Case Report
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Diagnostic pitfalls in neonatal hypertyrosinemia: a case report

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ABSTRACT

Hypertyrosinemia results from abnormality in tyrosine metabolism. Acquired hypertyrosinemia is notably more common than inherited types and typically presents with profile suggestive of secondary aetiology on biochemical testing. Herein, we present an unusual case of a day 16-of-life baby girl who was screened for inborn errors of metabolism (IEM). She presented with jaundice, hypotonia, lethargy and had hepatomegaly on examination. She was treated for sepsis with multiorgan involvement, requiring escalation of intravenous antibiotics and assisted ventilation. Her dried blood spot (DBS) showed moderate elevation of tyrosine (408umol/L, N:10-182) with low Phe:Tyr ratio (0.15µmol/L, N:0.32-3.45). Plasma amino acid showed isolated hypertyrosinemia at 807µmol/L (N:5-167) with mild, non-significant elevations of other liver metabolites. No succinylacetone peak seen with urine organic acids, making the diagnosis of inherited Tyrosinemia type I less likely despite the characteristic findings from DBS, plasma amino acids, and presenting clinical signs. Repeated IEM screening two weeks later revealed a non-diagnostic profile across both DBS and plasma amino acids in light of resolving sepsis and clinical improvement. This case highlights the challenges associated with incompatible biochemical testing in a child with a high index of suspicion for inherited Tyrosinemia. In our case, repeated screening ruled out inherited Tyrosinemia, suggesting the initial picture of hypertyrosinemia to be likely due to liver dysfunction and impaired activity of liver enzymes that are responsible for tyrosine catabolism.

Keywords: *Inborn errors of metabolism; hypertyrosinemia; liver dysfunction and sepsis*

INTRODUCTION

Tyrosine is mainly broken down in the liver, with a smaller amount being processed in the kidneys (Van Spronsen, Burlina, & Vici, 2022). Inherited disorders related to tyrosine degradation have been found in five of the six enzymatic steps involved in this process. Normally, tyrosine levels in the body are controlled by phenylalanine hydroxylase (the producing enzyme) and the first enzyme responsible for breaking it down (tyrosine aminotransferase) (Van Spronsen et al., 2022). When the second enzyme (4-hydroxyphenylpyruvate dioxygenase) is deficient due to inheritance or acquired reasons, it leads to elevated levels of tyrosine, known as hypertyrosinemia (Van Spronsen et al., 2022).

Acquired hypertyrosinemia is notably more common than inherited types (Adnan & Puranik, 2022) and typically presents with a profile suggestive of secondary aetiology on biochemical testing. Acquired hypertyrosinemia may occur in several health conditions such as severe liver failure or hepatocellular dysfunction, nutritional deficiency such as vitamin B6, folate or vitamin C deficiency, medications that interfere with tyrosine metabolism, renal dysfunction leading to accumulation of tyrosine, hyperthyroidism and others (El-Shabrawi & Kamal, 2013).

We aim to highlight the challenges associated with incompatible biochemical testing in a child with a high index of suspicion for inherited Tyrosinemia and review the pathophysiology of acquired hypertyrosinemia associated with liver dysfunction.

CASE PRESENTATION

Herein was a baby girl delivered at borderline prematurity at 36 weeks via spontaneous vertex delivery. There was no history of leaking liquor, and she was admitted to nursery shortly after birth for presumed sepsis due to preterm delivery. Antibiotics were completed for 3 days and she was discharged well following sterile culture.

She initially presented to us on day 6 of life, appearing lethargic and was noticed to be sleeping most of the time with reduced feeding. On examination, the child appeared weak and jaundiced. Anterior fontanelle was soft, not bulging or depressed. Per abdomen was soft with mild hepatomegaly. Other systemic examination was unremarkable. There were no features of urinary tract infection on biochemical testing, CRP was less than 6 mg/dL, and glucose monitoring was stable. She was treated for presumed sepsis and was covered with intravenous ampicillin 50 mg/kg 8-hourly and gentamicin 4 mg/kg once daily. Initial blood gases showed no metabolic acidosis with normal anion gap.

