Case Report

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2023.48.007606

A Case Report of a Female Child with Tyrosinemia Type I in Southern Philippines During the Covid-19 Pandemic

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ARTICLE INFO

Received: January 04, 2022

Published: January 18, 2023

Citation: Tracy Eloise Mae L Sta Maria, Conchita Abarquez and Genelynne J Beley. A Case Report of a Female Child with Tyrosinemia Type I in Southern Philippines During the Covid-19 Pandemic. Biomed J Sci & Tech Res 48(1)-2023. BJSTR. MS.ID.007606.

ABSTRACT

Tyrosinemia type I (also called Hepatorenal Tyrosinemia) is a rare autosomal recessive metabolic disorder that presents with a severe progressive disease course leading to premature death if not treated. It is caused by a deficiency of the enzyme fumarylacetoacetate hydrolase (FAH) which is needed in the final breakdown of tyrosine. The FAH gene is mapped in chromosome 15q25.1. The manifestations begin in the first month of life and the earliest and major effect of the disease is on the liver. This case report discusses one of the first few cases of Tyrosinemia type 1 in the Southern Part of the Philippines diagnosed by newborn screening and monitored by the newborn screening continuity clinic.

Keywords: Tyrosinemia Type 1; Nitisinone; Newborn Screening; Continuity Clinic

Abbreviations: FAH: Fumarylacetoacetate Hydrolase; ENBS: Expanded Newborn Screening; BCG: Bacillus Calmette Guerin; OPV: Oral Polio Vaccine; PCV: Pneumococcal Conjugate Vaccine; PAA: Plasma Amino Acids; PT: Prothrombin Time; INR: International Normalized Ratio; PTT: Partial Thromboplastin Time; AFP: Alpha Fetoprotein; L41P: Leucine With Proline at Codon 41; VUS: Variant Of Uncertain Significance; 4-HPPD: 4-Hydroxyphenylpyruvate Dioxygenase; TAT: Tyrosine Aminotransferases; Faa: Fumarylacetoacetate; MAA: Maleylacetoacetate; SA: Succinylacetone; SAA: Succinyl Acetoacetate; CH: Congenital Hypothyroidism; CAH: Congenital Adrenal Hyperplasia; Gal: Galactosemia; PKU: Phenylketonuria; HCY: Homocystinuria; G6PD: Glucose-6-Phosphate Dehydrogenase; MSUD: Maple Syrup Urine Disease; PHE: Phenylalanine; Tyr: Tyrosine; PHPPD: Para Hydroxyphenylpyruvic Acid Dioxygenase; PSOD: Philippine Society Of Orphan Disorders; DOH: Department of Health; NBSCC: Newborn Screening Continuity Clinics

Introduction

This is case report of a female child who had elevated level of succinylacetone in her newborn screening test on the second day of life. She was immediately recalled by the newborn screening follow-up team for confirmatory testing and metabolic specialist evaluation. Ancillary diagnostic testing to assess liver functions showed high levels of alkaline phosphatase, alpha fetoprotein and deranged coagulation studies. Her plasma amino acid analysis showed elevated tyrosine level. Molecular testing detected a homozygous pathogenic variant in the FAH gene and the result was consistent with Tyrosinemia type 1. Molecular testing of the parents was also done, and both were confirmed to carry a heterozygous pathogenic variant in their FAH gene. The patient was started on low natural protein diet and was treated with Nitisinone. She remains symptom-free with normal growth and development. The clinical course of the patient emphasizes the need for early detection of Tyrosinemia type 1 through newborn screening. The case illustrates how early diagnosis and management can improve patient outcomes and delay disease progression.

