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Short Communication

Long-term outcomes in Amish patients diagnosed with propionic acidemia

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ABSTRACT

Propionic acidemia (PA) occurs at a higher incidence within the Amish; however, sensitivity of newborn screening and its impact on long-term clinical outcomes has not been reported in this population. This study reviewed screening data and health records of 20 Wisconsin Amish patients diagnosed with PA. Newborn screening did not identify all cases; however, early detection did offer appreciable long-term protection from neurological sequelae. This is the first report summarizing PA cases within the Amish.

1. Introduction

The Amish in the United States (US) descended from 200 European immigrants who fled religious persecution in the 1700s [1]. This small founder population, combined with few converts and infrequent outside marriages, led to increased incidence of inherited disorders, including propionic acidemia (PA) [2,3]. PA, a disorder of amino acid and odd-chain fatty acid metabolism, is caused by a defect in propionyl-CoA carboxylase enzyme, and Amish patients share a common homozygous missense variant (c.1606A > G) in the PCCB gene [3]. Individuals with PA typically present with severe neonatal metabolic crisis and have significant long-term complications [4–6]. However, Amish patients with the common variant may be asymptomatic or present with a milder phenotype of cardiomyopathy or metabolic decompensation and neurologic sequelae outside the neonatal period (unpublished data).

The Wisconsin NBS program identifies newborns with PA using acylcarnitine analysis by tandem mass spectrometry as a first tier test. Propionylcarnitine (C3) and the ratio of propionylcarnitine to acetylcarnitine (C3/C2) are the primary markers for this disease [7]. Specimens with elevated markers reflex to second tier testing for methylmalonic and methylcitric acids to delineate the type of abnormal propionate metabolism. Specimens are collected between 24 and 48 h after birth with screening results available by day 5 and treatment initiated within the first week of life.

This study assesses the efficacy of the Wisconsin NBS algorithm to detect Amish PA and summarizes long-term outcomes for patients identified by screening, as compared to clinical presentation or family history.

2. Materials and methods

A comprehensive retrospective chart review approved by the University of Wisconsin (UW) Institutional Review Board was performed on 20 Wisconsin Amish diagnosed with PA. Ages of patients ranged from 0 to 30 years.

3. Results

3.1. Newborn screen

NBS data was available for eight patients with PA; seven were detected at birth (Table 1). Initially, patients were identified by an elevated C3 (normal < 6.92 μM) and C3/C2 ratio (normal < 0.20). The algorithm was later modified by lowering the C3 cutoff (normal < 5.0 μM) and incorporating second tier testing for methylcitric acid. This cutoff change was implemented based on historical screening data and comparison to other programs [8]. The C3 concentration in seven patient samples ranged 5.47–15.05 μmol/L (median, 7.68) and C3/C2 ratio ranged 0.21–0.44 (median, 0.29). Five of the seven patients were detected using both algorithms, while two patients were identified using the lower C3 cutoff. The specimen collected from case #7 was analyzed in duplicate due to a family history. Only one set of values flagged as abnormal. One case (#8) was not identified by NBS because C3 and C3/C2 values were in the normal range.

3.2. Clinical outcomes

All seven patients identified by NBS were asymptomatic at diagnosis. To date, two of the seven patients experienced cardiac

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Table 1
Newborn screening data for propionic acidemia cases in Wisconsin Amish.

Case	Sex	Time of collection	Acylcarnitine profile		Second tier testing		Diagnosis confirmation
			C3[a]	C3/C2	MMA	MCA	
			nml < 5.00 μM (*Cases 1 through 4*) nml < 6.92 μM (*Cases 5 through 8*)	nml < 0.20	nml < 3.00 μM	nml < 1.00 μM	
PA cases: Identified by newborn screening							
1	F	41 h	9.05	0.29	0.21	2.12	Homozygous c.1606A > G
2	M	48 h	10.08	0.44	0.16	3.39	Homozygous c.1606A > G
3	F	36 h	5.47	0.27	0.28	3.26	Homozygous c.1606A > G
4	M	31 h	15.05	0.41	0.14	2.98	Homozygous c.1606A > G
5	M	24 h	7.27	0.35	NA	NA	Homozygous c.1606A > G
6	F	96 h	7.68	0.26	NA	NA	Abnormal urine organic acids (presence of methylcitric acid)
7[b]	F	96 h	4.28 5.92	0.16 0.21	NA	NA	Abnormal urine organic acids (presence of methylcitric acid)
PA case: Missed by newborn screening							
8	F	38 h	3.11	0.13	NA	NA	Normal urine organic acids; Homozygous c.1606A > G

[a] From 2000 to 2010, normal C3 value was < 6.92 μM (cases 5 through 8). From 2011 to current, normal C3 value is < 5.00 μM (cases 1 through 4).
[b] Specimen evaluated in duplicate due to a family history of Propionic acidemia.

Table 2
Clinical outcomes for patients with propionic acidemia.

