Case Report

Classical Neonatal Propionic Acidaemia: Diagnostic and Management Pitfalls

TYS **Lui**, GPG **Fung**, KM **Belaramani**

Abstract   Propionic acidaemia is an inborn error of metabolism classified under the category of organic acidaemias. This disease is caused by the deficiency of propionyl-CoA carboxylase enzyme. Initial presentation can be subtle with subsequent rapid deterioration. Newborn Screening for inborn error of metabolism can provide an early diagnosis and thus prompt treatment can be given, preventing mortality and morbidity.

Key words   Hyperammonaemia; Inborn error of metabolism; Proprionic acidaemia, newborn screening

Introduction

Propionic acidaemia (PA) is an inborn error of metabolism (IEM) classified under the category of organic acidaemias. This disease is caused by the deficiency of propionyl-CoA carboxylase (PCC) enzyme. Severe forms of the disease can present within the first few days of life with deterioration of general condition, metabolic acidosis and hyperammonaemia. It can be fatal if diagnosis and treatment is delayed. Early recognition and timely treatment can be achieved by universal newborn screening for IEM. We present a case of PA with a non-specific clinical presentation to illustrate the importance of Newborn Screening for IEM (NBSIEM).

Department of Paediatrics and Adolescent Medicine, United Christian Hospital, 130 Hip Wo Street, Kwun Tong, Kowloon, Hong Kong SAR, China

TYS **Lui** (呂德祐)   *MRCPCH, MBBS(HK)*
GPG **Fung** (馮寶姿)   *FHKAM, FHKCPaed*

Department of Paediatrics and Adolescent Medicine, Hong Kong Children's Hospital, 1 Shing Cheong Road, Kowloon Bay, Kowloon, Hong Kong SAR, China
KM **Belaramani**   *MBBS(HK), FHKCPaed, FHKAM*

Correspondence to: Dr TYS **Lui**
Email: lty856@ha.org.hk

Case Presentation

History

Baby S was a female baby born at a gestation of 41 weeks by spontaneous vaginal delivery, weighing 3.2 kilograms. Apgar scores were 9 at 1 minute and 10 at 5 minutes. Antenatal history was uneventful.

Breast-feeding was initiated after birth, but she developed vomiting and respiratory distress on Day 1 of life. She was transferred to the special care baby unit (SCBU) for management. Chest radiography revealed a small spontaneous pneumothorax. Blood gas showed no acidosis, and sepsis screen was negative. Respiratory distress improved with oxygen supplement. She was kept nil by mouth from Day 2-4 of life due to suboptimal respiratory condition. Feeding was resumed on Day 5 of life, but she still had intermittent vomiting one to two times per day. Therefore, feeding could only be advanced cautiously. Full feeds was eventually attained on Day 15 of life, but intermittent vomiting around once a day persisted.

Despite adequate caloric intake, she continued to have weight loss (maximum weight loss 10.8%). Repeated investigations including blood gas, glucose, renal function test, CRP and abdominal radiographs on Day 15-18 of life were normal. However, feeding performance continued to deteriorate and by Day 21 of life, she developed drowsiness, lethargy with poor sucking effort. Physical examination at this juncture showed a sleepy, hypotonic baby with normal

power and reflexes, and no evidence of raised intracranial pressure. She had no seizures all along.

Both parents were Pakistani by ethnicity, and they had a consanguineous fifth degree family relationship. Father's brother and mother's sister were married and had given birth to six children in Pakistan, of which two died due to unknown cause during the neonatal period (Figure 1).

Further investigations were performed in view of neurological deterioration. Complete blood count, electrolytes, liver function test, glucose and lactate were normal. Venous blood gas showed no acidosis (pH 7.45; HCO3 24 mmol/L; BE 0.2 mmol/L). Urine ketone and reducing substances were negative. Electrocardiogram, Echocardiogram, Computer tomography of the brain and electroencephalography were normal. However, ammonia was markedly elevated to 353 μmol/L. With the available results, it was difficult to differentiate the cause of hyperammonaemia since both urea cycle defects and organic acidaemia could present with a similar picture.