Case Description

This is a case of SA, a 14-month-old female child, who was born on July 29, 2020 and lives in Cabantian, Davao City. The patient tested positive in her newborn screening test result. She was born to a 23-year-old G2P2 (2002) mother who had unremarkable pregnancy and delivery. SA was delivered full term (Ballard Score of 38 weeks) and appropriate for gestational (birth weight of 3700 grams) age via normal spontaneous vaginal delivery at a local hospital. Her APGAR score was 8 and 9. Essential intrapartum and newborn care was given. SA was directly roomed-in with the mother and was exclusively breastfed. Expanded newborn screening (ENBS) was done immediately after the 24th hour of life. Patient was managed as a well-baby and was discharged after 48 hours of life with no complications. On the 6th Day of life, the ENBS result showed elevation of the primary analyte for Tyrosinemia Type I which is succinylacetone. The result was immediately relayed by the Newborn Screening Center Mindanao Follow-up Nurse to the newborn screening team of the hospital. An urgent repeat testing was recommended.

On the 8th day of life, repeat NBS was done revealing persistent elevation of succinylacetone. Immediate confirmatory testing was requested but in light of the COVID pandemic, specimen transmittal to confirmatory testing center in the University of the Philippines Manila was not feasible. Patient was immediately recalled and was assessed thoroughly based on the symptom checklist which revealed unremarkable signs and symptoms. Diagnostic studies to assess the hematologic, hepatic and renal system of the patient was also requested and facilitated. The parents were not able to immediately comply with the diagnostic testing because of the limitations of clinical laboratories operating during the pandemic. Upon completion of the diagnostic work-up and pending confirmatory testing such as plasma amino acid analysis and urine organic acid analysis, the patient was started on low natural protein diet and Nitisinone at 1 mg/kg/day. The patient has good compliance with the medications, metabolic diet and regular clinical follow up at the newborn screening continuity clinic of SPMC. Past medical history includes two hospital admissions at 1 month of age due to a single episode of seizure and at one year of age due to Acute Gastroenteritis with some dehydration. She has neither food and drug allergy, nor history of atopy. She has no recurrent infections, no prior surgery and has no history of blood transfusions.

The feeding history started with exclusive breastfeeding immediately after birth. However, after confirmation of the metabolic disorder she was shifted to a metabolic diet with restriction of natural protein using a special medical milk formula that has zero tyrosine and phenylalanine. Her metabolic diet is being handled by the dietician in SPMC. The patient's immunization record is at par with age. She has already received the following vaccines:

a) Hepatitis B and Bacillus Calmette Guerin (BCG) given at birth;

b) 3 doses of Penta Vaccine (DTwP -Hib-Hep B), Oral Polio Vaccine (OPV), Pneumococcal conjugate vaccine 13 (PCV) at 6th, 10th, and 14th weeks old;

c) 2 doses of Influenza vaccine at 6th and 7th months old;

d) Measles vaccine at 9 months old.

No booster vaccine is given yet to the patient. All vaccines were administered at the local health center. No adverse effect following immunization was reported. The developmental milestones of the patients are also at par with age. Gross motor skills like sitting without support, rolling back to stomach, standing without support and walking alone were achieved at five, 6, 10 and 11 months, respectively. She was able to reach for objects at 4months of age. Do the thumb-finger grasp at 7 months and can turn pages of book by age 10 months. At age 7 months, she can follow one-step command with gesture, says "Mama" at age 8 months and points to objects at 10 months of age. She can stare at own hand at age 5 months, uncover toys at 7 months and perform egocentric symbolic play at age 11 months.

The family history is unremarkable. The pedigree (Figure 1) is noncontributory. The parents are not in consanguineous relationships. On physical examination, she was seen awake, active, not in respiratory distress and with stable vital signs as follows: heart rate of 122 beats per minutes, respiratory rate of 32 cycles per minute, temperature of 36.8 degrees Celsius, oxygen saturation

of 97% at room air. The patient had a weight of 10 kilograms, height of 80 centimeters and head circumference of 44cm. On the growth charts, anthropometrics shows the patient is nutritionally well. The rest of the physical and neurologic examinations are unremarkable. Newborns referred to metabolic centers for elevated tyrosine and/or succinylacetone for HT-1 should be seen as soon as possible for clinical and laboratory evaluations. The most important initial test is blood or urine SA level. If there is high suspicion Tyrosinemia type 1, plasma amino acids (PAA) and liver function tests including prothrombin time (PT), international normalized ratio (INR), partial thromboplastin time (PTT) and α-fetoprotein (AFP) should be evaluated at the first visit.

