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Case Report

Novel mutation causing propionic acidemia associated with unexplained autoimmune thyrotoxicosis

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ABSTRACT

Propionic acidemia (PA) is a rare autosomal recessive inborn error of metabolism (IEM) with relatively higher prevalence in the United Arab Emirates (UAE). Absence of propionyl-CoA carboxylase (PCC) enzyme classically leads to acute decompensation in the early neonatal period. We report a novel homozygous frameshift variant *c.2158_2159insT; p.*Glu720Valfs*14 (NM_000282.3) in the last exon of the PCCA gene which led to a severe presentation of PA in a newborn Emirati female. Uniquely the diagnosis remained unclear since newborn screening revealed an isolated elevation in plasma proprionylcarnitine (C3) while urinary organic acids remained persistently negative for the classic biochemical abnormalities even during the period of critical illness. Additionally, the patient had an unexplained diagnosis of neonatal thyrotoxicosis. This case explores possible underlying causes through an extensive literature search. To date, there have been no similar reported cases in existing literature.

1. Introduction

Propionic acidemia (PA) is an IEM characterized by accumulation of propionic acid due to deficiency of propionyl-CoA carboxylase (PCC) enzyme (EC 6.4.1.3) [1]. It is inherited through an autosomal recessive pattern. While global incidence is between 1:50,000 and 1:100,000, consanguinity leads to a higher number in middle-eastern countries [2]. Specifically, estimated birth prevalence in the UAE is between 2.2 and 4.9 cases per 100,000 births [3].

We report a newborn with PA associated with isolated elevation of plasma proprionylcarnitine (C3). The unique biochemical profile created a diagnostic challenge since typical markers in urine were initially not detected. In addition, the patient was incidentally discovered to have hyperthyroidism associated with positive thyroid antibodies.

PA can present in the newborn period or infancy, and later during childhood or adolescence; the variants are referred to as neonatal and late onset PA respectively [4,5]. Presentation in the first few days of life is an acute metabolic emergency [4]. Symptoms may mimic that of neonatal sepsis and occur suddenly [5]. They include poor feeding, vomiting and decreased activity with rapid progression towards encephalopathy that manifests as lethargy, seizures, or coma and can result in death [1]. This is frequently accompanied with severe ketoacidosis, hyperammonemia, and hyperglycinemia [1,6].

The late onset variant presents at any age after the neonatal period as a relapsing-remitting form with recurrent episodes of metabolic decompensation triggered by catabolic stress such as inter-current infection, prolonged fasting or following increased intake of protein-rich foods [4,5]. Alternatively, the chronic progressive form has an insidious onset and presents with hypotonia, failure to thrive or developmental delay [5]. Patients with late onset PA usually have high-anion gap metabolic acidosis, lactic acidosis and hyperammonemia [1,5].

Abbreviations: IEM, Inborn Errors of Metabolism; PA, Propionic Acidema; MMA, methlymalonic acid; TSH, Thyroid Stimulating Hormone; FT3/FT4, Free T3/Free T4; TRAB, Thyroid Receptor Antibodies; UAE, United Arab Emirates; PCC, Propionyl-CoA Carboxylase; C3, proprionylcarnitine; PICU, pediatric intensive care unit; OA, Organic Acids; AA, Amino Acids; HD, hemodialysis; TPN, Total parenteral nutrition; MRI, Magnetic Resonance Imaging; G-CSF, growth colony stimulating factor; TPO, Thyroid Peroxidase; TSI, Thyroid Stimulating Immunoglobulins.

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Similar to the neonatal form, late onset PA may develop symptoms related to encephalopathy such as seizures or other life-threatening complications such as pancreatitis, stroke, bone marrow suppression and cardiomyopathy [1]. If left untreated these metabolic derangements may rapidly lead to cardiorespiratory failure and death [1].

Both varieties of PA may lead to cardiomyopathy which is a major cause of morbidity and both dilated and hypertrophic types have been described. Cardiac dysfunction may continue to progress even in patients whose metabolic parameters are stable [5]. Neurologic deterioration is most detrimental and includes delayed myelination, white matter changes, basal ganglia abnormalities, cerebellar hemorrhage, and cerebral atrophy. Hypothyroidism has been reported in two patients [1].

PA is classically diagnosed through a well-established process beginning with a national newborn screening program and should reveal an elevated propionylcarnitine (C3) level [1,4]. Subsequently, urine organic acid analysis reveals an elevated 3-hydroxypropionate level and the presence of methylcitrate, tiglylglycine, propionylglycine and lactic acid [1,7]. In addition, other plasma amino acid abnormalities include elevated glycine, normal or decreased glutamine and a mild to moderate increase in lysine [1,7,8].