While awaiting further metabolic investigation results, acute management of hyperammonaemia was nevertheless initiated without further ado. Sodium Benzoate, arginine, levocarnitine and biotin were started. Patient was kept fasted. Protein was withheld, and a high calorie regime (100 to 110 kcal/kg/d) was provided by parenteral nutrition. Ammonia level decreased from 353 μmol/L to 199ìmol/L within 6 hours after initiation of treatment. The first free Carnitine level was 982.7 μmol/L (Reference 19.3-53.9 μmol/L), however it was only taken after commencement of Levocarnitine.

Sodium benzoate was further increased from 250 mg/kg/d to maximum dose (500 mg/kg/d) and two doses of Carglumic acid (100 mg/kg/dose) were given. Ammonia further decreased to 71 μmol/L the within the next 15 hours. As the ammonia levels decreased, clinically the baby's drowsiness and lethargy improved, and she became much more alert and responsive.

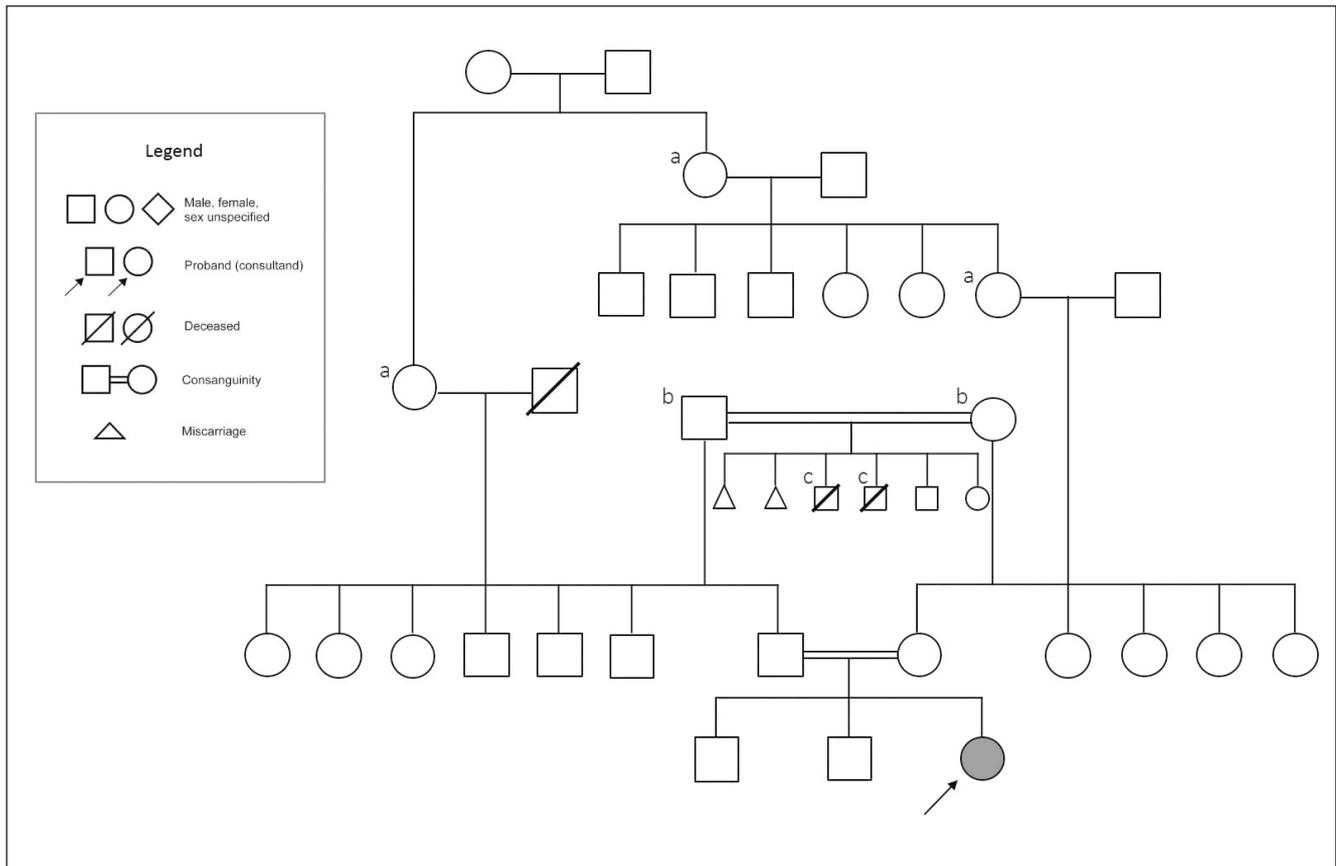Dried blood spot test (DBS) became available within 24