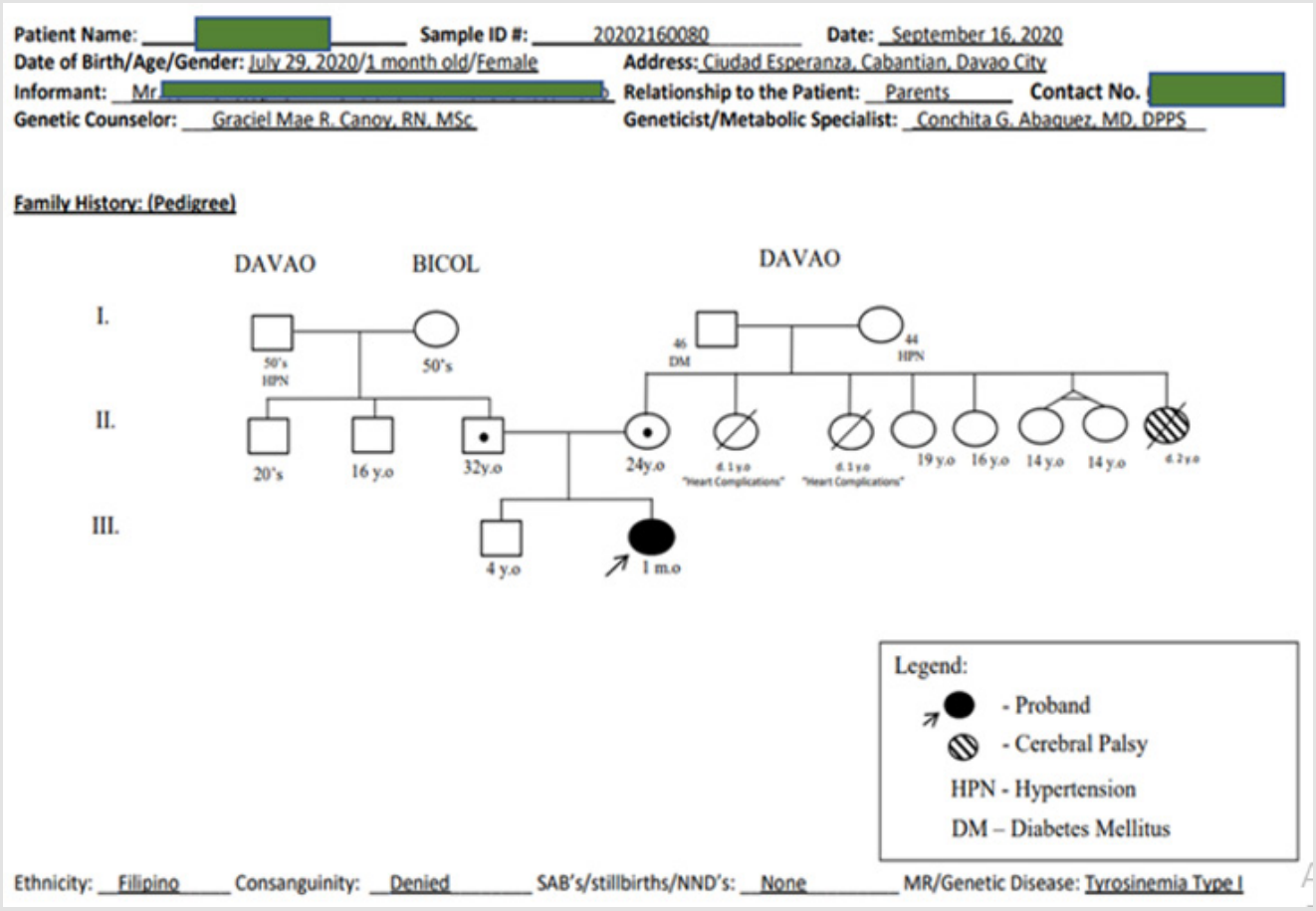

Figure 1: Family Pedigree.