2. Case report

A full-term female was admitted to the pediatric intensive care unit (PICU) with hyperammonemic encephalopathy for initiation of hemodialysis on the fourth day of life. Her symptoms began on the second day of life at the referring center with poor feeding and increasing lethargy rapidly followed by seizures. Her condition worsened over 24 h due to progressive encephalopathy and respiratory failure requiring mechanical ventilation.

A detailed history revealed an unremarkable perinatal history and healthy albeit consanguineous parents as well as one healthy female sibling and a negative family history for inherited diseases. Newborn examination had been normal. On arrival to PICU the patient was mechanically ventilated and bedside examination revealed generalized hypotonia with exaggerated deep tendon reflexes. There was no dysmorphism, organomegaly or other abnormality.

Investigations by the referring facility included work up for neonatal sepsis and first line testing for an IEM. Results were remarkable for high anion metabolic acidosis with a serum bicarbonate level of 12 mEq/L and worsening, severe hyperammonemia which had peaked at 1400 micromol/L within 24 h of symptom onset. Urine was collected after fluids containing dextrose were given and was negative for ketones. Impaired renal function was noted with elevated creatinine and urea, 107 and 9.8 micromol/l respectively. Bone marrow suppression was apparent with leukopenia (1.4 × 10^9/L), lymphopenia (0.78 × 10^9/L) and neutropenia (0.98 10^9/L). She was also bacteremic with a positive blood culture growing *methicillin sensitive staphylococcus aureus*.

Following review of these investigations, her admitting diagnosis was an organic acidemia due to an abnormally elevated C3 level detected on newborn screening (Table 1). Formal quantitative testing of plasma acylcarnitine levels also raised suspicion for propionic academia due to elevated C3 along with low carnitine levels and absence of methylmalonic acid (MMA) in plasma (Table 2). Meanwhile, urine organic acid (OA) testing only showed elevation of lactate and phenylacetic acid (Table 2). In addition, serum amino acid (AA) level testing pre-dialysis showed low glutamine and citrulline, elevated lysine while glycine and homocysteine levels were normal (Table 3). However, a urine OA profile later repeated at two months of age and after discharge from the hospital finally showed presence of 2-methylcitric acid. At this time, the patient had recovered from her metabolic decompensation and the diagnosis of propionic acidemia had already been confirmed genetically (Table 2).

Hyperammonemia was managed with urgent hemodialysis (HD) along with ammonia scavenger medications in the form of intravenous sodium phenylacetate and sodium benzoate as well as parenteral levocarnitine and oral carglumic acid. While her diagnosis remained unclear, Biotin was started at a dose of 20 mg per day as well as thiamine was also empirically provided. Total parenteral nutrition (TPN) delivered an adequate glucose infusion rate of 12 mg/kg/min, along with Intralipids at a dose of 3 g/kg/day. As a complication of HD, she developed hypotension and significant electrolyte disturbances including hyponatremia, hypokalemia, hypocalcemia, hypophosphatemia and hypomagnesemia necessitating transition to continuous renal replacement therapy. Dialysis was stopped within ten days of admission after ammonia levels normalized and was consistently maintained at levels below 100 micromol/l.

Notably, while undergoing the HD and medical management for hyperammonemia, the patient developed sudden cardiopulmonary arrest and was successfully resuscitated. An echocardiogram showed a generalized myocardial dysfunction with severe pulmonary hypertension in addition to a moderate sized patent ductus arteriosus and a small atrial septal defect. Treatment for pulmonary hypertension included inotropes along with higher ventilator support parameters in addition to inhaled nitric oxide which was eventually weaned in response to improvement.

Her course was further complicated due to recurrent seizure episodes which resolved with phenobarbital. An initial cranial ultrasound showed multifocal echogenicity in the basal ganglia suggestive of an acute brain insult. Brain magnetic resonance imaging (MRI) revealed hyperintense signals within the white matter suggestive of edema. In addition, subtle subcortical U fiber high signals on T1 and FLAIR sequences indicated

Table 1
Newborn screening via blood spot.

(Units = uM)	1st sample	2nd sample
C0 (Free carnitine)	4 (Low)	3 (Low)
C2 (Acetylcarnitine)	9 (Normal)	6.5 (Low)
C3 (Propionylcarnitine)	10.5 (High)	6 (Below the cutoff)

Table 2
Organic acidemia testing.

