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Unusual Presentation of Propionic Acidemia as Isolated Cardiomyopathy

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Summary

Propionic acidemia (PA) is an autosomal recessive disease that results from deficiency of propionyl-CoA carboxylase (PCC). In virtually all reported cases of PA, the phenotype includes metabolic acidosis and/or neurological deficits. We report on a 14-year-old Asian male with PA who presented with isolated cardiomyopathy without any episodes of metabolic acidosis or evidence of any neurocognitive deficits. On routine metabolic screening, the patient was found to have urine organic acids suggestive of PA. Biochemical and genetic characterization confirmed a PCC deficiency with two novel mutations in *PCCB*: IVS7+2 T>G (c.763+2 T>G) and p.R410Q (c.1229 G>A). Residual enzyme activity likely explains our patient's mild phenotype. Splicing mutations tend to result in a milder phenotype as these mutations may still produce small amounts of normal enzyme. In addition, the similar p.R410W mutation has been shown to have partial residual activity.

Moreover, this case illustrates the important but under-recognized manifestation of isolated cardiomyopathy as the sole clinical presentation in PA. A thorough metabolic evaluation should be performed in all pediatric patients with cardiomyopathy. Such an evaluation has important implications for clinical management and genetic counseling.

Introduction

Propionic acidemia (PA; OMIM #606054) is an autosomal recessive disease that results from propionyl-CoA carboxylase (PCC; EC 6.4.1.3) deficiency (Fenton et al 2001) with an estimated incidence of about 1:50,000 (Desviat et al 2004). Most affected individuals have life-threatening episodes of metabolic acidosis with ketosis, hyperammonemia, or pancytopenia which can result in mental retardation and/or early mortality. In the most severe cases, symptoms such as vomiting, altered mental status, hypotonia, and abnormal movements or seizures can present in the neonatal period. In late-onset disease, patients often present with milder symptoms during an intercurrent illness (Perez-Cerda et al 2000). Atypical presentations, including acute basal ganglia necrosis (Perez-Cerda et al 1998) and adult-onset chorea (Sethi et al 1989), have been observed without documented metabolic acidosis (Nyhan et al 1999). However, in virtually all reported cases of PA, the phenotype includes metabolic acidosis and/or neurological deficits.

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Conflict of Interest Notification Page

None.

PCC is a biotin-dependent enzyme found in the mitochondrial matrix that is necessary for metabolism of propionate arising from four essential amino acids (isoleucine, valine, threonine and methionine), odd-chain fatty acids, and the side chain of cholesterol, along with other metabolites. Specifically, it catalyzes the carboxylation of propionyl-CoA to D-methylmalonyl-CoA (Fenton et al 2001). PCC is a dodecameric enzyme composed of six α and six β -subunits (Gravel et al 1980; Kalousek et al 1980), encoded by *PCCA* on 13q32 (Kennerknecht et al 1990) and *PCCB* on 3q13.3-q22 (Kraus et al 1986). Numerous mutations in *PCCA* and *PCCB* have been reported in PA.

In this report, we present a 14-year-old male with PA who presented with isolated cardiomyopathy without any episodes of metabolic acidosis or evidence of any neurocognitive deficits. Biochemical and genetic characterization confirmed a PCC deficiency due to two novel mutations in *PCCB*, IVS7+2 T>G and p.R410Q.

Case Presentation

The proband, a 14-year-old Asian male with no significant past medical history, was born to nonconsanguineous parents from China. His prenatal, birth, and neonatal history were all unremarkable. He reached all his developmental milestones at an appropriate time and was an honors student in the ninth grade. He was active in school sports such as tennis and swimming. He had no history of myopathy or growth problems.

Several months before presentation, he had progressive exercise intolerance followed by one week of worsening symptoms accompanied by nausea and diarrhea. He was found to have an irregular pulse which on further testing was identified as bigeminy. An echocardiogram showed a markedly dilated left ventricle (interventricular septum in systole 0.81 cm; left ventricular end-diastolic dimension 8.03 cm) with severely diminished function and a fractional shortening of 8 %. The apex of the left ventricle was noted to have trabeculation suggestive of noncompaction (Figure 1). Right ventricular function was also poor.

On physical exam his weight was 55.4 kg (50th-75th percentile), and height was 172 cm (75th percentile). He had mild jaundice, icteric sclerae, bilateral rales, an S3 gallop, hepatomegaly 5 cm below the right costal margin, splenomegaly 2 cm below the left costal margin, ascites, and poor peripheral pulses with prolonged capillary refill time. His muscle tone was normal, and no dysmorphic features were noted.

Due to his poor cardiac function, he was listed and received an orthotopic heart transplant after three days on a paracorporeal biventricular assist device. His post-transplant course was unremarkable, and he was discharged home 10 days after his transplant. The pathology on the explanted heart showed marked gross hypertrophy of the left ventricle (left ventricle thickness 1.9 cm) with endocardial thickening. Sections from the left ventricle showed moderate to marked hypertrophy of myocytes and scant interstitial fibrosis (Figure 2). Incidental findings included focal injury related to assist device placement and a mild hypersensitivity-type myocarditis.

On metabolic screening as part of his cardiomyopathy evaluation, the patient was found to have abnormal urine organic acids with elevated methylcitric acid and trace amounts of tiglylglycine suggestive of PA. One pre-transplant and four post-transplant urine samples all demonstrated similar findings. Concurrent plasma acylcarnitine testing showed marked elevation of propionylcarnitine (20.70 μ mol/L). However, glycine levels were never elevated on plasma amino acid testing. Given the unusual clinical presentation, he was evaluated for a B12 deficiency, but B12 levels were normal (867 pg/mL), homocysteine was low (4.3 μ mol/L), and serum methylmalonic acid was normal (0.14 μ mol/L).

