Indian Journal of Obstetrics and Gynecology Research 2020;7(4):579–583

Content available at: https://www.ipinnovative.com/open-access-journals

Indian Journal of Obstetrics and Gynecology Research

Journal homepage: www.ijogr.org

Original Research Article

A clinical informatics approach and metabolic signatures of propionic acidemia (PA)

C R Subhasree[1,*], S Subramaniam[1], S Shyama[2], A T Arasar Seeralar[3]

[1]*Dept. of Biochemistry, Regenix Super Specialty Laboratories Private Ltd, Affiliated to University of Madras, Chennai, Tamil Nadu, India*
[2]*Dept. of Biochemistry, Apollo Hospitals, Chennai, Tamil Nadu, India*
[3]*Dept. of Neonatology, Institute of Child Health and Hospital for Children, Madras Medical College, Chennai, Tamil Nadu, India*

ARTICLE INFO

Article history:
Received 26-08-2020
Accepted 01-09-2020
Available online 07-12-2020

Keywords:
Hyperammonaemia
Propionic Acidemia
Metabolic disorders
Lethargy
Inborn errors of metabolism
Neonatal period
Autosomal recessive

ABSTRACT

Hyperammonaemia is a metabolic disease that can be known as ammonia levels in the bloodstream which can result in brain damage only if treated properly early at birth. Human disorders implicated in the nervous system's inborn metabolism defects are organic aciduria with secondary hyperammonaemia. Most organic aciduria during neonatal period or early infancy become clinically apparent. The metabolic disorders involved are metabolic stress state with extreme levels of hyperammonaemia above 1000 μmol / L which is the discriminative feature for metabolic disorders diagnosis. We presented this case which has been identified by unique test as propionic acidemia to demonstrate that severe high levels of ammonia can be seen in organic acidemias. A propionic acidemia is caused by a carboxylase deficiency of propionyl-CoA that accumulates toxic compounds that affect brain metabolism. This is classified as a haematological disorder under the hereditary metabolic disease. Propionic acidemia is an inherited metabolic condition in which the body was incapable of adequately processing such protein catabolism and oxidation defects. In most cases, within a few days after birth, the characteristics of this condition become obvious. The primary signs include poor eating, diarrhea, appetite loss, hypotonia, and lethargy. Mutations in the PCCA (alpha unit) and PCCB (beta unit)genes cause propionic acidemia; it has an autosomal recessive pattern of inheritance.

1. Introduction

Propionic Acidemia (PA, OMIM #606054) is one of the intoxication type organic acidemias which often present in the neonatal period with lethargy, poor feeding, and vomiting and can progress to coma if not identified and treated appropriately.[1] Inborn errors of metabolism can have a severe impact on human health, so comprehensive diagnostic neonatal screening is used for early diagnosis to avoid potentially catastrophic physical and neurological effects. These defects can cause a build-up of toxic metabolites, resulting in serious, often fatal, disease early in life. Neonatal blood screening with mass spectrometry (MS) is now commonly used to test new-borns for a wide array of inborn errors of metabolism using specific metabolites for diagnosis. PA results from a defect in the enzyme propionyl-CoA carboxylase, which catalyses the biotin-dependent conversion of propionyl-CoA to methylmalonyl-CoA. MMA results from deficiency of the immediately downstream enzyme methylmalonyl-CoA mutase, which catalyses the vitamin B12-dependent conversion of methylmalonyl- CoA to succinyl-CoA. Patients have considerable variability in symptoms and clinical prognosis, which are correlated with genetic locus.

* *Corresponding author*.
E-mail address: c.r.subhasree@gmail.com (C. R. Subhasree).

https://doi.org/10.18231/j.ijogr.2020.123

2. Materials and Methods

The Institutional Human Ethical committee approval is from Madras Medical College, Chennai: Approval No. 32042018 and was obtained consent form from parents for the participation of this research study. Liquid Chromatography -Mass Spectrometry Analysis (LC-MS/MS) was done at metabolic lab, Department of biochemistry, at Institute of child health and hospital for children, Chennai.

