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Case Report

Concurrent non-ketotic hyperglycinemia and propionic acidemia in an eight year old boy

Paul S. Kruszka [a], Brian Kirmse [b], Dina J. Zand [b], Kristina Cusmano-Ozog [b], Elaine Spector [c], Johan L. Van Hove [c], Kimberly A. Chapman [b,*]

[a] National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA
[b] Department of Genetics and Metabolism, Children's National Health Center, Washington, DC, USA
[c] Section of Clinical Genetics and Metabolism, University of Colorado, Denver, CO, USA

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ABSTRACT

This is the first reported case of a patient with both non-ketotic hyperglycinemia and propionic acidemia. At 2 years of age, the patient was diagnosed with non-ketotic hyperglycinemia by elevated glycine levels and mutations in the *GLDC* gene (paternal allele: c.1576_1577insC delT and c.1580delGinsCAA; p.S527Tfs*13, and maternal allele: c.1819G>A; p.G607S). At 8 years of age after having been placed on ketogenic diet, he became lethargic and had severe metabolic acidosis with ketonuria. Urine organic acid analysis and plasma acylcarnitine profile were consistent with propionic acidemia. He was found to have an apparently homozygous mutation in the *PCCB* gene: c.49C>A; p.Leu17Met. The patient was also treated with natural protein restriction, carnitine, biotin, and thiamine and had subjective and biochemical improvement.

1. Introduction

Despite our effort to classify all of an individual's findings under one genetic or metabolic diagnosis, individuals can have more than one disorder. Whole exome studies have illustrated the possibility of more than one diagnosis within a single complex patient. However, how often do we think about more than one

* Corresponding author at: Division of Genetics and Metabolism, Children's National Health System, 111 Michigan Ave NW, Suite 1950, Washington, DC 20010, USA. Fax: +1 202 476 5650.
E-mail addresses: Paul.kruszka@nih.gov (P.S. Kruszka), Bkirmse@childrensnational.org (B. Kirmse), dzand@childrensnational.org (D.J. Zand), kcozog@childrensnational.org (K. Cusmano-Ozog), Elaine.Spector@ucdenver.edu (E. Spector), Johan.Vanhove@ucdenver.edu (J.L. Van Hove), kchapman@childrensnational.org (K.A. Chapman)

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biochemical cause and thus, pursue further evaluations to examine more than one cause explaining findings in a single patient? Here, we present a patient who has non-ketotic hyperglycinemia (NKH) and a delayed diagnosis of propionic acidemia (PA).

Elevations in plasma or serum glycine can be several different disorders including non-ketotic hyperglycinemia or ketotic hyperglycinemia. Non-ketotic hyperglycinemia (NKH) is a neurobiochemical disorder in which the glycine cleavage system (encoded by the genes *GLDC*, *AMT*, and *GCSH*) is unable to function resulting in elevated glycine [1]. Patients with NKH often present in the neonatal period with lethargy and seizures. Furthermore, patients with an attenuated form of NKH can present later in infancy, have variable degree of developmental delays, hyperactivity, and choreatic movements. Individuals with NKH have elevated levels of glycine in plasma and in CSF and have an elevated CSF:plasma glycine ratio. Typically, they do not have ketones in plasma or urine [1].

In contrast, ketotic hyperglycinemia, predominately caused by the organic acidurias, propionic acidemia, (PA, from mutations in the genes *PCCA* and *PCCB*) and the methylmalonic acidurias (MMAs), presents with increased ketones in urine and serum [2]. Individuals with PA have characteristic elevations in the organic acids, 3-hydroxypropionic acid and methylcitrate, but can also have increased plasma glycine levels. These individuals usually present with ketoacidosis and symptoms such as lethargy, vomiting and can develop coma [2,3]. Seizures can occur, but usually during acidosis episodes [4].

2. Case report

Several hints presented throughout the history of this patient indicate that there may be more than one cause of his symptomatology. These included a need for carnitine at one year of life and multiple episodes of metabolic ketoacidosis.

The patient's birth history was unremarkable with normal growth parameters, but he had poor breast feeding early on requiring readmission for dehydration and was started on formula. At one month of age, the patient presented with seizures. He had a normal brain MRI, an EEG with “a left focal seizure focus”, and he was treated with phenobarbital and valproate. By 2 months of age, the infant demonstrated upper extremity extensions, eye rolling, and repetitive mouth movements. These movements did not correlate with seizures on video EEG, although the EEG demonstrated right and left hemispheric sharp and slow waves.

By 1 year of age, the EEG showed hypsarrhythmia and the patient was diagnosed with intractable seizures and epileptic encephalopathy. He was admitted with metabolic acidosis with a low bicarbonate of 2.5 mmol/L, fever, and continued to have seizures. By history, he was also diagnosed with low total and free carnitine levels, and started on supplementation with carnitine. Biochemical testing was reportedly done at this time at another institution, including urine organic acids and they were reportedly not diagnostic.

At 2 years of age, patient was found to have choreiform-like movements. He was diagnosed with NKH after finding elevated glycine levels in plasma and CSF with an elevated ratio of CSF: plasma glycine. The diagnosis was confirmed by identification of two mutations in the *GLDC* gene: paternal: c.1576_1577insC delT and c.1580delGinsCAA; p.S527Tfs*13, and a missense mutation on the maternal allele c.1819G>A; p.G607S. This mutation affects a fully conserved amino acid, is predicted to be deleterious by Polyphen-2 [5], and has been observed in another patient with NKH (Van Hove, unpublished observation).

Between the ages of 1 and 8 years, the patient had multiple hospitalizations for metabolic acidosis and ketosis. He made little developmental progress resulting in an inability to ambulate and no functional speech. At 8 years of age after being placed on ketogenic diet for better seizure management, he became lethargic and had severe metabolic acidosis with ketonuria. Urine organic acid analyses were repeated and showed a large peak of 3-hydroxypropionic acid (Fig. 1A), and the acylcarnitine profile revealed elevated propionylcarnitine at 1.2 μmol/L (age normal < 0.88 μmol/L) (Table 1).

The patient was treated with natural protein restriction, carnitine, biotin, and thiamine with resolution of the metabolic acidosis and of the propionate metabolites in the urine organic acids profile (Fig. 1B). Very few differences are apparent in other metabolic measures (Table 1).

The diagnosis of propionic acidemia was confirmed by finding an apparently homozygous mutation in the *PCCB* gene: c.49C>A; p.Leu17Met. There was no normal sequence identified in this sample. This change has been described in one other patient who had an additional two mutations. However, this amino acid is