	Week 1–4	Week 5–7	Week 36
	Decompensation PICU	Stable - Inpatient	Follow up - Clinic
Acylcarnitine profile (nmol/ml)			
Propionylcarnitine (C3)	5.85 (High)	427 (High)	38 (High)
Total carnitine	9 (Low)	2463 (High)	135 (High)
Free carnitine	1 (Low)	1540 (High)	54 (Normal)
Urine organic acid: metabolites detected			
	• Lactic acid • Phenylacetic acid	• 2-Methylcitric acid	• 3-OHpropionic acid • Propionylglycine • Tiglylglycine • Methylcitric acid

Table 3
Plasma amino acid profile.

	Patient level	Reference Range
Glutamine	367 μmol/L (Low)	430–678 μmol/L
Glycine	415 μmol/L (High)	184–356 μmol/L
Alanine	76 μmol/L (Low)	257–423 μmol/L
Citrulline	8 μmol/L (Low)	9–21 μmol/L
Arginine	42 μmol/L (Low)	50–76 μmol/L
Threonine	92 μmol/L (Low)	139–223 μmol/L
Valine	109 μmol/L (Low)	126–220 μmol/L
Ornithine	37 μmol/L (Low)	70–162 μmol/L
Lysine	437 μmol/L (High)	147–261 μmol/L
Homocysteine	9 μmol/L (Normal)	8–10 μmol/L

hyperammonaemic injury consistent with a neurometabolic insult.

Severe hematologic decompensation also occurred while she was critically ill and consisted of an isolated leucopenia that progressed to severe pancytopenia and abnormal coagulation. Multiple transfusions were needed and included packed red blood cells, platelets, fresh frozen plasma, cryoprecipitate and growth colony stimulating factor (G-CSF) which led to gradual resolution.

In light of her worsening clinical condition including tachycardia and heart failure, the diagnostic work up was expanded and revealed an unexpected result. Thyroid function testing (TFT) at the age of seven days revealed an elevated free T4 (FT4) level of 48.1 pmol/l (*reference range: 10.6–39.8 pmol/l)* and a suppressed thyroid stimulating hormone (TSH) level of 0.008 IU/L (*reference range: 0.430–16.100 IU/L*) whilst free T3 (FT3) was 5.20 pmol/l (*reference range: 3–8 pmol/l*). A thyroid ultrasound was normal. Further testing showed elevated Thyrotropin Receptor antibodies (TRAB) measuring more than 40 IU/L and Thyroid Peroxidase (TPO) antibodies of more than 600 IU/ml as well as increased Thyroglobulin antibodies at the level of 2167 IU/ml.

The abnormal TRAB level was suggestive of neonatal Graves' disease, however, inexplicably maternal testing did not detect corresponding thyroid antibodies. Treatment was started with Carbimazole at a dose of 1 mg twice daily. After one week of treatment, FT4 remained elevated and accordingly the frequency of Carbimazole was increased to thrice daily and one week of Iodine solution was also provided (Fig. 1). Despite these measures, FT4 remained at more than 100 pmol/l whilst TSH was still low at 0.007 milliIU/L necessitating the addition of intravenous methylprednisolone at a dose of 2 mg per kilogram per day (Fig. 1). After two days of intravenous steroid use, T4 levels finally normalized. By the age of five weeks, TRAB remained positive while FT4 levels declined to a nadir of 7.1 pmol/l making "block-replacement" therapy necessary (Fig. 1). This was done via Levothyroxine supplementation and simultaneous Carbimazole dose reduction.

Despite the absence of typical biochemical findings, propionic acidemia remained the most likely diagnosis and was finally confirmed through exome sequencing which revealed a novel homozygous frameshift variant *c.2158_2159insT; p.*Glu720Valfs*14 (NM_000282.3) in the last exon of the PCCA gene. Both parents were found to be heterozygous carriers for the detected variant in the PCCA gene.

After one month in PICU the patient was successfully transitioned to the general ward and oral ammonia scavenger medications, Sodium Benzoate and Sodium Phenylbutyrate, as well as Carnitine supplementation were continued. Nutrition was provided with a combination of protein restricted formula along with a metabolic formula (Propimex-1) via a nasogastric tube. Carbimazole and levothyroxine for hyperthyroidism in addition to phenobarbital for seizures were also continued. The patient clinically improved and displayed increasing alertness. At two months of age, she was discharged home in stable condition.

