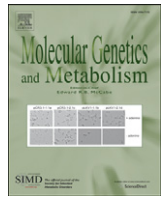




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## Conference Proceedings

## Natural history of propionic acidemia

Loren Pena <sup>a,\*</sup>, Jill Franks <sup>b</sup>, Kimberly A. Chapman <sup>c</sup>, Andrea Gropman <sup>c</sup>, Nicholas Ah Mew <sup>c</sup>, Anupam Chakrapani <sup>d</sup>, Eddie Island <sup>e</sup>, Erin MacLeod <sup>c</sup>, Dietrich Matern <sup>f</sup>, Brittany Smith <sup>b</sup>, Kathy Stagni <sup>g</sup>, V. Reid Sutton <sup>h</sup>, Keiko Ueda <sup>i</sup>, Tiina Urv <sup>j</sup>, Charles Venditti <sup>j</sup>, Gregory M. Enns <sup>k</sup>, Marshall L. Summar <sup>c</sup>

<sup>a</sup> University of Illinois College of Medicine at Chicago, Chicago, IL, USA

<sup>b</sup> Propionic Acidemia Foundation, Highland Park, IL, USA

<sup>c</sup> Children's National Medical Center, Washington D.C., USA

<sup>d</sup> Birmingham Children's Hospital, Birmingham, UK

<sup>e</sup> Transplant Program, Georgetown University, Washington D.C., USA

<sup>f</sup> Mayo Clinic, Rochester, MN, USA

<sup>g</sup> Organic Acidemia Association, Pinole, CA, USA

<sup>h</sup> Department of Molecular and Human Genetics, Baylor College of Medicine and Texas Children's Hospital, Houston, TX, USA

<sup>i</sup> Tufts Medical Center, Boston, MA, USA

<sup>j</sup> National Institutes of Health, Bethesda, MD, USA

<sup>k</sup> Stanford University, Palo Alto, CA, USA

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## ABSTRACT

Propionic acidemia is an organic acidemia that can lead to metabolic acidosis, coma and death, if not treated appropriately in the acute setting. Recent advancements in treatment have allowed patients with propionic acidemia to live beyond the neonatal period and acute presentation. The natural history of the disease is just beginning to be elucidated as individuals reach older ages. Recent studies have identified the genomic mutations in the genes *PCCA* and *PCCB*. However, as of yet no clear genotype–phenotype correlations are known. As patients age, the natural progression of propionic acidemia illuminates intellectual difficulties, increased risk for neurological complications, including stroke-like episodes, cardiac complications, and gastrointestinal difficulties, as well as a number of other complications. This article reviews the available literature for the natural history of propionic acidemia.

## 1. Introduction

Propionic acidemia (PA), an autosomal recessive disorder of amino acid and odd-chain fatty acid metabolism, was initially described in 1961 and characterized by elevations in glycine in both plasma and urine [1,2]. The biochemical defect involves the conversion of propionyl-CoA to methylmalonyl-CoA by the enzyme propionyl-CoA carboxylase (PCC). Deficient oxidation of propionate was demonstrated in 1969 by Hsia et al., with enzyme deficiency demonstrated in hepatocytes of an affected patient in 1970 by Gompertz et al., and in fibroblasts of an affected patient by Hsia et al. in 1971 [3–5]. Treatment with a low protein diet was described by Brandt et al. in 1974 [6].

A number of complications related to PA have been described since the original case was published. An international consensus conference was hosted by Children's National Medical Center in

Washington, D.C. on January 28–30, 2011, during which various aspects of PA were discussed. Complications related to PA were described in the natural history section, which is summarized in this document. A recurrent theme during discussion of the natural history of the disorder was that, although many complications of PA are well known to the metabolic community, information on the life history and complications of the disorder are limited. The limitations are partly related to communication in the form of case reports or case series with a limited number of individuals, and very few prospective studies. There is also a paucity of studies addressing the pathophysiology of disease and clinical correlates for complications. Our discussion of the natural history of PA served as a review of our current understanding of the clinical aspects of the disorder and highlighted the need for translational research to extend this knowledge such as the recently launched European registry study.

