Short Communication

Life-threatening presentations of propionic acidemia due to the Amish *PCCB* founder variant

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A B S T R A C T

Although individuals of Amish descent with propionic acidemia (PA) are generally thought to have a milder disease phenotype, we now have a better understanding of the natural history of PA in this population. Here we describe two Amish patients with emergent presentations of PA, one with metabolic decompensation and another with cardiogenic shock. PA can present with life-threatening metabolic decompensation or an adult-onset severe cardiomyopathy. We discuss critical clinical implications of this observation.

1. Introduction

Propionic acidemia (PA, MIM 606054) is an inborn error of metabolism affecting catabolism of propiogenic amino acids and odd-chain fatty acids. It is caused by biallelic variants in one of two genes, *PCCA* and *PCCB*, encoding the subunits of the biotin-dependent propionyl-CoA carboxylase. The phenotypic spectrum includes metabolic decompensation, epilepsy, hypotonia, cardiomyopathy, and prolonged QT interval [1]. Most recognized individuals with PA experience metabolic decompensation [2].

PA is known to occur more commonly in the Amish-Mennonite communities [3] due to a founder missense variant in *PCCB* (c.1606A > G; p.Asn536Asp). While there is a limited understanding of genotype-phenotype correlation in PA, individuals with null variants with no residual enzyme activity typically have a more severe biochemical phenotype [4]. The common *PCCB* variant found in Amish individuals has been suggested to have significant residual enzyme activity and be associated with milder, occasionally asymptomatic, clinical phenotype [5] despite the fact that genotype-phenotype correlation is poorly understood in PA [1,6]. Recent data suggest that patients with this variant can present with metabolic decompensation [5], and cardiomyopathy is part of the phenotype. In rare cases, adult-onset cardiomyopathy with no known history of metabolic decompensation has been described even in individuals with other variants

[7].

Patients with PA due to the Amish founder variant sometimes are managed without protein-restriction and specific medical management that is typical in the care of PA due to other variants [1,8,9]. This is likely due to a combination of factors, including that not all cases are identified by newborn screening (NBS) and thus treatment is initiated after feeding patterns and food preferences are established; the assumption that residual enzyme activity predicts milder clinical disease; and the perceived resistance to dietary protein restriction in the community.

Below we describe two unusual presentations of PA in patients of Amish ancestry: metabolic decompensation in a 3-year-old child and adult-onset cardiomyopathy in a previously asymptomatic individual. Although uncertain, it was thought that these individuals are related, but details of the possible relationship are not known. There are important clinical implications of these cases as discussed below. These cases should heighten awareness for the possibility of a more severe clinical course of PA in the Amish population and the importance of follow-up evaluation and long-term management of such patients.

Case 1:. A 3-year-old Amish girl born full term, 3240 g in weight, and normal NBS with C3 3.48 μM (cut-off < 5.00 μM) and C3/C2 0.23, presented with encephalopathy after several days of abdominal pain and vomiting. She had a profound anion gap (30) metabolic acidosis

Table 1
Summary of the Clinical Characteristics of Cases 1 and 2

	Case 1	Case 2
Age of diagnosis	3 years	27 years
Initial presentation	Metabolic decompensation	Cardiogenic shock
Cardiomyopathy	No	Yes
Long QT	Yes	No (of many EKGs, only two showed QT interval > 450 msec)
Pancreatitis	No	No
Plasma propionylcarnitine	15.02 μM	39.6 μM
C3/C2 ratio	0.78	5.68
Urine organic acid analysis at presentation	Methylcitrate present, no tiglylglycine, propionylglycine, or 3-hydroxypropionic acid reported[a]	Tiglylglycine and methylcitrate present, no propionylglycine or 3-hydroxypropionic acid reported
Molecular confirmation of *PCCB* c.1606A > G	Homozygous	Homozygous
Other	Elevation of plasma BCAA: leucine 359 uM (reference 60–230), isoleucine 209 uM (reference 30–130), valine 681 uM (reference 140–350), and alloisoleucine 6 uM (reference not detectable)	Variant of uncertain significance identified in *MYH6*

[a] Case 1 represented at age 4 years with an acute illness. At that time, urine organic acids included methylcitrate, tiglylglycine, and 3-hydroxypropionic acid (no propionylglycine was reported).