2.1. Algorithm: Hyperammonaemia (>200 μmol/L)

1. Increased anion gap >25 mmol/L, Urine ketone positive leads to organic aciduria's.
2. Respiratory alkalosis, increased plasma citrulline or urine oxalate increase leads to urea cycle disorder.
3. Characteristic Urine smell, Urine DNPH test positive with abnormal amino acid profile leads to amino acid disorder
4. Premature baby with respiratory distress in the first day of life leads to transient Hyperammonemia.
5. Biochemical findings in propionic acidemia include: Common laboratory abnormalities during acute decompensation include: High-anion gap metabolic acidosis, Lactic acidosis, elevated plasma and urinary ketones, Low to normal blood glucose concentration, Hyperammonemia, Neutropenia, anemia, and thrombocytopenia.
6. Plasma acylcarnitine profile: Elevated propionyl carnitine (C3)
7. Urine organic acids: Elevated 3-hydroxypropionate Presence of: Methyl citrate, Tiglylglycine, Propionyl glycine, Lactic acid.
8. Plasma amino acids: Elevated glycine.

2.2. Metabolic pathways

Propionyl CoA precursors include isoleucine, threonine, methionine, valine and odd chain fatty acids, and cholesterol side chains. Deficient in propionyl -CoA-carboxylase activity is the enzyme defect between propionyl CoA and methyl malonyl CoA production. With biotin supplementation it inhibits the urea cycle and citric acid. Those are metabolites involved in the 3-OH propionic acid, 3-methyl citrate, and propionyl carnitine deficiency of this enzyme which were elevated in the blood. In propionic acidemia the biochemical effect is increased organic acids which lead to ketosis and metabolic acidosis with secondary hyperammonemia and hyperglycinemia. OA are all inherited autosomal-recessive disorders mainly affecting degradation of branched-chain amino acids. Hyperammonaemia is attributable to the decrease in and inhibition by toxic metabolites of acetyl coenzyme A (CoA) from NAGS and CPS1 activities. Hyperammonaemia in these diseases is accompanied by severe metabolic acidosis with high gap in anions and ketonuria. The diagnosis is made by chromatography of urinary organic acid and the acylcarnitine profile of the plasma.

2.3. Catalytic activity and function

Protein: Propionyl-CoA carboxylase alpha chain, mitochondrial (PCCA)[EC:6.4.1.3] A biotinyl-protein. Also carboxylates butanoyl-CoA and catalyses transcarboxylation. Reaction:

ATP + hydrogen carbonate + propionyl-CoA = (S)-methyl malonyl CoA + ADP + H^+ + phosphate

Protein: Propionyl-CoA carboxylase beta chain (PCCB) [EC:6.4.1.3 2.1.3.15] (acetyl CoA Carboxy transferase) Reaction:

[biotin carboxyl-carrier protein]-N6-carboxybiotinyl-L-lysine + acetyl-CoA = [biotin carboxyl-carrier protein]-N6-biotinyl-L-lysine + malonyl-CoA.

2.4. Clinical description

Phenotype varies from severe neonatal-onset forms with high mortality and poor outcome with a later onset to milder forms. In both cases the risk of relapses from life-threatening episodes of metabolic decompensation and severe organ failure dominates the clinical course. Despite the procedure, the outcome remains disappointing with no significant differences between MMA and PA.[2] The diagnosis is based on the presence of these compounds in body fluids, which were identified by the examination of organic acid in the urine and the profile of acylcarnitine in the blood. The therapy is focused on high energy low-protein diet, carnitine supplementation, and metronidazole. Some patients with methylmalonic aciduria (MMA) respond to pharmacological doses of vitamin B12.[3,4] Due to the poor long-term prognosis, liver transplantation has recently been attempted to cure this underlying metabolic defect as a recent conventional treatment therapy. Neonatal onset PA is the most common clinical form of PA.[5] In the first few days of life, infants with: lethargy, poor feeding, vomiting, untreated hypotonia may progress to encephalopathy and cardiorespiratory insufficiency. In children, signs can be apparent before NBS results are visible. Late Onset can raise a variety of concerns including developmental delay, intellectual disability, hypotonia, failure to thrive.[6]

2.5. Rare case presentation

A new-born boy at 11 days of life brought with complaints of breathing difficulty, abdominal distension, thrombocythemia, mild hypotonia, refusal to feed with fever for Two days. The baby was lethargic and dusky with Prolonged CRT (cardiac re synchronization Therapy) at the time of admission, with Heart rate 170 per minute, Respiratory rate 68 and oxygen saturation (SpO2) 97%, diffused O2 crying and with poor activity. Sub coastal