Table 1.

Age at Collection	Succinylacetone (NV <5 umol/L)	Tyrosine (NV<450 umol/L)	Reported Result	Comments
1 day 6 hours	6.34	120.6	Borderline	Urgent repeat collection is required.
8 days 3 hours	5.9	834.6	Elevated	Immediate confirmatory testing of PAAA & UOAA are required to rule out a diagnosis.

Patient SA had expanded newborn screening taken immediately after 24th hours of life and was repeated on day 8 of life. The reported screening results from the newborn screening center laboratory showed elevation of the primary analyte, succinylacetone and comments on results are shown below (Table 1). All urgent results were immediately relayed by the Newborn Screening Center Mindanao Follow-up Nurse to the NBS follow up team of SPMC. Immediate confirmatory testing was requested but in light of the

COVID pandemic, specimen transmittal to confirmatory testing center in the University of the Philippines Manila was not feasible. Patient was immediately recalled and was assessed thoroughly based on the symptom checklist which revealed unremarkable signs and symptoms. Baseline diagnostic studies to assess the hematologic, hepatic and renal system and establish the extent of disease and needs of the patient were done. The CBC showed anemia, and thrombocytopenia of 130. The bleeding parameters revealed prolonged APTT of more than 3.9 times the control, and a deranged PT with INR of 2.8. Blood chemistry studies showed normal creatinine level but the alkaline phosphatase and serum alpha fetoprotein (AFP) were both elevated. The urine sample was sent to the Biochemical Genetics Laboratory of the Institute of Human Genetics, National Institute of Health for urine organic acid analysis. The result showed elevated 4-hydroxyphenyllactate and 4-hydroxyphenylpyruvate and presence of N-acetyl tyrosine but with absence of succinylacetone. The patient underwent urine organic acid analysis when she was already 5 months of age when transmittal of biologic specimen was already feasible.

At this time, the patient was already on restricted natural protein and was maintained on nitisinone medication. This explains the absence of succinylacetone in the urine organic acid analysis. Succinylacetone is a sensitive and specific marker for the detection Tyrosinemia type 1. Additionally, plasma amino acid analysis was done at 7 months of age and revealed elevated plasma tyrosine levels of 371 umol/L (NV 22-108). The patient was also confirmed by molecular testing. After getting an informed consent for DNA testing and after the pre-test genetic counseling, a buccal sample was collected from the patient for DNA analysis and was sent to a genetic laboratory in California, USA. The result showed a homozygous missense mutation at coding DNA sequence 122 of exon 2 of the FAH gene, replacing leucine with proline at codon 41 (L41P) of the FAH protein (c122T>C p.Leu41Pro). The variant was initially classified as variant of uncertain significance (VUS) because it was not present in population databases (gnomAD no frequency) and there was insufficient evidence to determine the role of the variant in the disease. The variant qualified for complimentary family testing as part of the VUS resolution program. The parents were then informed of the result through a post-test genetic counseling and were also recommended to undergo parental DNA testing. After consenting, both parents were provided pre-test genetic counseling. Parental DNA testing revealed that each parent carried a heterozygous variant L41P confirming the diagnosis of Tyrosinemia Type 1. The variant then was reclassified as pathogenic, and the genetic laboratory submitted an updated DNA test result for the patient (Figure 2).