During outpatient follow up, she was weaned off of ammonia scavengers as ammonia levels remained normal. To date, she remains on carglumic acid as a chronic maintenance treatment. She continues to receive carnitine supplementation as well as prophylactic metronidazole for ten days every month to reduce propionate-producing anaerobic gut flora. Phenobarbital has been stopped and she has had no seizure recurrence. During outpatient follow up at the age of two months, thyroid function was normal and antibodies were no longer present allowing for all thyroid related treatment to be discontinued. On further follow up at the age of 11 months, TFT and thyroid autoantibodies remained negative. Currently, she is gaining weight although her length and head circumference remain along the third percentile. Neurodevelopmentally, prognosis remains guarded but hopeful with her milestones at 16 months as follows: response to sounds, a social smile, head control, rolling over and sitting independently.

3. Discussion

PA is characterized by the accumulation of propionic acid as well as 3-OH propionate, methylcitrate, and high glycine [1]. Cholesterol, odd chain fatty acids and the essential amino acids i.e. valine, isoleucine, threonine, methionine are all dietary sources of propionate [1].

Since several metabolic pathways are disrupted, propionic acidemia can be a diagnostic challenge because of the variety of biochemical abnormalities that may occur [6]. While propionate is a toxic metabolite in itself, when it is not converted to methylmalonyl CoA, the TCA cycle is disrupted leading to further impairment of energy production [1]. Furthermore, the urea cycle and process of oxidative phosphorylation are both impaired [4].

Biochemical abnormalities classically include high-anion gap metabolic acidosis, lactic acidosis, hypoglycemia, moderate

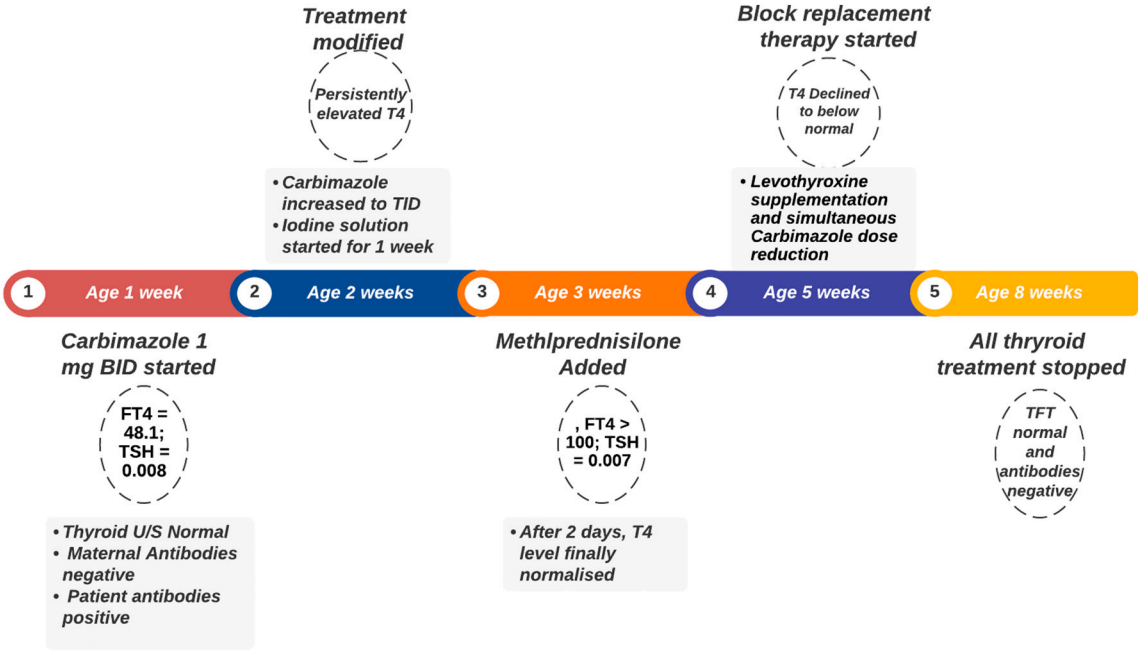

Fig. 1. Timeline depicting abnormal TFT and corresponding treatments.

hyperammonemia and elevated ketones in plasma and urine [1]. All these factors were noted in our patient as well cytopenias which are classically characteristic of organic acidemias [1].

