Molecular Genetics and Metabolism Reports 8 (2016) 4–7

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

Case Report

Successful pregnancy and delivery in a woman with propionic acidemia from the Amish community☆

Jessica Scott Schwoerer [a,*], Sandra van Calcar [b], Gregory M. Rice [a], James Deline [c]

[a] Department of Pediatrics, University of Wisconsin, Madison, WI, USA
[b] Department of Molecular and Medical Genetics, Oregon Health and Science University, Portland, OR, USA
[c] LaFarge Medical Clinic, LaFarge, WI, USA

ARTICLE INFO

Article history:
Received 12 May 2016
Accepted 12 May 2016
Available online 2 June 2016

Keywords:
Propionic acidemia
Inborn errors in metabolism
Cardiomyopathy
Pregnancy
Organic acidemias

ABSTRACT

Propionic acidemia (PA) is an inborn error of protein metabolism with a variable clinical presentation ranging from neonatal encephalopathy to seemingly asymptomatic individuals who present with cardiomyopathy or sudden death. PA is recognized in the Amish population, often with an early asymptomatic course and eventual cardiac complications. Thus, Amish women with PA may reach reproductive age without clinical sequelae, but are at increased risk for metabolic decompensation during pregnancy, delivery and postpartum period. We describe the care of an Amish woman with PA during her first pregnancy and delivery.

Introduction

Propionic acidemia (PA, OMIM #606054) is an inborn error of metabolism (IEM) caused by a deficiency in propionyl-CoA-carboxylase (PCC), an enzyme with two subunits, A and B, encoded by genes PCCA and PCCB [1]. This enzyme is important in the metabolism of the amino acids isoleucine, valine, threonine and methionine as well as odd chain fatty acids. Reduced enzyme activity leads to an accumulation of organic acids including propionic acid and methylcitrate which are toxic to tissue including the brain and myocardium.

PA can present at any age throughout the lifespan. The severe neonatal form presents with encephalopathy and profound acidosis and hyperammonemia within the first few days of life. Milder forms of PA can present in infancy or early childhood with metabolic decompensation in the setting of a stressor, often an intercurrent illness. During decompensations, individuals with PA are prone to brain injury resulting in developmental delay, seizures and movement disorders caused by injury to the basal ganglia [1]. Recently, a later onset cardiac phenotype has been associated with PA. These patients have few, if any, symptoms during infancy, but can present with dilated cardiomyopathy, arrhythmia and/or sudden death in older children and adults [2–9].

PA is a rare disorder with an incidence in the general population of 1/50,000–1/100,000 births [10]. In the Old Order Amish and Mennonite communities (also referred to as Plain communities), its incidence is higher with a common mutation in the beta subunit of propionyl-CoA-carboxylase, PCCB c.1606 A > G [11]. Although the incidence remains unclear, over 75 individuals in Amish and Mennonite communities throughout the United States have been described with PA over the last 20 years (personal communication – Dr. Holmes Morton 12/18/15). The clinical phenotype most commonly seen in the Amish and Mennonite variant includes seizures (febrile and afebrile), cognitive impairment, hyperactivity-attention deficit disorder, keto-acidemia with coma and risk of basal ganglia necrosis, and most strikingly cardiomyopathy, long QTc and arrhythmias [12,13]. In the plain communities, there are clinically healthy individuals who are not recognized to have PA until death of a family member prompts testing (personal experience).

As with other metabolic disorders, optimal intrapartum management for PA is unclear, even in asymptomatic women who may or may not be on treatment for their disorder. Except for phenylketonuria (PKU), literature on pregnancy care in women with IEM and infant outcomes is scarce. Concerns during pregnancy include maintaining metabolic control throughout pregnancy and, in particular, during the perinatal and postpartum period – a time of significant stress and protein turnover [14]. This is the first case report to describe a pregnancy and intrapartum management for a woman with PA from the Amish community.

Case report

A 21 year old woman from the Old Order Amish community presented for initial prenatal assessment at approximately 27 weeks gestation. She was diagnosed with PA at the age of 18 months after an older

Abbreviations: PA, Propionic acidemia; IEM, Inborn error in metabolism.

☆ Financial support and disclosure: There are no financial disclosures by any author.

* Corresponding author at: 1500 Highland Ave. Rm 341, Madison, WI 53705.
E-mail address: jscottschwoerer@pediatrics.wisc.edu (J. Scott Schwoerer).

http://dx.doi.org/10.1016/j.ymgmr.2016.05.003

brother presented in metabolic crisis. She was asymptomatic. Diagnosis was based on urine organic acid analysis with the characteristic pattern of elevations in methylcitric acid, propionylglycine, tiglylglycine and 3-hydroxypropionic acid. She was also carnitine deficient. She was hospitalized at age 3 with lethargy but improved rapidly with treatment. She had three seizures in early childhood associated with acute illness, but none as an adult. She did not require additional hospitalizations or surgery. She reported no learning difficulties. The patient self-restricted her protein intake. She did not take a medical formula for PA or any dietary supplements. She had not been seen in a metabolic clinic since age 5 due to distance from the metabolic clinic and financial concerns. Family history included two affected siblings. One has learning difficulties and seizures and the other developed a cardiomyopathy at age 20. The patient's husband was tested and did not carry the common Amish mutation for PA.