Enzymatic analysis of lymphocytes demonstrated low PCC activity (12.8 and 15 pmol/min/mg protein on two occasions, normal 70). Activity of 3-methylcrotonyl-CoA carboxylase was also slightly low (19 and 23.4 pmol/min/mg protein on two occasions, normal 31). Concurrent analysis of pyruvate carboxylase activity was normal.

Following the diagnosis in the proband, his two brothers, ages 12 and 10 years, were evaluated. Urine organic acid testing and cardiac evaluation were normal in both brothers.

Methods

Blood was collected from the patient after providing informed consent for a Columbia University IRB approved research study. Genomic DNA was isolated from blood using the Puregene DNA Isolation Kit (Qiagen, Valencia, CA). The entire coding region of *PCCA* and *PCCB* including intron-exon boundaries was amplified by PCR (*PCCA* primers available upon request; *PCCB* primers previously described by Rodriguez-Pombo et al in 1998). Sequencing of PCR fragments was performed according to the manufacturer's instructions on an ABI 377 DNA Sequencer (Applied Biosystems, Foster City, CA). DNA sequence results were analyzed with Sequencher 4.7 software (Genecodes, Ann Arbor, MI).

Results and Discussion

Sequence analysis revealed two novel mutations in *PCCB*: an intron 7 splice site mutation, IVS7+2 T>G (c.763+2 T>G) and a missense mutation in exon 12, p.R410Q (c.1229 G>A) (Figure 3). Results were verified bidirectionally. Sequencing for *PCCA* was normal.

The IVS7+2 T>G variant occurs at a conserved splice site (Perez et al 2003; Richard et al 1997) which would be predicted to lead to exon skipping. Splicing mutations often result in a milder phenotype as these mutations may still produce small amounts of normal protein product (Clavero et al 2004) which can moderate disease severity. Moreover, it has been postulated that different splicing mutations could be influenced by tissue-specific expression which would explain phenotypic variability (Desviat et al 2006).

The p.R410Q mutation occurs at the same residue as the common Asian p.R410W mutation in a highly conserved region of *PCCB*. The p.R410W mutation has been reported in multiple individuals of different ethnic backgrounds (Gravel et al 1994; Tahara et al 1993, Yang et al 2004). This codon is located at the inter-trimer interface and is predicted to alter the active site conformation (Desviat et al 2004). Patients homozygous or heterozygous for the p.R410W mutation have been shown to have partial residual activity in expression analyses (Perez-Cerda et al 2003).

While there are other reports of patients with mild disease or intermittent symptoms, our patient is atypical in that he had been completely asymptomatic without any metabolic decompensation for the 14 years prior to his presentation with heart failure. There is heterogeneity in disease manifestations, and there have been reports of individuals with normal physical and mental development without dietary restriction (Perez-Cerda et al 2000). However, those patients all had periodic episodes of metabolic acidosis with ketoacidosis, hyperammonemia, and hyperglycinemia.

The most similar reported case of late-onset PA was in a compound heterozygote for the p.R410W and IVS10-11del6 mutations. This patient was well until he presented at 5 years and 10 months of age with persistent vomiting. Despite high residual PCC activity and attempted therapy, deep coma developed; and the patient died of cardiac arrest 16 days after admission to the hospital illustrating the lack of correlation between enzyme activity and ultimate clinical prognosis (Perez-Cerda et al 1998).

Cardiomyopathies are known to be associated with inborn errors of metabolism such as mitochondrial disorders, fatty acid oxidation defects, carnitine deficiency, and glycogen storage diseases. However, there are only a few reports of cardiomyopathy associated with organic acidemias. There is a report of six patients with PA and cardiomyopathy (Massoud and Leonard 1993). The cardiomyopathy was fatal in three patients and resolved in the other three. All six individuals were diagnosed with PA in early childhood and had neurologic sequelae from their underlying metabolic disease.

In 2005, Mardach and colleagues reported an 8-year-old with PA and multiple episodes of metabolic acidosis but near-normal cognitive and neurological abilities who developed heart failure secondary to hypertrophic cardiomyopathy. Cardiac pathology was similar to findings in our patient and included increased myofiber size with enlarged, hypochromatic nuclei.

These cases illustrate the important but under-recognized role that cardiomyopathy can play in PA. Previous authors have raised the need for routine cardiac evaluation in patients with organic acidemias (Mardach et al 2005; Massoud and Leonard 1993). Our case also illustrates the importance of doing a thorough evaluation to search for a possible underlying metabolic etiology on all pediatric patients with cardiomyopathy, even in cases of apparently isolated cardiomyopathy. Such an evaluation is important as it influences both pre and post-transplant management. Moreover, other individuals in the family may at risk, and families need accurate counseling on the risk of recurrence.

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A list of abbreviations

PA	Propionic acidemia
PCC	Propionyl-CoA carboxylase

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Figure 1.

Top panel: 2D M-mode measure of ventricle size and function in the parasternal short axis view demonstrating severe left ventricular dilation and poor function with a shortening fraction of 8% (normal 28–40%). Bottom panel: The lateral wall of the severely dilated left ventricle shows features of noncompaction toward the apex.

Figure 2.
H&E stain showing myocardium with myocyte hypertrophy and scant interstitial fibrosis.

Figure 3.

Electropherograms of *PCCB* mutations with sequence shown above with wild-type sequence below for reference. A. The IVS7+2 mutation results in a T to G change 2 bp after exon 7 and is predicted to affect splicing. B. The p.R410Q (c.1229 G>A) mutation in exon 12 is a highly conserved amino acid.