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A statewide commitment to the problems of intellectual disability June 2024

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Propionic Acidemia
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Introduction
Propionic acidemia is the most common type of organic acidemia, but it is rare among all metabolic disorders. It is estimated to affect 1/20,000 to 1/250,000 individuals globally. 1 This disorder was initially described in 1961 as having elevations of glycine in plasma and urine.2 Alternative names for Propionic acidemia include Propionyl-CoA carboxylase deficiency, PCC deficiency, ketotic hyperglycinemia, and hyperglycinemia with ketoacidosis and leukopenia.3 It affects both amino acid and fatty acid metabolism.2 ,4 While the disorder has been known for many years, given its rarity and heterogeneity of symptoms, prior to its inclusion in the newborn screen, it was difficult to recognize and treat early in the course. The natural progression of disease includes intellectual difficulties, neurologic complications, cardiac complications, and gastrointestinal difficulties.2 If not recognized and treated quickly, this disorder can lead to metabolic acidosis, coma, and death.

Epidemiology
The incidence of propionic acidemia varies around the world. The incidence of propionic acidemia among live births is estimated to be 1:105,000-1:130,000 in the United States.6 The incidence is higher in the Middle East with an incidence of 1:28,000 in Saudi Arabia and up to 1:2000-1:5000 among some Saudi tribes.6 However, the highest reported incidence is among Greenland Inuits at 1:1000.1,6 Rates of incidence are higher in areas with higher rates of consanguinity.1,3

Pathophysiology
Propionic Acidemia is a rare inborn error of metabolism inherited via an autosomal recessive mechanism. Thus, it impacts males and females equally. It is a disorder caused by a deficiency in the enzyme propionyl-CoA carboxylase. This enzyme catalyzes the conversion of propionyl-CoA to methylmalonyl-CoA.6 Propionyl-CoA carboxylase deficiency is caused by mutations on either of the two genes that encode the subunits of the enzyme, PCCA or PCCB.2,6

The metabolism of branched chain amino acids, odd-numbered fatty acids, cholesterol side chains, thymine, and uracil are impacted.5 Propionyl-CoA carboxylase deficiency results in the accumulation of propionic acid in the blood and urine.6 The ineffective conversion of propionyl-CoA to methylmalonyl-CoA reduces the availability of substrates in the Krebs Cycle for aerobic respiration.6

URL: https://www.ncbi.nlm.nih.gov/books/NBK92946/

Clinical Features
Propionic acidemia can be divided into two subdivisions: neonatal onset and late onset. The disorder presents with a wide range of symptoms depending on level of enzyme activity, intake of propionic precursors and the presence of catabolic stressors.3,6

Neonatal onset propionic acidemia is characterized by symptoms in the first few weeks of life. These are previously healthy newborns who develop worsening symptoms of poor feeding, vomiting, dehydration, lethargy, and fatigue.1,3,6 Lab work is significant for anion gap metabolic acidosis, ketonuria, hypoglycemia, hyperammonemia, and cytopenia.3 If these infants are not recognized and treated promptly, they can progress to encephalopathy with seizures, coma, and death.3,6

Late onset propionic acidemia is significant for a milder course of disease. These individuals may initially be asymptomatic until experiencing a metabolic crisis during illness, surgery, or fasting. They may have a more chronic presentation of organ dysfunction including developmental regression, chronic vomiting, protein intolerance, failure to thrive, hypotonia, cardiomyopathy, and dystonia and/or choreoathetosis secondary to a basal ganglia infarction.3,6

Any person with propionic acidemia can develop a metabolic crisis and have rapid deterioration. These episodes are precipitated by stressors including illness, surgery, or fasting. Episodes are caused by the catabolic breakdown of proteins releasing propriogenic amino acids that cannot be processed in patients with propionic acidemia.6 This is a medical emergency, especially in the presence of hyperammonemia.