Age at presentation/ diagnosis	Age at last evaluation	Clinical presentation	Hospitalization	Long-term complication
Identified by newborn screening (7 cases)				
Neonate	13 years	Asymptomatic	Yes, Cardiac arrest	Cardiac related sudden death at age 13
Neonate	9 years	Asymptomatic	None	Asymptomatic
Neonate	5 years	Asymptomatic	Yes, Metabolic decompensation	Prolonged QT arrhythmia
Neonate	4 years	Asymptomatic	None	Seizure, precipitated by illness
Neonate	3 years	Asymptomatic	None	Asymptomatic
Neonate	2 years	Asymptomatic	None	Asymptomatic
Neonate	6 months	Asymptomatic	None	Asymptomatic
Identified by clinical presentation (7 cases)				
5 years	26 years	Metabolic decompensation	Yes, Metabolic decompensation	Seizure disorder, Movement disorder, Learning difficulties
3 years	24 years	Metabolic decompensation	Yes, Metabolic decompensation, cardiomyopathy	Cardiomyopathy
8 years	11 years	Seizures, Learning difficulties	None	Seizure disorder, Learning difficulties
8 months	10 years	Metabolic decompensation, Seizures	Yes, Metabolic decompensation	Movement disorder, Learning difficulties, Poor weight gain
5 years	5 years	Poor weight gain	None	Poor weight gain
23 month	2 years	Metabolic decompensation	Yes, Metabolic decompensation	Seizures, Movement disorder
6 months	2 years	Metabolic decompensation, Poor weight gain	Yes, Metabolic decompensation	Asymptomatic
Identified by family history (6 cases)				
18 months	21 years	Poor weight gain	Yes, Metabolic decompensation	Asymptomatic
Neonate	20 years	Asymptomatic	Yes, Seizures and cardiomyopathy	Seizure disorder, Cardiomyopathy, Prolonged QT arrhythmia
19 years	20 years	Learning difficulties, Poor weight gain	None	Learning difficulties, Poor weight gain
24 months	17 years	Asymptomatic	None	Seizure disorder, Cardiomyopathy, Prolonged QT arrhythmia
1 month	14 years	Asymptomatic	None	Cardiomyopathy
3 years	12 years	Asymptomatic	None	Asymptomatic

complications: one with cardiomyopathy and arrhythmia resulting in sudden death and one with prolonged QT arrhythmia. One patient experienced a seizure, precipitated by illness, but did not have any subsequent neurologic abnormalities. The other four patients remain asymptomatic (Table 2).

Seven patients were diagnosed by clinical presentation and five experienced at least one hospitalization due to metabolic decompensation, defined as acidosis and/or hyperammonemia. Ages at diagnosis ranged from six months to eight years (median 63 months). Six of the seven patients receiving clinical care experienced long-term complications including cardiomyopathy and neurologic abnormalities (seizure disorders, movement disorders, learning difficulties) and/or poor weight gain. One patient remained asymptomatic, although the last evaluation was more than 19 years ago.

Six patients were identified after a sibling was diagnosed. Age range at diagnosis was 1 month − 19 years (median, 21 months). Four patients were asymptomatic at identification and two patients experienced either learning difficulties or poor weight gain, but the diagnosis of PA was not suspected. Long-term cardiac complications and seizure disorders were present in two patients. One patient experienced

cardiomyopathy and one patient experienced learning difficulties. Two patients remained asymptomatic.

4. Discussion

This study of the Wisconsin Amish supports the unpublished observation that PA due to the homozygous c.1606A > G in *PCCB* may cause a milder biochemical and initial clinical phenotype when compared to published studies of genetically heterogeneous populations of PA patients.

Wisconsin identified seven Amish newborns with PA by screening. In one case, family history prompted duplicate analysis and only one set of values was above the cutoffs. Differences in analyte concentration within a specimen are common risk factors in analysis of dried blood spots [9]. One case of PA was missed by NBS. This false negative specimen was collected shortly after birth when patient was critically ill with pulmonary hypertension and receiving parenteral nutrition. Anabolic patients may not display abnormal metabolite concentrations. These two cases demonstrate that the current, more stringent C3 cutoff (normal < 5 μM), may not detect a mild biochemical phenotype. As of 2018, incorporation of 2nd tier testing for all neonates identified as Amish has been implemented. In the future, molecular testing for all Amish patients may be warranted.

In a previous report of PA patients with heterogeneous genotypes, 63% were symptomatic prior to screening [10]. In our cohort of patients identified by newborn screening, all were asymptomatic prior to diagnosis; providing evidence that homozygous variant (c.1606A > G in *PCCB)* may cause a milder phenotype within the neonatal period.

Our data also suggests that NBS and early intervention can improve the overall long-term risk for neurological complications, presenting as seizure disorders, movement disorders, and learning difficulties. Several patients who presented clinically had long term neurologic sequelae, while only one of the seven patients identified through screening experienced seizures during an acute illness. Long term neurologic outcomes may be better with knowledge of the disorder and education for illness care.

Prior reports described cardiomyopathy in PA patients as a presenting sign or symptom, lethal complications of acute decompensation, or as chronic complication of the disorder [4–6,11–14]. Of the twenty patients, 5 experienced cardiomyopathy or cardiac related sudden death regardless of the method for diagnosis. This is comparable with a previously reported rate of 19% for cardiomyopathy and 30% for arrhythmia in the non-Amish PA population [11]. Previous data suggested improved cardiac function with treatment among Amish patients [15], yet our data did not support this finding. Two patients identified through screening experienced cardiac complications; one resulting in cardiac related sudden death. This event in the presumptively treated cohort may be due to limited access to health care during illness or poor compliance with recommended therapy. Important to note, two patients identified by family history were asymptomatic from both cardiac and neurologic complications suggesting that compliance with recommended therapy may not be the only contributor to a favorable outcome.

Limitations to this study include interpretability of data due to a small sample size. NBS has only been performed for PA since 2000, and patients identified by screening represent a younger cohort, resulting in lower frequencies of long-term complications compared to individuals that presented clinically. A comprehensive, longitudinal study of PA in the Amish needs to be conducted to delineate effectiveness of interventions.

In summary, modifications to the Wisconsin NBS algorithm has improve identification of PA patients with the homozygous genotype c.1606A > G in *PCCB* gene. The long-term benefits of screening were demonstrated by the improved neurological outcomes; however, the minimization of cardiac complications could not be appreciated. This is the first report addressing detection and the long-term benefits of screening for PA in the Amish Community.

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