Initial screening is performed through analysis of a dried blood spot for acylcarnitines revealing an elevated C3 [1,2]. This can be followed by confirmatory testing through a serum acylcarnitine analysis which should also show an elevated C3 [1]. In our case, only isolated elevated C3 was noted throughout the period that the neonate was critically ill. Further testing for secondary markers including methionine, C3/C2 and C3/C16 ratios can be helpful in increasing diagnostic accuracy [1]. Furthermore, a serum amino acid profile should have high glycine and lysine levels whilst serum glutamine levels remain low or normal [1,4,8]. Most importantly, a urine organic acids analysis is diagnostic and usually reveals a high 3-hydroxypropionate along with the presence of methylcitrate, tiglylglycine, propionylglycine and lactic acid [2]. Uniquely, our patient only manifested these abnormalities several weeks after improving including the presence of 2-methylcitric acid which in the presence of normal MMA level, supports the diagnosis of PA. However, other urinary markers such as 3-OH propionic acid, propionylglycine, 3-OH-isovaleric acid, and tiglylglycine remained either undetectable or were recorded only in trace amounts.

Isolated elevated propionylcarnitine (C3) has been studied in a case series of three patients, however unlike the reported case, they had extremely mild disease without recurrent decompensation [9]. In fact, one of the three patients only manifested in the newborn period with a mildly elevated ammonia and required treatment with ammonia scavengers, levocarnitine and IV fluids [9]. Their urine organic acid profile was significant for only moderate elevations in methylcitric acid and 3-hydroxypropionate [9]. The other two reported patients had abnormal newborn screenings and diagnosis was confirmed via genetic testing [9]. Their urine organic acid profiles were normal and they remained asymptomatic and are currently doing well on a protein restricted diet [9].

There are two genes involved in propionic acidemia, PCCA and PCCB, with nearly half of disease-causing variants found on the PCCA gene [10]. Irrespective of the gene involved, missense mutations are most common. Other mutations include small insertions, deletions or splicing mutations which generally result in a frameshift [11]. PCCA null variants cause the most severe form of disease while splice and missense mutations contribute to milder forms [4]. Remarkably, a novel mutation has been discovered in our patient which was previously classified as variant of unknown significance. A shift in the reading frame is caused by variant c.2158_2159insT p.(Glu720Valfs*14 starting at codon 720.

Understandably, the clinical manifestations of neonatal onset PA may be misdiagnosed as neonatal sepsis due to its vague presentation including hypotonia, hypoactivity, poor feeding and lethargy [7]. However, in our case the atypical laboratory findings posed a further diagnostic challenge. An elevated C3 in newborn screening can also be caused by diseases other than PA or methylmalonic academia (MMA), such as disorders of intracellular cobalamin metabolism and vitamin B12 deficiency [1]. Classical findings of high anion gap metabolic acidosis with hyperammonemia, elevated urinary ketone bodies, absence of methylmalonic acid in urine with normal homocysteine and vitamin B12 levels can help differentiate organic acidemias from other disorders presenting with acute deterioration and encephalopathy [7].

When distinguishing among organic acidemias, both have elevations of 2-methylcitric acid and 3-hydroxypropionic acid but MMA characteristically has an abnormally high level of methylmalonic acid detected on urinary organic acid analysis [1,7]. 2-methylcitric acid was finally detected in the urine only after our patient improved.

Mitochondrial disorders should be considered in cases of hyperammonemia, metabolic acidosis, ketonuria, and hypoglycemia [1]. Similarly, urea cycle disorders may also present with severe hyperammonemic encephalopathy without ketoacidosis [6]. A high glutamine level is usually seen in this group compared to the organic acidemias, although there may be an overlap [6].

Other rare possibilities include carbonic anhydrase VA deficiency which can present similarly with hyperammonemic encephalopathy during the neonatal period combined with hyperlactatemia and ketonuria [1]. A urine organic acid profile shows elevated 3- hydroxypropionic acid, propionylglycine, and methylcitric acid as well as 3-methylcrotonylglycine, 3-hydroxybutyric, alpha-ketoglutaric, and 3 hydroxyisovaleric acids [12]. Meanwhile, the plasma amino acid analysis shows an elevation in glutamine, alanine and low to normal citrulline [12]. Pyruvate carboxylase deficiency may also be considered which causes a malfunction of the citric acid cycle and gluconeogenesis [13]. The neonatal form is severe, causing hepatomegaly, cerebellar signs, and abnormal movements [13]. The laboratory findings include elevated levels of citrulline, proline, lysine, ammonia and a low glutamine level [13,14,15]. The hyperammonemia, hyperlysinemia and low glutamine levels were observed in our patient, however, the distinctive factor was the elevated propionyl carnitine which is found solely in organic acidemias.