Long term manifestations of propionic acidemia include intellectual impairment, increased risk for cardiomyopathy and cardiac arrhythmias, seizures, neurologic abnormalities, movement disorders, optic atrophy, retinal abnormalities, and pancreatitis.1,3,6

Table 1
Summary of complications reported in PA.

Organ system	Complication
Central nervous system	● Delayed development or reduced IQ in 10/17 patients [12] ● Seizures in 9/17 patients 12 – Types: generalized tonic–clonic, absence, atonic, focal, focal with generalization, myoclonic – Onset at 7 days–4 years ● Metabolic stroke [13,14,21] ● Extrapyramidal symptoms [12,16] ● Cerebral atrophy [12,16,17] ● Optic nerve atrophy [23,24] – Diagnosed at age 2–20 years
Cardiovascular system	● Cardiomyopathy [25-27] – Age at diagnosis 5–23 years – Most often dilated ● Arrhythmia [28,29] – Prolonged QT – Ventricular ectopic beats – Sinus bradycardia/sinus arrest
Gastrointestinal system	● Pancreatitis [36-38] – Youngest presentation: 18 months of age
Immune system	● Pancytopenia [43,44] ● Myelodysplasia with neutropenia [46]
Endocrine system	● Hyperglycemia [47,48] – 2 Cases, both younger than 1 year of age and both during initial presentation ● Premature ovarian failure (1 report) [55]
Renal system	● Renal failure (1 report) [55]
Integumentary system	● Generalized or localized exfoliative rash [50-52]

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Diagnosis
The Department of Health and Human Services recommends propionic acidemia screening as part of it's Recommended Uniform Screening Panel. This is a list of recommended disorders for states to screen for as part of their universal newborn screening. As such, propionic acidemia screening is present on all newborn screens in the United States and its territories.7 The expanded newborn screen measures levels of C3 (propionylcarnitine) via mass spectrometry on dried blood spots.1,6 C3 is a byproduct produced during fatty acid metabolism, and elevated levels are concerning for propionic acidemia.4,6 Secondary markers include methionine, C3/C2 ratios, and C3/C16 ratios.6 False positives can be reported on newborn screens if the specimen was collected before 24 hours of life, if the infant received carnitine supplementation, prematurity, hyperbilirubinemia, or with maternal B-12 deficiency.4

Prenatally, propionic acidemia can be diagnosed in multiple ways. It can be identified via an elevated methylcitrate level in amnionic fluid, mutations in PCCA or PCCB genes identified by fetal DNA or by deficient activity of the propionyl-CoA carboxylase enzyme obtained via amniocentesis or chorionic villus sampling.1,3 Prenatal or preimplantation testing should be discussed with family members of affected individuals.6

Further testing of newborns or symptomatic patients is significant for elevated 3-hydroxypropionate, elevated glycine, and the presence of methylcitrate, tiglylglycine, propionylglycine, and lactic acid. Confirmatory testing is via genetic testing to confirm biallelic pathogenic variants in PCCA, PCCB, or deficient enzyme activity.3,6 As part of the propionic acidemia workup, particularly in sick patients, the following labs should also be evaluated: blood

gas, electrolytes, urine ketones, plasma ammonia, complete blood count, plasma ammino acids, total and free carnitine and acylcarnitine, urine organic acids, amylase, and lipase.

Genetic Testing
Mutations in propionic acidemia can be identified in either the PCCA or PCCB gene. Approximately 50% of pathogenic variants are attributed to mutations in PCCA, and 50% are attributed to mutations in PCCB.6 Identification of genetic mutations in probands can be done via serial single-gene testing, use of a multigene panel that includes PCCA and PCCB, or via comprehensive genomic testing.6 Multigene panels may include a variety of methods including sequence analysis, deletion/duplication analysis, and/or non-sequencing-based tests.6 Comprehensive genomic testing includes exome sequencing and genome sequencing. These types of tests should be considered if the other testing methods fail to confirm a diagnosis of propionic acidemia.