During close monitoring over the next few days, she was noted to have intermittent desaturation with shallow breathing, hence was started on bi-level positive airway pressure (BiPAP) (Pressure 12/6, rate 40, FiO_2 30%, iT 0.5). Lumbar puncture was not performed in view of thrombocytopenia (Platelet: $14x10^3/\mu L$, N=150-450 $x10^3/\mu L$) (Table 1). Antibiotics were escalated to Meropenem 40mg/kg/dose 8 hourly and were continued for 14 days. Cultures were sterile and she was weaned off to room air three days later.

Table 1

Routine laboratory investigations during the course of illness

Timeline	Day 8 admission	Day 13 admission	Day 17 admission	Day 20 admission	Outpatient (14 days after discharged)
Hb *(g/dL)*	8.3	8.9	8.8	7.8	12.3
Platelet *(× $10^3/\mu L$)*	14	86	120	135	233
TWC *(× $10^3/\mu L$)*	8.2	14.5	11.3	10.6	13.2
ANC *(× $10^3/\mu L$)*	1.7	3.2	2.6	3.5	2.7
Sodium *(mmol/L)*	-	139	138	138	135
Potassium *(mmol/L)*	-	5.8	4.7	4.3	4.7
Urea *(mmol/L)*	-	2.4	1.7	2.2	4.2
Creatinine *(µmol/L)*	-	33	28	27	15
Total protein *(g/L)*	42	51	57	49	50
Albumin *(g/L)*	43	30	36	33	35
DB/IB *(µmol/L)*	114/144	86.7/112	94.3/127.7	80.6/98.4	48.8/55.2
ALP *(IU/L)*	627	944	916	694	398
AST *(IU/L)*	180	220	279	245	96
ALT *(IU/L)*	209	66	65	67	60

Note: ALT=Alanine transaminase; ALP=Alkaline phosphatase; ANC=Absolute neutrophil count; AST=Aspartate transaminase; DB=Direct bilirubin; Hb=Haemoglobin; IB=Indirect bilirubin; TWC=Total white cell count.

Despite observable clinical improvement, she was noted to have persistent conjugated hyperbilirubinaemia with transaminitis at Day 16-of-life (Total bilirubin: 258 µmol/L, N: 1.7-20.5; Direct hyperbilirubinemia: 44%; AST: 180 IU/L, N: 5-40; ALT: 209 IU/L, N:7-56; ALP: 627 IU/L, N: 20-140), raising the suspicion of possible inborn errors of metabolism (IEM). There was, however, no family history of inherited metabolic diseases, she was the youngest of 3 siblings (the rest were otherwise healthy and thriving), and the parents were non-consanguineous.

Her dried blood spot (DBS) showed moderate elevation of tyrosine (408µmol/L, N:10-182) with low Phe:Tyr ratio (0.15µmol/L, N:0.32-3.45). Plasma amino acids showed isolated hypertyrosinemia at 807µmol/L (N:5-167) with mild, non-significant elevations of other liver metabolites (Figure 1). Urine organic acids showed increased