Figure 1   Family Tree. [a] Father's mother & mother's GM are sister. [b] Father's brother married mother's sister. [c] Deceased at 3-4 days and 6-7 days respectively.

hours and showed a significantly elevated Glycine 634 µmol/L (Reference 115-270 µmol/L) and C3 carnitine 20 µmol/L (Reference 0.50-2.0 µmol/L). The DBS result was highly suggestive of either PA or methylmalonic acidaemia (MMA) and the baby was treated accordingly. Vitamin B12, folate, beta-hydroxybutyrate, homocysteine were normal. Plasma amino acids showed elevated glycine (881 µmol/L), with mild elevations in leucine (169 µmol/L), lysine (356 µmol/L) and valine (242 µmol/L). Urine organic acid showed significant elevation of methylcitric, propioylglycine, tiglyglycine, and 3-hydroxypropionic acids which is diagnostic of PA. This diagnosis was genetically confirmed and a homozygous mutation in the beta subunit of the PCC gene (PCCB) was detected (NM_000532.4:c.1498+2T>C). Genetic screening of the parents has been done, and their carrier status were confirmed.

The baby was subsequently managed by a low protein diet, and carnitine and biotin supplement. She is currently 11 months old.

Discussion

PA was first described in 1961.[1] It is a rare organic aciduria with an autosomal recessive inheritance. It results in the deficiency of propionyl CoA carboxylase which impairs the metabolism of branched-chain amino acids.

Worldwide incidence is estimated to be 1:100,000 to 1:150,000, with a higher incidence of up to 1:2000-5000 in some populations (e.g. Saudi Arabia).[2] Currently, there is no local data on incidence or prevalence of PA in Hong Kong. However, incidences in the Asia-Pacific region have well been reported with the incidence of PA in China and Taiwan being reported to be 1 in 116,000 and 1 in 464,000 which is comparable to the world-wide incidence.[3,4] Japan, however, has an unexpectedly high incidence of PA of 1 in 41,000 due the presence of a common mutation (Y435C) in the PCCB gene which causes a milder phenotype.[5]

Majority of PA cases present in the neonatal period. Other clinical presentations have been described in infants, children and adults. The reason for the phenotypic variation is likely related to genotype and propionyl CoA carboxylase activity.[6] The classical neonatal PA usual presents within the first few days of life with non-specific symptoms including deterioration of general condition, unstable temperature, weight loss, dehydration, vomiting, irritability, hypotonia, hypertonia, lethargy, or even coma and seizure. Grünert et al reported that 78% of PA cases

present within the first 5 days of life.[7] Pena et al on the other hand reported that 39% of PA cases were diagnosed within the first week of life and an additional 25% were diagnosed within the first month of life.[8] This discrepancy between presentation and diagnosis is likely due to the lack of newborn screening, non-specific nature of presentation, presentation being attributed to sepsis which is a more common entity in neonates, and lack of awareness amongst frontline staff. In our case, Baby S too presented clinically with poor feeding and respiratory issues within the first 5 days of life but her diagnosis was delayed and made at 3 weeks of life.