## 2. Genotype–phenotype correlations

The PCC holoenzyme is a dodecamer composed of an equal number of alpha and beta subunits [7]. PCC deficiency is caused by mutations

\* Corresponding author at: Department of Pediatrics, Division of Genetics, 840 S. Wood St., 12th floor, MC 856, Chicago, IL 60612, USA. Fax: +1 312 355 0739.

E-mail address: [lpna@uic.edu](mailto:lpna@uic.edu) (L. Pena).

on either of the two genes that encode the subunits, *PCCA* or *PCCB*. Although affected individuals are most commonly compound heterozygotes, a number of homozygotes for mutations in either *PCCA* or *PCCB* have been described. Attempts have been made to establish genotype–phenotype correlations by measuring residual enzyme activity and providing clinical data in addition to mutation information.

Mutations are most commonly found in the *PCCB* gene, with the most common mutation, c.1218\_1231del14ins12, found in 32% of mutant alleles in a mixed Caucasian population [8]. Seven homozygotes for this mutation have been reported in literature, all having early onset of symptoms, developmental delay, and hypotonia [9,10]. A common mutation in the *PCCB* gene in the Japanese population, c.1304T>C (p.Y435C), comprises 25% of mutant alleles in the Japanese population and has been characterized as mild [8,11]. A number of mutations in the *PCCA* gene have also been reported, with variable age of onset and symptoms.

Although a number of publications provide clinical and molecular data, the fact that compound heterozygosity is present in the majority of patients makes it difficult to establish genotype–phenotype correlations. Enzyme activity for various mutations has been measured in fibroblasts, leukocytes, and *in vitro* systems, thus making direct comparisons between clinical data and residual enzymatic activity difficult. A database for *PCCA* and *PCCB* mutation is maintained by Jan Kraus, PhD at <http://cbs.lf1.cuni.cz/pcc/pccmain.htm> (last accessed on July 11, 2011). It may be helpful to consider a repository of information that includes molecular and enzymatic data with clearly defined clinical parameters for time of onset, severity, and range of symptoms.

### 3. Developmental outcomes

Published information on developmental outcomes on individuals with PA is quite limited. Haberlandt et al. (2009) published cognitive and school performance information based on retrospective review of 17 patients with PA [12]. Ten of the patients were reported to have reduced IQ or delayed cognitive development, and many of the patients were reported to attend regular school with support (no further details). Results of a survey study with recruitment, through the Propionic Acidemia Foundation, indicates that approximately three-quarters of responders had delays in gross motor, fine motor, or language development, and over half of responders that had attended school required an individualized learning plan (Pena and Burton, submitted).

### 4. Neurological status

A number of neurological complications have been observed in the setting of PA (Table 1). Please refer to article by Schreiber and Gropman in this volume for a more extensive review of neurological complications in PA.

Briefly, neurological complications in PA include seizures, abnormalities in the basal ganglia (some with concomitant neurological symptoms), extrapyramidal symptoms, and brain atrophy. Patients may have different types of seizures, including generalized tonic-clonic, focal (with or without generalization), myoclonic, and atonic [12]. Age at first seizure ranged from 7 days to 9 years among the patients presented [12]. Several cases of acute-onset neurological symptoms have been described, also known as metabolic strokes. Interestingly, symptom onset may not necessarily occur concurrently with a metabolic crisis. Haas et al. (1995) describe a 9 year old patient with recurrent acute-onset of lethargy and abnormalities in the caudate, globus pallidus, and putamen on brain MRI performed during one of the episodes [13]. Scholl-Bürgi et al. (2009) also describe recurrent focal neurological symptoms with reversible brain MRI changes in the basal ganglia in one patient between 9 and 10 years of age [14]. Extrapyramidal symptoms, such as choreoathetosis and dystonia, have also been