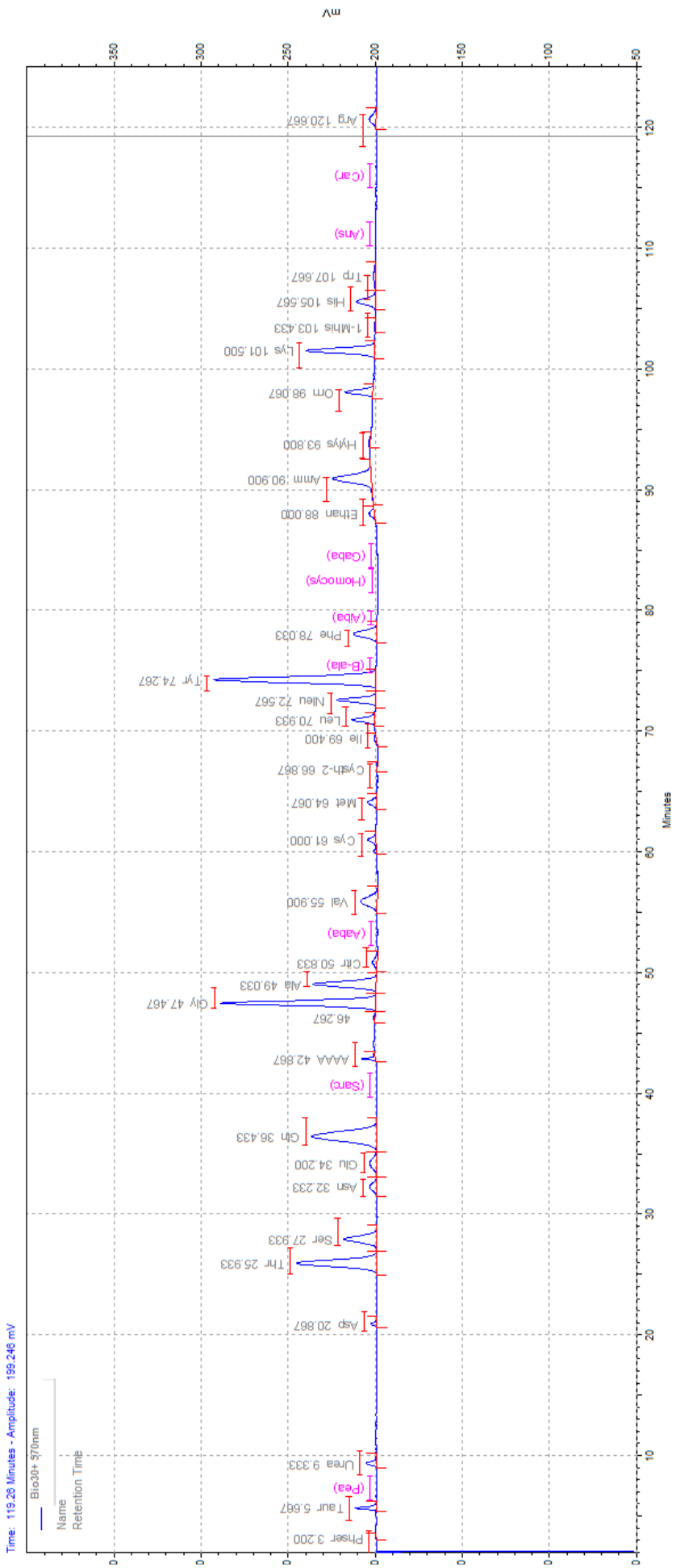


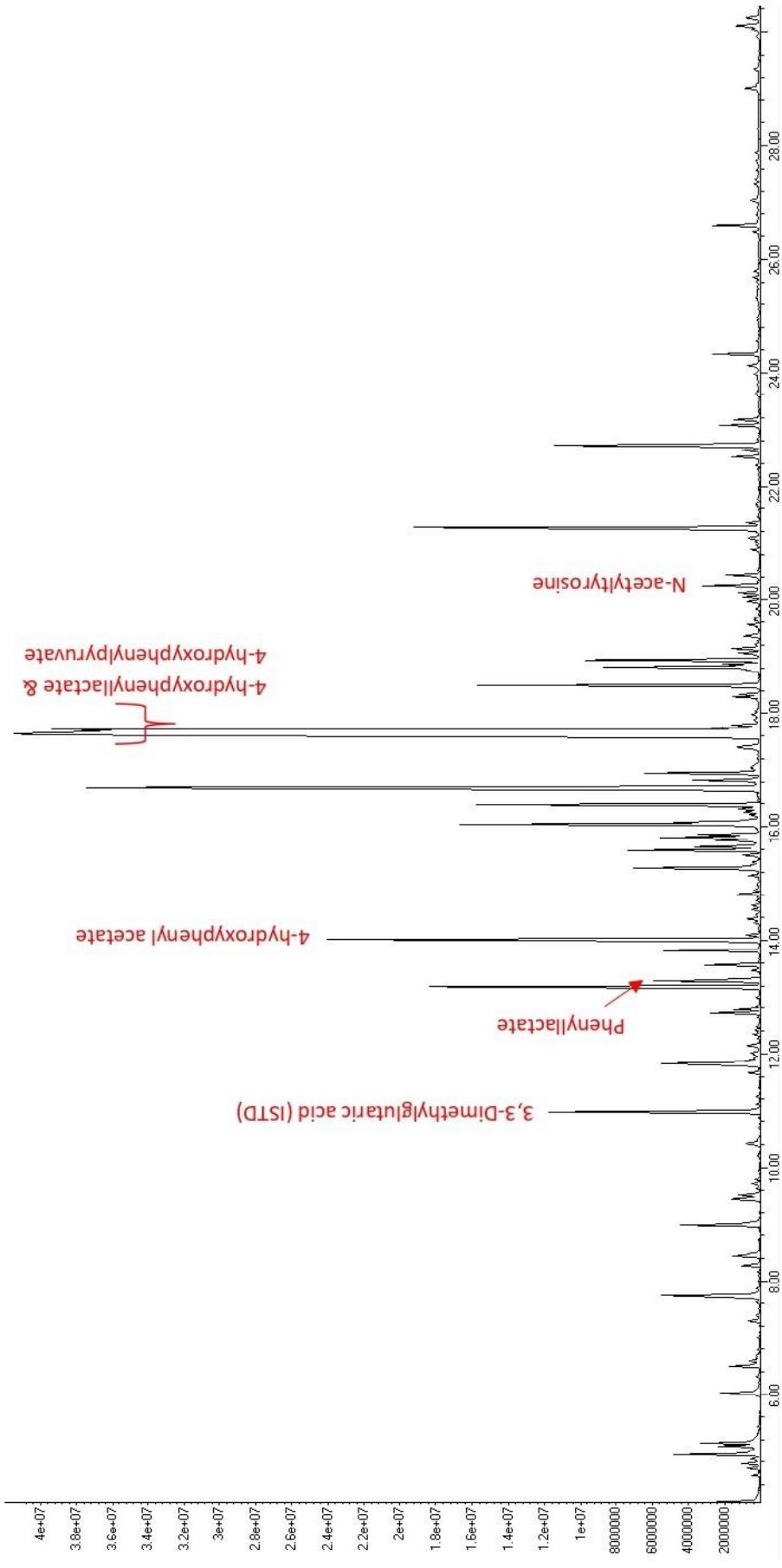
Figure 1

Plasma amino acids analysed by ion-exchange chromatography

Note: Plasma amino acid profile showing isolated hypertyrosinemia with non-significant elevations of few other amino acids (glutamine, glycine and threonine).

Figure 2

Urine organic acids showing elevated levels of liver metabolites



Note: Liver metabolites (as labelled). Marked increased in excretion of 4-hydroxyphenyllactate with mild increased in excretion of 4-hydroxyphenylacetate and citrate. Presence of 4-hydroxyphenylpyruvate, phenyllactate and N-acetyltyrosine peak. No succinylacetone peak seen, therefore Tyrosinemia Type I is less likely.

in liver metabolites (Figure 2), however no succinyl acetone peak was seen, making the diagnosis of inherited Tyrosinemia type I less likely despite the characteristic findings from DBS, plasma amino acids, and the presenting clinical signs.

Repeated IEM screening two weeks later revealed a non-diagnostic profile across both DBS and plasma amino acids in light of resolving sepsis, transaminitis, and clinical improvement. She was discharged well after 20 days hospitalisation.

DISCUSSION

Herein, we presented an unusual case of a Day 16-of-life baby girl who was screened for inborn errors of metabolism (IEM). She presented with jaundice, hypotonia, lethargy and had hepatomegaly on examination. She was treated for sepsis with multiorgan involvement - severe transaminitis, conjugated hyperbilirubinemia, thrombocytopenia and hypoalbuminemia, requiring escalation of intravenous antibiotics and assisted ventilation.

The case is unique as the initial testing showed isolated hypertyrosinemia in the absence of classical features of liver dysfunction on plasma amino acid (no marked elevation of methionine, phenylalanine, ornithine, arginine, citrulline), making the suspicion of inherited Tyrosinemia high on our list. However, the negative urine screening for succinyl acetone peak on urine organic acid made the diagnosis of Tyrosinemia type I less likely despite the characteristic findings on plasma amino acids, DBS and clinical signs and symptoms. Repeated testing 2 weeks later had ruled out inherited Tyrosinemia.