The patient was evaluated during her pregnancy at 27 weeks, 33 weeks, and 37 weeks gestation. She did not have early prenatal care or an obstetrical ultrasound. An echocardiogram was performed at her first visit and showed a normal ejection fraction at 60–65%. EKG showed normal QT interval of 0.36 s and T wave inversion in the inferior and lateral leads. Fundal height was 23 cm at 27 weeks, felt to be normal given her petite body habitus. By 37 weeks gestation, the fundal height was 36 to 37 cm, consistent with normal fetal growth. She was evaluated by the metabolic team at 33 weeks. Recommendations included supplementation with biotin (10 mg/d) and L-carnitine (50 mg/kg/d) in addition to continuing a multivitamin and iron supplement. Diet history suggested low protein intake and plasma amino acid profile showed levels of some essential amino acids at the low end of concentrations expected for women without an IEM at >30 weeks gestation [15]. Thus, a 10% increase in protein intake was recommended.

The patient presented to the birthing center in early labor at 37 3/7 weeks gestation. Membranes had ruptured spontaneously 4 h prior to arrival (onset of labor). An IV line was placed 6 h after rupture of membranes and 10% dextrose in normal saline (D10NS) was started at 150 ml/h (1.5× maintenance for patient) and continued throughout labor. Patient was also encouraged to drink glucose containing fluids. The glucose infusion rate from intravenous fluids was ~3.8 mg/kg/min. The urine initially showed a small amount of ketones, however after initiation of IV fluids, urine ketones became negative and remained so. Blood samples for electrolytes and serum ammonia were drawn at 6 h after onset of labor and every 4 to 6 h through the course of labor to evaluate for any sign of acidosis or hyperammonemia indicating metabolic decompensation. These labs were normal initially and remained so. L-carnitine was given intravenously at 50 mg/kg of pre-pregnancy weight, followed by an additional 10 mg/kg every 4 h throughout labor. A total of 80 to 90 mg/kg was given through the course of labor. At 14 h of labor, Pitocin was initiated to augment labor. Ampicillin was given at a dose of 2 g intravenously at 18 h after spontaneous rupture of membranes. Delivery occurred at 19 h and 45 min after onset of labor and was uncomplicated. The infant was generous in size at 3930 g with moderate molding of the fetal head. Newborn exam was normal. The infant appeared to be approximately 38 weeks gestation. APGARs were 9 and 10 at 1 and 5 min respectively. There was no neonatal hypoglycemia. There were no maternal obstetric complications such as perineal lacerations or postpartum hemorrhage. Mother and infant did well postpartum and were discharged about 4 h after birth. Complications suggesting compromised metabolic control were not reported after discharge.

For the post-partum period, the patient was instructed to reduce dietary protein intake, but consume adequate calories from carbohydrate sources to reduce protein catabolism. An extra 500 kcal/day was recommended. She reported no concerns. At 1 year of age, the infant has normal growth and development.

Discussion

Cardiac complications are commonly reported in propionic acidemia; one survey of 54 patients, (age range 3 months to 33 years) found 19% with cardiomyopathy and 30% with arrhythmia, although a distinction between the subunit and mutation was not evaluated [16]. In the Amish community, propionic acidemia is commonly associated with a cardiac phenotype, although neurological injuries such as metabolic strokes and associated neurologic sequelae, particularly during periods of catabolism, are also reported [12,13]. Given the often late presentation of the cardiac phenotype, affected individuals may remain healthy into adulthood and wish to start families. There is little in the medical literature providing guidance to clinicians for pregnancy and intrapartum management of women with propionic acidemia. Recent guidelines from Europe recommend close monitoring of protein and carnitine needs as pregnancy progresses and providing supplemental calories using IV glucose during labor and delivery to minimize possible decompensation during labor and delivery [17].

In the literature, only five pregnancies are described in 3 women with PA [18–20] (Table 1). Significant complications included development of preeclampsia in both pregnancies from one woman with mutations in PCCB subunit requiring delivery at 31 and 32 weeks gestation.

Table 1
Prior pregnancies in women with propionic acidemia in the literature[a].

	This report	Lagendonk et al. 2012	Van Calcar et al. 1992	Van Calcar 2015/clinic experience	Van Calcar 2015/clinic experience	Van Calcar 2015/clinic experience
Maternal age at delivery (years)	21	26	22	26	28	30
Diagnosis	Diagnosed at 18 months due to presentation of a sibling		Diagnosis at 6.5 years with hypotonia, growth failure, slow motor development and h/o 3 metabolic decompensations	(Same patient as Van Calcar et al. 1992)	Diagnosis at age 4 with metabolic decompensation	Same patient
Treatment during pregnancy	Biotin, carnitine, protein self-restriction	Biotin, carnitine	Whole protein restriction, medical formula, carnitine	Whole protein restriction, medical formula, carnitine	Whole protein restriction, medical formula, carnitine, biotin	Whole protein restriction, medical formula, carnitine, biotin
Complications during pregnancy	None	None	None	None	Slowed fetal growth, Preeclampsia	Preeclampsia
Gestational age at delivery (weeks)	37	40	37	36.5	31	32
Delivery interventions	IV glucose	IV glucose	No glucose (short labor)	IV glucose	IV glucose	IV glucose
Delivery/postpartum complications	None	Placenta previa	None	None	Preeclampsia	Preeclampsia
Infant outcomes	Normal	Normal	Normal	Normal	Normal	Normal

[a] Table summarizing case reports from references [18,19,20].