(pH 6.96, bicarbonate 4 mM), hyperammonemia (115 μM), and ketosis (serum beta-hydroxybutyrate 10.75 mM; reference range: 0.02–0.27). Plasma propionylcarnitine and the C3 to C2 ratio were elevated and diagnostic of PA (Table 1) without elevation in methylmalonic acid. Plasma branched-chain amino acids (BCAAs) were elevated with alloisoleucine present, which resolved when well. The cause of the elevated BCAAs is not known; we speculate that accumulation of metabolites such as propionyl-CoA may be interfering with BCAA catabolism by inhibiting branched-chain ketoacid dehydrogenase complex activity, although the intermittent form of MSUD has not been ruled out. During hospitalization, an electrocardiogram showed sinus rhythm with a prolonged QTc interval. Echocardiogram demonstrated a mildly dilated ascending aorta with an anatomically normal aortic valve and normal biventricular size and function. Targeted testing of the *PCCB* founder variant identified homozygosity. She was managed with intravenous nutrition to promote anabolism (high glucose infusion rate and intralipid), initial protein restriction (with subsequent introduction of intact protein balanced with medical formula lacking propiogenic amino acids), and L-carnitine. She is now followed by the biochemical genetics outpatient clinic, and to date there are no neurologic deficits.

Case 2:. A 27-year-old Amish woman presented with new-onset severe dilated cardiomyopathy following delivery of her fourth child via urgent cesarean section for acute decompensated heart failure. She had no known history of cardiomyopathy, and her prior three pregnancies were uneventful. She had left ventricular hypertrophy, and her left ventricular ejection fraction was about 15%. She underwent diuresis guided by central venous pressure monitoring, experienced ventricular fibrillation arrest, and required extracorporeal membrane oxygenation. Ultimately, she required placement of a left ventricular assist device as a bridge to planned heart transplantation. PA was diagnosed based on elevated propionylcarnitine and urine organic acid analysis demonstrating tiglylglycine and methylcitrate in the setting of normal methylmalonic acid (Table 1). Targeted testing of the *PCCB* founder variant confirmed homozygosity. In addition to mechanical support, she was managed with diet and L-carnitine. She is actively undergoing evaluation for heart transplantation and follows closely with the biochemical genetics outpatient clinic.

A broad genetic panel was ordered to evaluate other causes of cardiomyopathy and heart disease that could contribute to her phenotype. This panel was non-diagnostic. A single variant of uncertain significance was identified in *MYH6* (a gene implicated in autosomal dominant hypertrophic and dilated cardiomyopathy), *KCND3* (a gene implicated in spinocerebellar ataxia type 19 and autosomal dominant Brugada syndrome, conditions inconsistent with her phenotype), and

ALMS1 (a gene implicated in an autosomal recessive condition inconsistent with her phenotype). She has an asymptomatic sister who is also homozygous for the *PCCB* founder variant. The sister had a normal echocardiogram just days prior to the delivery of her third child that was normal. Her sister and other immediate relatives declined testing for the three variants identified on the proband's cardiomyopathy gene panel testing.

2. Discussion

Case 1 adds to the limited literature describing metabolic decompensation in Amish individuals with PA and normal NBS. The experience of our group and others who follow Amish patients has been that episodic severe metabolic decompensations are possible, but rare. Due to the possibility of metabolic decompensation, careful monitoring and management, particularly during intercurrent illness, should be provided similar to the management of patients with PA due to other variants. We do not make specific dietary or medical recommendations for PA in Amish individuals based on anecdotal experience; rather we suggest that on a case-by-case basis, conservative management be considered in individuals of Amish descent.

Case 2 had an unusual presentation of adult-onset severe dilated cardiomyopathy with no prior metabolic decompensation. In this case, it is possible that the *MYH6* VUS or other genetic factors may have contributed to the development of cardiomyopathy. Others have suggested that Amish women with the *PCCB* founder variant may be asymptomatic in early life but be at increased risk for metabolic decompensation from PA during and after pregnancy [10]. We propose that all Amish patients with cardiomyopathy should be evaluated for genetic and metabolic etiologies since this could have implications for medical management.

Both cases presented here suggest the value of early diagnosis by (NBS). Reported NBS detection rates and testing algorithms for Amish individuals with PA [5], consistent with experience with the Ohio Amish population (personal experience JKB, LLK, and SEM), suggest that setting cut-offs for NBS markers low enough to identify all affected infants would lead to an unacceptably high false positive rate in both the overall, and the Amish, population. Likewise, using different NBS cut-off values for specific sub-populations is not feasible within the existing NBS framework. Targeted screening for newborns of Amish descent with molecular testing of the *PCCB* founder variant could be considered in the future if the community were interested and supportive of this approach.

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