In addition to non-specific clinical symptoms, non-specific laboratory results could also result in delayed diagnosis. Organic acidaemias usually show severe metabolic acidosis, ketosis and hyperammonaemia.[2,9] In our case, Baby S had hyperammonaemia but no metabolic acidosis or ketosis. Although hyperammonaemia is present in 90% of PA cases at presentation,[10] ammonia is usually not the first-line investigation ordered by most paediatricians when encountering a neonate with non-specific symptoms. Blood gas analysis is a more routine investigation in neonates but this too was not so useful in our case because it was repeatedly normal. Studying neonates with PA, Grünert et al, found that one third of the cases had no metabolic acidosis.[10] Another retrospective review, Al-Makadma et al, also found one sixth of patients without metabolic acidosis.[11] Absence of metabolic acidosis may be falsely reassuring to a paediatrician and hinder early recognition.

It was well described that the variation of presentation and absence of metabolic acidosis in organic acadaemia may be associated with the variation of genotype.[6] In Baby S, we also postulate that the absence of metabolic acidosis may also be caused by inadequate protein intake, which is a frequent presentation in babies suffering from IEM. However, more observation or further studies are needed to prove our postulation. Therefore, we advocate that in neonates with insidious deterioration of feeding or general condition, especially with family history of unexplained neonatal deaths or consanguinity, suspicion of metabolic conditions and their work-up should be initiated early.

There are well written guidelines on management of neonatal hyperammonaemia.[9] They usually include stopping protein intake, starting 10% dextrose infusion, initiation of ammonia scavenging drugs, and collection of urine and blood sample for diagnosis.[9]

Sodium benzoate is the first ammonia scavenger that has been used for many years. It lowers serum ammonia

levels by conjugating with glycine to form Hippurate, which will then be excreted by kidney[12] Sodium phenylacetate works by a similar mechanism as sodium benzoate. Hemodialysis is considered if hyperammonaemia is not controlled by medical treatment. However, dialysis services may not be readily available. Recent literature suggest that carglumic is a more effective in treating hyperammonaemia in organic acidaemias and may reduce the need for hemodialysis. Propionyl Co A suppresses N-acetylglutamate synthase (NAGS) which is an activator of carbamoyl phosphate synthetase 1, which converts ammonia to urea in the first step of urea cycle.[9,12,13] Carglumic acid is a synthetic structural analogue of NAGS and as such is a specific intervention for hyperammonaemia in PA. Chakrapani et al studied 98 hyperammonaemia episodes and concluded that ammonia scavengers when used in combination with carglumic acid is more effective in rapidly reducing ammonia levels at a dose of greater than 100 mg/kg, generally well tolerated and can be given orally or via nasogastric tube.[14] The latter being very important since intravenous access can be a problem when PA patients are in a state of acute decompensation. In Baby S, the response to sodium benzoate was suboptimal initially. However, after addition of carglumic acid, ammonia levels decreased rapidly to normal range. Although more large-scale studies are needed before carglumic acid can be recommended for initial management of organic acidaemias, this modality of treatment may be considered in cases of hyperammonaemia refractory to conventional therapy like this case.

Since it was first described, the mortality of neonatal onset PA has been decreasing from 85% in the 1980s to 41.5% in the 1990s[15] to 8% in more recent studies.[10] The reasons for this include increased awareness amongst paediatricians regarding organic acidaemias, readily available laboratory testing of ammonia, and newborn screening. We postulate that newborn screening is pivotal in the reduction in mortality.

NBSIEM varies worldwide in terms of the disease coverage and the turnaround time but most tandem-mass spectroscopy based NBSIEM cover organic acidaemias and have a turnaround time of 7 days. Both MMA and PA show elevated C3 levels on the NBSIEM DBS and this will alert paediatricians of the possibility of organic acidaemia. In many cases the turnaround time of NBSIEM is suboptimal for organic acidaemias, because as mentioned before 78% cases of PA present within the first 5 days of life and decompensate before the availability of the NBSIEM result.[7] Despite this delay, Grunert et al reported that there

was tendency towards a lower mortality rate in the NBS screened babies versus selectively screened patients (0% vs 12%).[10] This is probably because although the baby presents before 5 days of life, not all have had severe decompensations like in the case of Baby S. Baby S would have been picked up and treated much earlier had there been NBSIEM. Although NBSIEM reduces mortality, long term data is needed to show any benefit for clinical outcomes including neurocognitive development and other long term complications.[10]