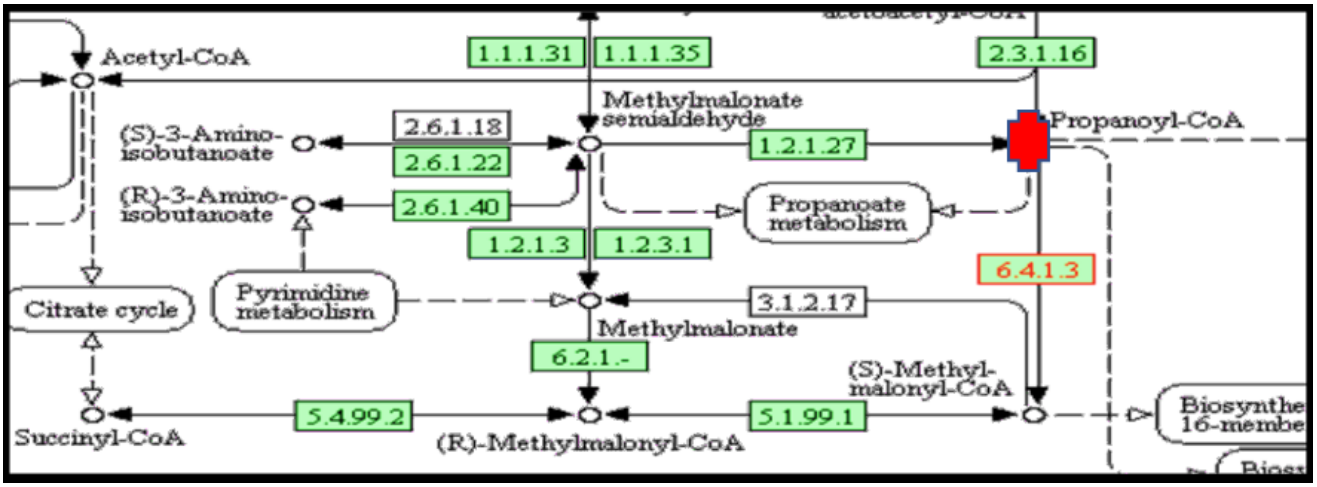

Fig. 1: Source: The KEGG (Kyoto Encyclopaedia of genes and Genomes) Pathway (hsa00280) shows of the branched chain amino acids (Valine, leucine and isoleucine degradation [EC:No. 6.4.1.3] is responsible for Propionyl CoA carboxylase (PCC enzyme).Clinical description

retractions have seen in the Abdomen. Baby with pale appearance with pulse 148/min, lethargy with capillary blood glucose 50 mg/dl, with Spo2 99% saturation. Clinical Onset was at 11 days of life, with progressive life-threating Hypoxia ischemic encephalopathy with hyperammonaemia leads to failure to thrive, septicaemia with hyperbilirubinemia which relates to rule out Inborn errors of metabolism.

2.6. Maternal history

A mother with age of 30 years with 3° Consanguineous marriage. The baby was delivered to $G_5P_2L_2A_1D_0$ mother with a history of pregnancy-induced hypertension, delivered via LSCS has cried at birth. Baby with a history of poor cry leads to birth asphyxia, A full-term baby with appropriate gestational age with gravida of five(G_5). The mother's first with age of Seven years Male child, the second one is an ectopic pregnancy, third was aborted at Four months and fourth was aborted at third months. The present is the fifth baby with a severe complications life-threatening.

2.7. Clinical investigations

The ultrasonography of the neonatal cranium was normal, abdomen with hepatomegaly, but the spleen was normal, Brain with cerebral edema. After the severe complications at 13 days of life, on both computed tomography and magnetic resonance imaging, IEM shows diffuse cerebral edema, Atrophic changes, and bilateral basal ganglia involvement. The ECG shows the ventricular septic defect with patent foramen ovale (PFO+).

2.8. Laboratory findings

The lab findings are notable with hyperammonemia with serum ammonia levels of 1065 umol/L, with CRP(C-reactive protein) is 36 mg/L, with Hb (Haemoglobin) 13.5 g/L, PCV 36 with total WBC 6300 x10 $^{-6}\mu$l, with platelets decreased when on admission 1.3 Lakhs, Blood urea nitrogen was increased 20 mg/DL, Serum Creatinine was 0.8 mg/DL, Serum calcium was 9 mg/dl, Serum sodium 136 mEq/L, Serum Potassium was 5.5 mEq/L. The Urine metabolic screening shows the urine ketones positive. To rule out Inborn errors of metabolism for new-born's from capillary blood spots using gold-standard technology - Liquid chromatography Mass Spectrometry (LC-MS/MS) (Table 1). LCMS/MS Findings: The Interpretation shows the propinoylcarnitine (C3 – 43.5 μmol/L) was elevated. The ratio of the (c3/C2 – 247.27) which was found to be elevated, showed the positive screening for Propionic acidemia. GC – MS Findings: showed Elevated levels of 2-methyl citrate, 3-OH propionic acid.