3.1. *Association of propionic acidemia with autoimmune thyrotoxicosis – a first*

Regarding the significant and yet unexplained autoimmune related hyperthyroidism that occurred alongside metabolic decompensation, it must be mentioned that a similar case has never been previously reported. In fact, hyperthyroidism is rare in the newborn [16]. It is most commonly caused by transient Grave's disease due to transplacental passage of thyroid stimulating immunoglobulins (TSIs) from affected mothers or more rarely due to Hashimoto's thyroiditis [16]. Neonatal Graves's disease is estimated to occur in 1 in 50,000 neonates [17].

Neonatal thyrotoxicosis, irrespective of the underlying cause, may present with low birth weight, growth retardation, craniosynostosis, microcephaly, tachycardia, arrhythmia, irritability, jitteriness, and restlessness [16]. Ophthalmology related pathologies include periorbital oedema, lid retraction, and exophthalmos [16]. In severe forms, systemic and/or pulmonary hypertension with cardiorespiratory failure rarely occurs in neonates [18]. Interestingly, there has been reports of hyperammonemia as a rare manifestation of thyrotoxicosis [17,19]. The reported case did have cardiorespiratory instability as well as severe pulmonary hypertension which may be explained retrospectively by her diagnosis of neonatal thyrotoxicosis.

The diagnosis of neonatal Graves' disease is confirmed by an undetectable serum TSH and by high levels of FT4 and FT3 with positive TSH receptor stimulating antibodies [19]. In the case of our patient, she had high antibody levels but the mother was negative for any thyroid related antibodies.

Thyrotoxicosis should be treated with a thionamide, with or without iodide, or iodine containing contrast medium. Propranolol and corticosteroids should be considered in severe cases [16].

There are very few causes of hyperthyroidism reported in neonates which occur without maternal autoimmunity and these include Autosomal Dominant Non-Autoimmune Hyperthyroidism, McCune-Albright syndrome, Thyroid Receptor Beta Gene Mutation (M313T) and use of biotin [20]. In the reported case there was no evidence of maternal autoimmunity, however, there was no such underlying cause discovered.

We have hypothesized that thyroid function derangement in the reported patient could have been due to the use of empirical Biotin. This is because of an extensive literature search which revealed well established data related to biochemical hyperthyroidism in adults receiving Biotin [21]. In fact, the manufacturers of a widely used thyroid function assay, Roche Cobas TM,specifically advise an interval of at least 8 h after last biotin ingestion prior to thyroid function testing [21]. Moreover, one anecdotal case reported presence of TPO antibodies in an adult on Biotin supplementation while another article reported presence of TRAB antibodies in their patient [21,22]. In both these cases, FT3 and FT4 levels was elevated while TSH levels were suppressed because of biotin

immune assay interference [21]. Another case reported biochemical hyperthyroidism without phenotypical features in a newborn in which both mother and infant had been started on prophylactic Biotin due to positive family history of Biotinidase deficiency [23]. This condition is also referred to as biochemical neonatal hyperthyroidism [20,21].

Alternatively, there is the small although unlikely possibility that passage of TRAB occurred iatrogenically via blood transfusion in the first days of life. We found no such cases in the existing literature.

Overall, due to the patients critical illness, it was initially difficult to correlate the laboratory findings with the clinical picture in relation to possible thyrotoxicosis. However, the timeline of biochemical changes in relation to starting and stopping biotin and the lack of specific signs of hyperthyroidism strongly suggest biotin interference with the assay. This is also supported by the lack of thyroid receptor antibodies and lack of clinical history of thyroid disease in the mother.

4. Conclusion

Through this case we report several novel findings. Firstly, a gene mutation previously classified as variant of unknown significance in the PCCA gene has been confirmed to cause Propionic Acidemia. Her parents, who are consanguineous, are heterozygous carriers of the same PCCA variant at c.2158_2159insT (p.Glu720Valfs*14) which creates a shift in the reading frame starting at codon 720. This is also the first reported case of PA associated with biochemical evidence of autoimmune thyroiditis. Moreover, this is also the first case of a neonate with auto-immune thyroiditis while maternal serology was negative. Finally, this is the second ever reported case of PA where initial urine organic testing did not reveal the classic abnormalities required for diagnosis.

Declaration of Competing Interest

None.

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