**Table 1**  
Summary of complications reported in PA.

Organ system	Complication
Central nervous system	<ul style="list-style-type: none"> <li>● Delayed development or reduced IQ in 10/17 patients [12]</li> <li>● Seizures in 9/17 patients 12               <ul style="list-style-type: none"> <li>– Types: generalized tonic-clonic, absence, atonic, focal, focal with generalization, myoclonic</li> <li>– Onset at 7 days–4 years</li> </ul> </li> <li>● Metabolic stroke [13,14,21]</li> <li>● Extrapyramidal symptoms [12,16]</li> <li>● Cerebral atrophy [12,16,17]</li> <li>● Optic nerve atrophy [23,24]               <ul style="list-style-type: none"> <li>– Diagnosed at age 2–20 years</li> </ul> </li> </ul>
Cardiovascular system	<ul style="list-style-type: none"> <li>● Cardiomyopathy [25–27]               <ul style="list-style-type: none"> <li>– Age at diagnosis 5–23 years</li> <li>– Most often dilated</li> </ul> </li> <li>● Arrhythmia [28,29]               <ul style="list-style-type: none"> <li>– Prolonged QT</li> <li>– Ventricular ectopic beats</li> <li>– Sinus bradycardia/sinus arrest</li> </ul> </li> </ul>
Gastrointestinal system	<ul style="list-style-type: none"> <li>● Pancreatitis [36–38]               <ul style="list-style-type: none"> <li>– Youngest presentation: 18 months of age</li> </ul> </li> </ul>
Immune system	<ul style="list-style-type: none"> <li>● Pancytopenia [43,44]</li> </ul>
Endocrine system	<ul style="list-style-type: none"> <li>● Myelodysplasia with neutropenia [46]</li> <li>● Hyperglycemia [47,48]               <ul style="list-style-type: none"> <li>– 2 Cases, both younger than 1 year of age and both during initial presentation</li> </ul> </li> <li>● Premature ovarian failure (1 report) [55]</li> </ul>
Renal system	<ul style="list-style-type: none"> <li>● Renal failure (1 report) [55]</li> </ul>
Integumentary system	<ul style="list-style-type: none"> <li>● Generalized or localized exfoliative rash [50–52]</li> </ul>

observed as long-term sequelae in patients with PA from child- to adulthood [12,15,16].

Several observations suggest that neurological abnormalities may be related to localized metabolic derangements. For example, elevations in plasma lactate and ammonia and in CSF lactate, glutamine, glycine, and alanine were detected in a patient with neurological symptoms but no signs of catabolism [14]. Elevations in brain lactate level on magnetic resonance spectroscopy have also been described by Chemelli et al. (2000) in PA patients without evidence of metabolic decompensation [17]. Abnormalities in the basal ganglia and focal neurological deficits have also been observed in other organic acidemias such as glutaric acidemia type 1 and methylmalonic acidemia, but the mechanism for disease is unclear [18–20].

Evidence of cerebral atrophy has been described in multiple patients [17,12,16]. Additionally, post-mortem analysis of brain tissue in three patients had vacuolations and ischemic changes in the caudate and putamen as well as hemorrhagic changes to the caudate, putamen, globus pallidus, and ventral thalamus [21,22].

A small prospective case series of six patients with PA noted the development of optic nerve atrophy, with the youngest patient diagnosed at 2 years of age [23]. The authors noted no contributory family history, and comparison of glycine and valine levels did not reveal a correlation between these parameters and development of optic nerve atrophy. Williams et al. (2009) also report optic neuropathy with onset at 20 years of age and rapid initial progression [24]. This patient was also noted to have generalized brain atrophy and negative molecular testing for three mitochondrial point mutations most frequently involved in Leber Hereditary Optic Neuropathy.

### 5. Cardiac status

There are several cardiac complications seen in propionic acidemia including cardiomyopathy and arrhythmias (Table 1). Cardiomyopathy, usually dilated, has been described in a number of patients with PA. The largest case series reported a prevalence of 23% among the group studied [25]. The age of onset of symptoms and findings ranged between 4 weeks of age to adulthood [26,27], with only a portion of

the patients diagnosed during a metabolic crisis. Romano et al. (2010) attempted to investigate a relationship between development of cardiomyopathy and residual enzymatic activity, metabolites, or clinical course retrospectively among a group of 26 patients with PA [25]. A relationship between these parameters, however, could not be established.