Most affected individuals are compound heterozygotes, although homozygous mutations have been reported.2 Given the diversity of heterozygosity present in a majority of individuals with propionic acidemia, there has been difficulty establishing a genotype-phenotype correlation.2,6

Treatment and Management
In metabolic crisis, patients must be quickly treated to reverse catabolism. The underlying cause must be identified and treated. IV fluids with dextrose and electrolytes must be given, and alkalization therapy should be considered.1,3,6 Additional calories can be given via parenteral lipids, and if needed, insulin can maintain euglycemia. Restarting enteral feeds with reduced propiogenic precursors is also important in management. For hyperammonemia, N-carbamoylglutamate can help reduce ammonia levels, but if severe, hemodialysis may be needed.1,6

The primary home management of propionic acidemia is via dietary management with a low protein diet.1,3,6 By reducing intake of propiogenic precursors (isoleucine, valine, methionine, threonine) while simultaneously ensuring there is enough protein intake to prevent deficiencies or growth restriction, the effects of this disorder can be minimized.6 It is important that these individuals avoid fasting or excessive protein intake. Diet is typically managed under the direct care of a physician and dietician who use regular lab work to guide management. Some patients require special formulas and additional medications like levocarnitine, metronidazole or biotin supplementation in addition to a special diet.1,6

In patients with frequent crises or with severe disease, an orthotopic liver transplant may be needed.1,6 This generally improves the course of disease and reduces the frequency of crisis events, but risks of organ transplant and immunosuppression must be seriously considered before pursuing this pathway.1

Management also includes prevention of secondary complications. They are at increased risk for multiple cardiac abnormalities including dilated cardiomyopathy and arrhythmias2,6 This complication can occur at any age, but the risk of developing a cardiac issue increases with age.3 Cardiac screening via echocardiograms and EKGs is important, especially if they warrant further treatment by a specialist.2,6 These individuals are also at increased risk for seizures, neurologic abnormalities, and metabolic strokes. Neurologic changes can also lead to movement disorders like dystonia and choreoathetosis.2,3 They may need close follow up with a neurologist, and depending on their symptoms, a brain MRI or EEG may be beneficial.2,6 Additionally, these individuals require ophthalmologic exams to regularly assess their optic nerve for retinal changes and for evaluation of retinal changes.3,6 Although it is rare, these individuals are also at increased risk of pancreatitis. Although the mechanism is not clearly understood, monitoring of pancreatic function via regular lab work to screen for hypertriglyceridemia as well as prompt treatment if the patient develops pancreatitis is an important component of disease management.2,6

Individuals with propionic acidemia often have mild intellectual disability or delayed cognitive development.1,5 It is also common to have developmental delays, either globally or among a particular developmental category.6 Many require individualized learning plans at school or supplemental therapies (physical, occupational, and/or speech therapy).2,6

Patient Support Resources
Propionic Acidemia Foundation: https://www.pafoundation.com/wordpress/
NORD Rare Diseases: https://rarediseases.org/
Organic Acidemia Association: https://oaanews.org/

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About the RCPU:

The Raymond C. Philips Research and Education Unit began in 1978 when the legislature established section 393.20, F.S., of what is now known as the "prevention" legislation. It is named after Raymond C. Philips, who was the Superintendent of Gainesville's Tacachale (formerly Sunland) Center for 38 years, and was an acknowledged state and national leader in services for mentally retarded persons. The Unit is located on the Tacachale campus and is funded through a contract with the Department of Children and Families and the Department of Health.

The purpose of the R.C.P.U. is to treat, prevent, and/or ameliorate disorders of intellectual disability through medical evaluations, education and research. The unit provides direct evaluations and counseling to families and promotes service, education, and prevention projects. Some of the conditions currently under study at the RCPU involve Angelman, Velo-Cardio-Facial, Prader-Willi, Fragile X, Williams and Smith-Lemli-Opitz syndromes.

The R.C. Philips Unit is a resource for all Floridians interested in the diagnosis, treatment and prevention of mental retardation. Staff members are available for consultation and for educational programs for health.

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