3. Result & Discussion

Hyperammonaemia is an acute life-threatening condition which may cause severe neurological impairment and cerebral oedema.[7,8] Severe liver failure and the inherited metabolic diseases are the most common causes of hyperammonaemia in children. Ammonia, an NH3, is a major nitrogen source. Ammonia arises from protein breakdown, from the metabolism of amino acids, and is produced by the gut bacteria. Then ammonia is transported to periportal hepatocytes through portal circulation, where 90 percent of ammonia enters the urea cycle and is converted to urea. Because ammonia is not excreted (not water-soluble), (the remaining 10% is transmitted to derive

Table 1: Results of the new-born screening using LC-MS/MS for amino acids and acyl carnitine profiling

Analytes	Observed values (μmol/L)	Reference ranges (μmol/L)
I. Amino Acids Profiling:		
Alanine	0.81	0.35 – 4.52
Arginine	7.09	0.37– 33.10
Citrulline	0.92	0.40– 8.45
glutamate	0.93	0.12– 3.45
Leucine/isoleucine/Hydroxyproline	1.32	0.19– 3.01
Methionine	0.71	0.30– 3.14
Ornithine	0.5	0.30– 3.89
Phenylalanine	0.99	0.28– 3.15
Proline	0.82	0.26– 3.00
Tyrosine	0.39	0.22– 7.72
Valine	1.32	0.27– 3.03
Acyl– Carnitine Profiling:		
Free carnitine, C0	0.87	0.34 – 4.12
Acetyl carnitine, C2	0.19	0.17 – 4.27
Propionyl carnitine, C3	43.09 ↑↑	0.08 – 6.50
Propionyl carnitine /Acetyl carnitine (C3/C2 ratio)	247.27 ↑↑↑↑	0.18 – 5.00
Malonyl carnitine, C3DC	0.91	0.00 – 4.55
Butyryl carnitine, C4	2.24	0.31 – 6.60
3 – OH – isovalerylcarnitin, C5 – OH	1.19	0.00 – 5.5
Tiglylcarnitine	1.43	0.00 – 12.86
Glutaryl carnitine, C5 – DC	1.71	0.00 – 5.00
Hexanoyl carnitine, C6	2.75	0.00 – 6.00
Octanoyl carnitine, C8	2.13	0.33 – 8.22
Octenoylcarnitine, C8:1	1.00	0.00 – 14.38
Decanoylcarnitin, C10	1.25	0.31 – 5.54
Dodecadienoylcarnitine, C10:2	0.00	0.00 – 8.75
Tetradecanoylcarnitine, C14	0.43	0.26 – 7.30
Hexadecanoylcarnitine, C16	0.25	0.00 – 2.72
3 – OH – hexadecanoylcarnitine, C16 – OH	0.63	0.02 – 5.63
Octadecanoylcarnitine	0.39	0.00 – 2.77
Octadecenoylcarnitine	0.23	0.00 – 2.78
Succinylacetone	0.97	0.46 – 2.87
Adenosine	0.8	0.00 – 6.7
2 – deoxyadenosine	0.71	0.00 – 6.43
C26:0 – lysophosphatidylcholine	0.78	0.29 – 2.69
Argininiosuccinic acid	1.65	0.00 – 9.01
Glutamic acid	0.38	0.26 – 3.80

hepatocytes where ammonia is converted to glutamine via glutamine synthetase (GS), a lower system of ability.[9] Biochemical differences between the effects of chronic hyperammonaemia and the acutely increased concentration of ammonia point to a threshold effect of hyperammonaemia that may vary depending on the preceding levels of ammonia and the level of brain development. Unlike chronic hyperammonaemia, severe acute hyperammonaemia, on the other hand, leads to a decrease in ATP crisis situations with impaired consciousness due to acute hepatic encephalopathy or a decompensating inborn metabolism error, and a rapid rise in ammonia concentration.[10] Elevated levels of ammonia are parallel levels of propionic acid, and are a good metabolic decompensation indicator. Ammonia can reach extremely high levels, approaching those found with urea cycle deficiencies in individuals. A secondary urea cycle defect in which propionic acid or its metabolites are hypothesized to inhibit N-acetyl glutamate synthetase or carbamoyl phosphate synthase I activity[11,12] is often attributed to the increased ammonia seen in PA. The urea cycle disorders indicate that the results are dictated not only by the level of hyperammonaemia but more importantly by the length of time the ammonia is elevated. So it is important that hyperammonaemia (and acidosis) be treated quickly and aggressively.[13]

4. Source of Funding

None.