Disturbances in cardiac rhythm architecture have been described in multiple patients with PA. A prolonged QT interval on electrocardiogram has been detected in multiple patients. Prolongation of the QT interval on electrocardiography may be associated with development of arrhythmias such as torsades de pointes, syncope, and sudden death. Baumgartner et al. (2007) report a prolonged corrected QT interval (QTc), defined as greater than 440 ms, on 7 of 10 patients with PA observed over a period of 5 years [28]. The youngest patient at diagnosis was 3 years old. Two of the patients had experienced syncopal episodes. Five of the patients underwent exercise testing, and four of the five had further prolongation of the corrected QT interval with exercise. Additionally, two patients in the Baumgartner study had ventricular ectopic beats, couplets, sinus bradycardia/arrest on continuous monitoring but did not require treatment for these. Kakavand et al. (2006) had a similar experience of inducing prolongation of the QTc interval with stress testing in one patient with PA [29].

Although arrhythmias and cardiomyopathy are recognized complications of the disease, there is great variability in diagnostic parameters and limited understanding of biochemical factors that may be at play. Although cardiomyopathy has been described in individuals affected with primary carnitine deficiency [30], Romano et al. (2010) notes comparable plasma carnitine levels in patients with and without cardiomyopathy [25]. A report by Mardach et al. (2005) raises the question of whether plasma levels of free carnitine are reflective of free carnitine levels in myocytes [31]. The patient in this case report had normal plasma levels shortly before decompensation from undiagnosed dilated cardiomyopathy, yet post-mortem analysis of cardiac and skeletal muscle revealed low levels of total and free carnitine in cardiac muscle and normal levels in skeletal muscle. Very limited data are available regarding cardiac myocyte findings on biopsy, with observations of focal fibrotic lesions and increased myofiber size [31,25]. Electron transport chain studies from post-mortem samples in the Mardach et al. (2005) patient had reduced levels of complex I and III activities in both skeletal and cardiac muscle samples [31]. Mitochondrial dysfunction has previously been proposed as a potential etiologic factor in development of cardiomyopathy, and possibly on other complications. Several *in vitro* studies have suggested that metabolites related to PCC activity may have secondary effects on various biochemical pathways in the mitochondria, including the tricarboxylic acid cycle and electron transport chain, through accumulation of toxic metabolites and impairment of these mitochondrial functions [32-34,56].

## 6. Gastrointestinal complications

Although pancreatitis is an unusual occurrence in the pediatric population [35], it has been described in multiple organic acidemias, including PA [21,36-42]. The youngest reported presentation is at 18 months of age [36], and pancreatitis has been described in patients with and without signs of metabolic decompensation at presentation. Clinical presentation also appears to be variable among the patients described, with some having abdominal symptoms and initially normal pancreatic findings on abdominal ultrasound [38,37] and others with findings of pancreatic edema but no biliary stones [36]. Amylase and lipase levels were elevated in the majority of patients that had the measurements, irrespective of ultrasound results, with the exception of one case in Burlina et al. (1995) [38]. Postmortem findings, reported in two patients, include diffuse inflammation and fibrosis [21,38].

The pathophysiology leading to pancreatitis in the setting of PA is unclear. Hypertriglyceridemia is a known risk factor for development

of pancreatitis, with levels above 1000 mg/dL posing the greatest risk. Although not reported in all PA patients with pancreatitis, two of the cases had mild elevations in triglyceride levels [38,36]. There are several possible mechanisms for increased risk of developing pancreatitis in patients with PA. These include elevations in circulating levels of free fatty acids and/or odd chain fatty acids, chronic inflammation, and local impairment of metabolism. Levels of free fatty acids and odd chain fatty acids are not routinely measured in patients with PA, and measurement of odd chain fatty acids may not be clinically available.