Universal NBSIEM is still being implemented in Hong Kong in phases beginning 2015 and will be made available territory-wide in all government birthing units by 2020. We hope that universal NBSIEM will be able to pick up newborns with not only classical but those with atypical or non-specific presentation, of not only PA, but other IEM as well. Early recognition will result in earlier treatment which can reduce the mortality and morbidity.[9]

Conclusion

In PA, the diagnosis is often easily delayed due to three main reasons, one that it is an uncommon disease, two that its clinical presentation is rather non-specific, and three the lack of awareness amongst paediatricians about organic acidaemias and thus delayed use of carglumic acid. With the availability of NBSIEM, there is hope that the time-lag between presentation and diagnosis will be shortened and this in term will improve long-term outcome of this rare group of disorders.

Declaration of Interest

The authors declare that they have no financial or other conflicts of interest in relation to this publication.

References

1. Childs B, Nyhan WL, Borden M, Bard L, Cooke Re. Idiopathic hyperglycinemia and hyperglycinuria: a new disorder of amino acid metabolism. Pediatrics 1961;27:522-38.
2. Baumgartner MR, Hörster F, Dionisi-Vici C, et al. Proposed guidelines for the diagnosis and management of methylmalonic and propionic acidemia. Orphanet J Rare Dis 2014;9:130.
3. Gu X, Wang Z, Ye J, Han L, Qiu W. Newborn Screening in China: Phenylketonuria, Congenital Hypothyroidism and Expanded Screening. Ann Acad Med Singapore 2008;37(Suppl 3):107-10.
4. Shibata N, Hasegawa Y, Yamada K, et al. Diversity in the incidence

and spectrum of organic acidemias, fatty acid oxidation disorders, and amino acid disorders in Asian countries: Selective screening vs. expanded newborn screening. Mol Genet Metab Rep 2018;16: 5-10.

5. Yorifuji T, Kawai M, Muroi J, et al. Unexpectedly high prevalence of the mild form of propionic acidemia in Japan: Presence of a common mutation and possible clinical implications. Hum Genet 2002;111:161-5.

6. Pérez-Cerdá C, Merinero B, Rodrguez-Pombo P, et al. Potential relationship between genotype and clinical outcome in propionic acidaemia patients. Eur J Hum Genet 2000;8:187-94.

7. Grünert SC, Müllerleile S, Silva LD, et al. Propionic acidemia: Clinical course and outcome in 55 pediatric and adolescent patients. Orphanet J Rare Dis 2013;8:6. doi: 10.1186/1750-1172-8-6.

8. Pena L, Burton BK. Survey of health status and complications among propionic acidemia patients. Am J Med Genet A 2012;158A: 1641-6.

9. Häberle J, Boddaert N, Burlina A, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders. Orphanet J Rare Dis 2012;7:32.

10. Grünert SC, Müllerleile S, Silva LD, et al. Propionic acidemia: neonatal versus selective metabolic screening. J Inherit Metab Dis 2012;35:41-9.

11. Al-Makadma AS, Al-Asmari AM, Sandokji IA. 1024 Acidemia without Acidosis a Typical Presentation of Propionic Acidemia. Pediatr Res 2010;68:509.

12. De Las Heras J, Aldámiz-Echevarría L, Martínez-Chantar ML, Delgado TC. An update on the use of benzoate, phenylacetate and phenylbutyrate ammonia scavengers for interrogating and modifying liver nitrogen metabolism and its implications in urea cycle disorders and liver disease. Expert Opin Drug Metab Toxicol 2017;13:439-48.

13. Häberle J. Role of carglumic acid in the treatment of acute hyperammonemia due to N-acetylglutamate synthase deficiency. Ther Clin Risk Manag 2011;7:1-6.

14. Chakrapani A, Valayannopoulos V, Segarra NG, et, al. Effect of carglumic acid with or without ammonia scavengers on hyperammonaemia in acute decompensation episodes of organic acidurias. Orphanet J Rare Dis 2018;13:97.

15. North KN, Korson MS, Gopal YR, et al. Neonatal-onset propionic acidemia: Neurologic and developmental profiles, and implications for management. J Pediatr 1995;126:916-22.