Our case suggests that the initial picture of hypertyrosinemia to be likely due to liver dysfunction (Adnan & Puranik, 2022) secondary to sepsis. Sepsis may mimic a wide variety of non-infectious disease (Soans & Panambur, 2019), hence a systematic approach, meticulous assessment, and frequent evaluation is necessary to identify and exclude a sepsis mimic.

Sepsis may result in impaired activity of liver enzymes that are responsible for tyrosine catabolism. This includes the tyrosine aminotransferase, 4-hydroxyphenylpyruvate dioxygenase (4-HPPD), tyrosine hydroxylase (TH), homogentisate 1,2-dioxygenase (HGD), maleylacetoacetate cis-trans-isomerase (MAAI), and 4-fumarylacetotacetate hydrolase (FAH) (Alsharhan & Ficicioglu, 2020). Impaired activity of any of these enzymes that are responsible for tyrosine catabolism results in the accumulation of tyrosine that can be detected on amino acid panels. However, a typical profile of hypertyrosinemia secondary to a liver dysfunction as the underlying aetiology often had accompanying elevated liver metabolites in the plasma amino acids panel, which were absent in our case. We postulated that in certain cases of liver dysfunction, the liver metabolites may be less affected, most likely because of preserved transporter function or transporter redundancy that allows near-normal metabolism of these metabolites (Paulusma, Lamers, Broer, & van de Graaf, 2022).

On the other hand, hereditary tyrosinemia type 1, or the hepatorenal tyrosinemia is the most severe metabolic disorder associated with tyrosine degradation catabolic pathway. It is inherited as an autosomal recessive disorder caused by a deficiency of the enzyme fumarylacetoacetate hydrolase (FAH) (Kawabata, Kido, Yoshida, Matsumoto, & Nakamura, 2022; Morrow & Tanguay, 2017). The acute form of the disease is characterised by an early onset with severe multiorgan involvement affecting the liver and kidney functions, and the central nervous system due to the toxic accumulation of tyrosine metabolites, such as the succinyl acetone (El-Shabrawi & Kamal, 2013). Hence, elevated succinyl acetone, in DBS samples, or in plasma or urine, is the most reliable neonatal screening method and pathognomonic for inherited Tyrosinemia type 1. Apart from liver transplants, drugs blocking the pathway upstream of FAH, such as the NTBC/Nitisone has been effectively used together with a diet low in tyrosine and phenylalanine in its management (El-Shabrawi & Kamal, 2013; Morrow & Tanguay, 2017).

IEMs are clinically rich entities with multiple signs and symptoms, hence the road to accurate diagnosis starts with the clinician's suspicion, guided by general knowledge of IEMs, a thorough clinical evaluation, and a suggestive biochemical profile (Zhang et al., 2020).

CONCLUSION

In conclusion, biochemical testing should always be interpreted along with clinical symptoms and signs for an accurate clinical picture and diagnosis. A repeat testing is almost always indicated in such cases where either does not fit.

AUTHOR CONTRIBUTIONS

Karniza Khalid: Conceptualization, analysis, data collection, writing the first draft of the manuscript; Mohd Fazrul Shafiq Kamarudzaman: Conceptualisation, clinical management, data collection, writing the first draft of the manuscript; Siti Nurwani Ahmad Ridzuan: Data collection, analysis, critical review of the manuscript for scientific rigor; Nurul Izzati Hamzan: Data collection, analysis, critical review of the manuscript for scientific rigor; Norzahidah Khalid: Data collection, analysis, critical review of the manuscript for scientific rigor; Noor Hafizah

Hassan: Conceptualization, supervision, critical review of the manuscript for scientific rigor. All authors read and approved the final manuscript.

ETHICS APPROVAL

Ethics approval was waived in accordance with the NIH Guidelines for Conducting Research in MOH Institutions and Facilities (MOH/S/NIH/10.21(GU)-e), 3rd edn. (2021). Anonymity of the subject and confidentiality were well preserved throughout the writing. The study has been registered with the National Medical Research Registry, Ministry of Health Malaysia (NMRR ID-23-01476-7EQ).

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CONFLICTS OF INTEREST

The authors declare no conflict of interest in this work.

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