Although the data available to date are unclear on the mechanism and predisposing factors for pancreatitis in this population, the clinical scenarios remind us to have a low threshold for investigating the possibility of pancreatitis in PA patients, as this may be a life-threatening complication when untreated.

## 7. Immune dysfunction

Although immune dysfunction is thought to exist in propionic acidemia, there have been few multiple patient studies to confirm this observation. Initially pancytopenia can be seen especially during initial presentation and thought to be secondary to bone marrow suppression [43,44]. Another study showed depletion of T cells and B cells with normal IgM and IgG levels at autopsy [45]. In addition, a single report of myelodysplasia with neutropenia has been published [46]. There may be an increased risk for viral and bacterial infections in patients with PA; however, retrospective studies are lacking.

## 8. Other complications

Hypoglycemia is a commonly described finding during metabolic decompensation of organic acidemias, yet hyperglycemia has also been described, rarely in PA. It was the presenting symptom in a neonate and a 9 month old with PA, both treated initially as having diabetic ketoacidosis given the overlap of symptoms in both conditions [47,48]. Several patients have been noted to have insulin resistance [49]. The mechanism for this complication is not well understood.

An exfoliative rash has been described in multiple patients with organic acidemias, including PA. Although most frequently observed in the diaper area, it has also been observed in trunk, extremities, and face [50]. The skin findings are similar to those observed in acrodermatitis enteropathica; however, serum zinc and alkaline phosphatase levels have been in the normal range in all patients affected with a metabolic disease that had measurements [50-52]. Confluent parakeratosis was the main finding on a skin biopsy [52,51], which resolved with increased protein intake and improvement in branched chain amino acid levels, particularly isoleucine. Although the mechanism for the eruption is not understood, it is thought that isoleucine is essential for keratinocyte proliferation, and deficiency leads to growth arrest and decreased cell turnover [51].

An adult woman with PA was recently described with premature ovarian failure and renal insufficiency in her mid-30s, eventually requiring a renal transplant [55]. Any details regarding renal pathology for this patient were not available. Renal failure has been described as a common long-term complication in methylmalonic acidemia (MMA) and is characterized as a tubulointerstitial nephritis [56]. Studies in MMA *Mut*<sup>-/-</sup> mice observed megamitochondria in renal cells, reduced activity of several complexes in the electron transport chain, and evidence of oxidative stress in hepatic tissue [57]. Evidence of abnormal mitochondrial function and oxidative stress has been observed in PA [31,58-60]; thus it is possible that mitochondrial dysfunction may, at least, be involved.

Additional complications that have been observed include decreased bone density of unclear etiology [53,54]. There is no additional information regarding osteopenia and PA in the published literature. Postmortem examination of one patient affected with PA

notes severe atrophy of the adrenals, raising the possibility of adrenal insufficiency in this individual, although it is unclear whether this finding is related to PA [21].

## 9. Conclusion

The majority of our understanding of the life history of PA derives from case reports and small case series, primarily from retrospective review of records. A number of complications have been described to date and are summarized in Table 1. These descriptions may be useful as a foundation for making health maintenance recommendations in patients with PA. The pathophysiology of the other complications, however, is not currently understood. The possibility of a localized deficiency in energy metabolism has been raised. Several lines of evidence suggest that mitochondrial dysfunction may be present in affected individuals. These include deficient complex III and IV activity in skeletal muscle and liver tissue, and isolated complex III deficiency in cardiac muscle in a patient with PA [58], complex I and III in skeletal and cardiac muscle samples in another [31], and complex I, II, and V in skeletal muscle of a third individual [59]. Evidence for impaired response to oxidative stress has also been described in individuals affected with PA [58,60]. It is possible that secondary mitochondrial dysfunction contributes to multi-organ complications. Our understanding of the etiology of these findings, however, remains limited and in need of longitudinal, prospective studies. Postmortem studies of affected individuals would also extend our current understanding of PA.

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