5. Conflict of Interest

The authors declare that there is no conflict of interest.

Acknowledgements

The work was supported by the Dr. K. Pramila, Professor, Department of biochemistry and Dr. A.T. Arasar Seeralar, Professor, Neonatology, Institute of Child Health and Hospital for Children, affiliated to Madras Medical College, Chennai.

References

1. Shchelochkov OA, Carrillo N, Venditti C, Pagon RA. Propionic Acidemia. In: Adam MP, Ardinger HH, Pagon RA, editors. GeneReviews® [Internet]. Seattle: University of Washington; 2002. Available from: https://www.ncbi.nlm.nih.gov/books/NBK92946/.
2. Deodato F, Boenzi S, Santorelli FM, Dionisi-Vici C. Methylmalonic and propionic aciduria. *Am J Med Genet C Semin Med Genet*. 2006;142C(2):104–12. doi:10.1002/ajmg.c.30090.
3. Honjo RS, Casella EB, Vieira MA, Bertola DR, Albano LMJ, Oliveira LA, et al. Spondylocostal Dysostosis associated with methylmalonic aciduria. *Genet Test Mol Biomark*. 2009;13(2):181–3. doi:10.1089/gtmb.2008.0069.
4. Deodato F, Rizzo C, Boenzi S, Baiocco F, Sabetta G, Dionisi-Vici C, et al. Successful pregnancy in a woman with mut– methylmalonic acidaemia. *J Inherit Metab Dis*. 2002;25(2):133–4. doi:10.1023/a:1015632911801.
5. Deodato F, Boenzi S. Inborn errors of metabolism: an update on epidemiology and on neonatal-onset hyperammonemia. *Acta Paediatr*. 2004;93(445):18–21.
6. Lee TM, Addonizio LJ, Barshop BA, Chung WK. Unusual presentation of propionic acidaemia as isolated cardiomyopathy. *J Inherited Metab Dis*. 2009;32(S1):97–101. doi:10.1007/s10545-009-1084-1.
7. Johnson JA, Le KL, Palacios E. Propionic Acidemia: Case Report and Review of Neurologic Sequelae. *Pediatr Neurol*. 2009;40(4):317–20. doi:10.1016/j.pediatrneurol.2008.10.021.
8. Jiang Y, Shi Y, Shi Y. Methylmalonic and propionic acidemia among hospitalized pediatric patients: a nationwide report. *Orphanet J Rare Dis*. 2019;14.
9. Fraser JL, Venditti CP. Methylmalonic and propionic acidemias. *Curr Opin Pediatr*. 2016;28(6):682–93. doi:10.1097/mop.0000000000000422.
10. Longo N, Price LB, Gappmaier E, Cantor NL, Ernst SL, Bailey C, et al. Anaplerotic therapy in propionic acidemia. *Mol Genet Metab*. 2017;122(1-2):51–9. doi:10.1016/j.ymgme.2017.07.003.
11. Jurecki E, Ueda K, Frazier D, Rohr F, Thompson A, Hussa C. Nutrition management guideline for propionic acidemia: An evidence- and consensus-based approach. *Mol Genet Metab*. 2019;126(4):341–54. doi:10.1016/j.ymgme.2019.02.007.
12. Riemersma M, Hazebroek MR. Propionic acidemia as a cause of adult-onset dilated cardiomyopathy. *Eur J Hum Genet*. 2017;25(11).
13. Witters P, Debbold E, Crivelly K, Kerckhove KV, Corthouts K, Debbold B, et al. Autism in patients with propionic acidemia. *Mol Genet Metab*. 2016;119(4):317–21. doi:10.1016/j.ymgme.2016.10.009.

Author biography

C R Subhasree, Research Scholar

S Subramaniam, Lab Director & HOD

S Shyama, Professor, Consultant, Lab Services & HOD

A T Arasar Seeralar, Director and Superintendent, Professor

Cite this article: Subhasree CR, Subramaniam S, Shyama S, Seeralar ATA. A clinical informatics approach and metabolic signatures of propionic acidemia (PA). *Indian J Obstet Gynecol Res* 2020;7(4):579-583.