (100 mg/kg/day), and biotin (10 mg) for improving seizure control and psychomotor development. From age 9, he showed poor adherence to nutritional therapy with elevated levels of propionylcarnitine (C3) and ammonia and decreased levels of free carnitine (C0). Plasma levels of amino acids involved in the metabolic pathway were below the recommended range, with the exception of methionine and threonine. Total IQ assessed by WISC-R was 78 at 12 years of age (borderline).

He presented a bilateral visual loss at age 13. The ophthalmologic evaluation detected visual field contraction of all isopters in both eyes (remaining at 10 °). Visual acuity was 0.05 to 1 meter in both eyes. The fundus revealed pale papillae and dystrophic retina speckled with pigment migration, consistent with bilateral progressive optic neuropathy. Magnetic resonance imaging (MRI) of the brain and optic pathway was performed, demonstrating severe bilateral optic neuropathy (Fig. 1).

The second case: Female, 20 years old, parents without consanguinity, and a family history of three brothers who died in the neonatal period of undetermined cause. She presented at 11 months of age with focal seizures and hypotonia leading to the diagnosis of PA. After nutritional treatment was started with natural protein restriction (0.7 g/kg/day), L-carnitine (100 mg/kg/day), and biotin (10 mg/day) she progressively improved her psychomotor development. At age 9, she had a severe metabolic decompensation, subsequently metabolic control was irregular with elevation of C3, high ammonia and decreased free carnitine. The amino acids supplementation was poor. In the cognitive evaluation (WISC-R) at age 12, total IQ was 81 (low normal range).

At age 18, she presented progressive visual loss. Ophthalmologic evaluation found a decreased visual acuity in both eyes at 20 cm 20/800, color vision 0/10, visual field and ocular motility was preserved. The fundus showed a pale papillae whit small central excavation and an unaltered retina and macula, consistent with bilateral optic nerve atrophy. Brain and optic path MRI revealed bilateral optic neuropathy (Fig. 2).

Discussion

The pathophysiology of optic nerve atrophy in OA is still unknown, but the accumulation of neurotoxic substrates due to the metabolic block can produce the damage (Williams et al. 2009). This compromise can usually affect several organs as liver, bone marrow, kidney, pancreas, heart, and brain. The central nervous system and optic nerve are particularly susceptible to damage because of the high concentration of polyunsaturated fatty acids in mitochondrial membranes (Schreiber et al. 2012).

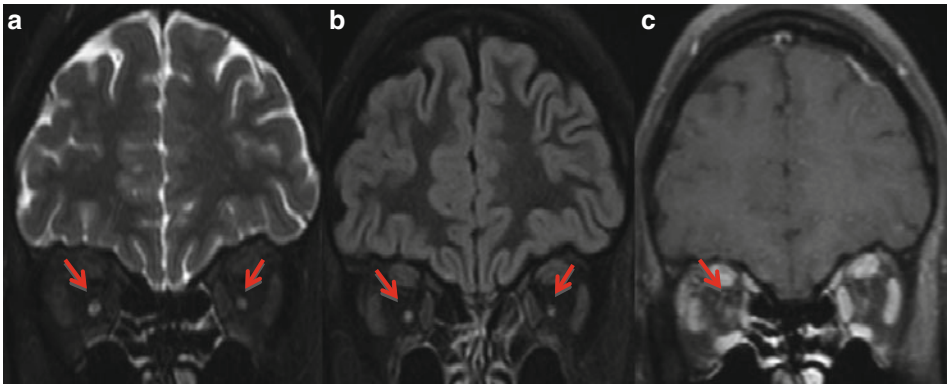

Fig. 2 MRI brain and orbits: Case 2 at 17 years old. Coronal images (**a**) T2-weighted STIR and (**b**) STIR-FLAIR, *red arrows* demonstrate hyperintense signal in intraorbital portions of both optic nerves. (**c**) T1FS-weighted contrast, *red arrow* shows discrete impregnation of optic nerves, *left* more evident

Moreover, the accumulation of propionyl-CoA in mitochondria induces ultrastructural changes, producing inhibition of pyruvate dehydrogenase, alpha-ketoglutarate dehydrogenase, complexes of the respiratory chain and glutathione synthetase. This favors the hypothesis of mitochondrial dysfunction induced by the accumulation of enzymatic block–derived compounds (Schwab et al. 2006). The oxidative phosphorylation is reduced generating cytotoxic free radicals which can induce apoptosis (Gallego-Villar et al. 2012). In addition, there are decreased cellular antioxidant reserves (alpha-tocopherol and glutathione) (Wajner and Goodman 2011; Mc Guire et al. 2009).

In this report, both patients had poor metabolic control for years, developing progressive optic neuropathy. In the literature, there is no consensus about the lack of adherence to treatment as the cause of this complication (Sutton et al. 2012). However, being a late complication, it could be influenced by an increased oxidative stress as a trigger. In addition, both patients have cognitive impairment in borderline range, which could be explained by a delayed diagnosis (de Baulny et al. 2005; Loren et al. 2012). We suggest an ophthalmologic evaluation in patients with OA and early visual loss symptoms. This could lead to early detection of this disabling complication (Sutton et al. 2012; Loren et al. 2012).There are some studies showing that cohorts of patients with OA detected with expanded newborn screening programs (NBS) have improved survival with better prognosis and quality of life (Dionisi-Vici et al. 2006; Hori et al. 2005; Schulze et al. 2003). However it is not clear that early detection by NBS can prevent long-term complications such as optic neuropathy, cognitive delay, or metabolic crises (Grünert et al. 2012). Our patients in this report show disabling complications at long-term follow-up, probably because they were already symptomatic at the time of diagnosis and had also a bad metabolic control.

Synopsis

Optic neuropathy complication organic acidemia.

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