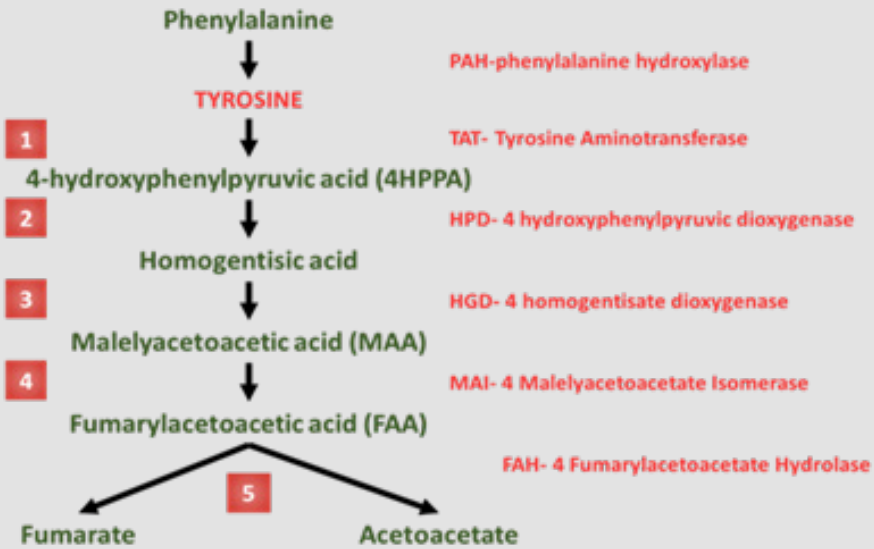

Figure 2: Tyrosine Normal Catabolic Pathway.

Discussion

This is a case of a 14-month-old female who tested positive for Tyrosinemia type 1 in the newborn screening test on the second day of life. The physical examinations were unremarkable, however, diagnostic tests showed deranged bleeding parameters, elevated serum alpha fetoprotein (AFP), elevated plasma tyrosine levels and a homozygous pathogenic variant in the FAH gene. Tyrosinemia is a genetic disorder characterized by disruptions in the multistep process that breaks down the amino acid tyrosine. [1] Tyrosine, a semi-essential amino acid, derived from liberation

of tyrosine from hydrolysis of dietary or tissue protein, or from hydroxylation of the essential amino acid phenylalanine, and is the starting point for the synthesis of catecholamines, thyroid hormones, and melanogenesis. Showing the catabolic sequence of tyrosine metabolism involving the 5 important enzymes. Any defects with these enzymes correspond to various inborn errors. In humans, hypertyrosinemia is defined by elevated blood levels of >200 μM. [2] Several inherited and acquired conditions can cause hypertyrosinemia. Most can be diagnosed by clinical history, physical examination. Hereditary causes include deficiencies of the enzymes fumarylacetoacetate hydrolase (FAH), tyrosine aminotransferase, and 4-hydroxyphenylpyruvate dioxygenase (4-HPPD). Acquired hypertyrosinemia may occur in severe hepatocellular dysfunction (liver failure), scurvy (vitamin C is the cofactor for 4- HPPD), and hyperthyroidism [1].

From the salient features that our index case presented, several diseases were considered (Figure 3). Next figure shows the phenylalanine and tyrosine metabolic pathways and the enzymatic defects leading to the different types of hereditary Tyrosinemia (Figure 4). Mutations of tyrosine aminotransferases (TAT) lead to Tyrosinemia Type 2 also called Oculocutaneous Tyrosinemia. The enzymatic site of the defect in oculocutaneous Tyrosinemia is in the hepatic tyrosine aminotransferase (TAT, L-tyrosine-2-oxoglutarate aminotransferase) [3]. The ocular and the cutaneous lesions in this disease are the result of the accumulation of tyrosine. It is manifested by corneal thickening, developmental delay and hyperkeratosis of palms and soles [4]. Signs and symptoms not present in our patient. Mutations of this 4HPPD lead to Tyrosinemia Type 3 (Primary Deficiency of 4HPPD), manifested as asymptomatic to severe mental retardation and neurologic abnormalities. In symptomatic patients, developmental delay, seizures, intermittent ataxia, and self-injurious behavior have been reported. [3] But unlike our patient liver and renal abnormalities are absent.

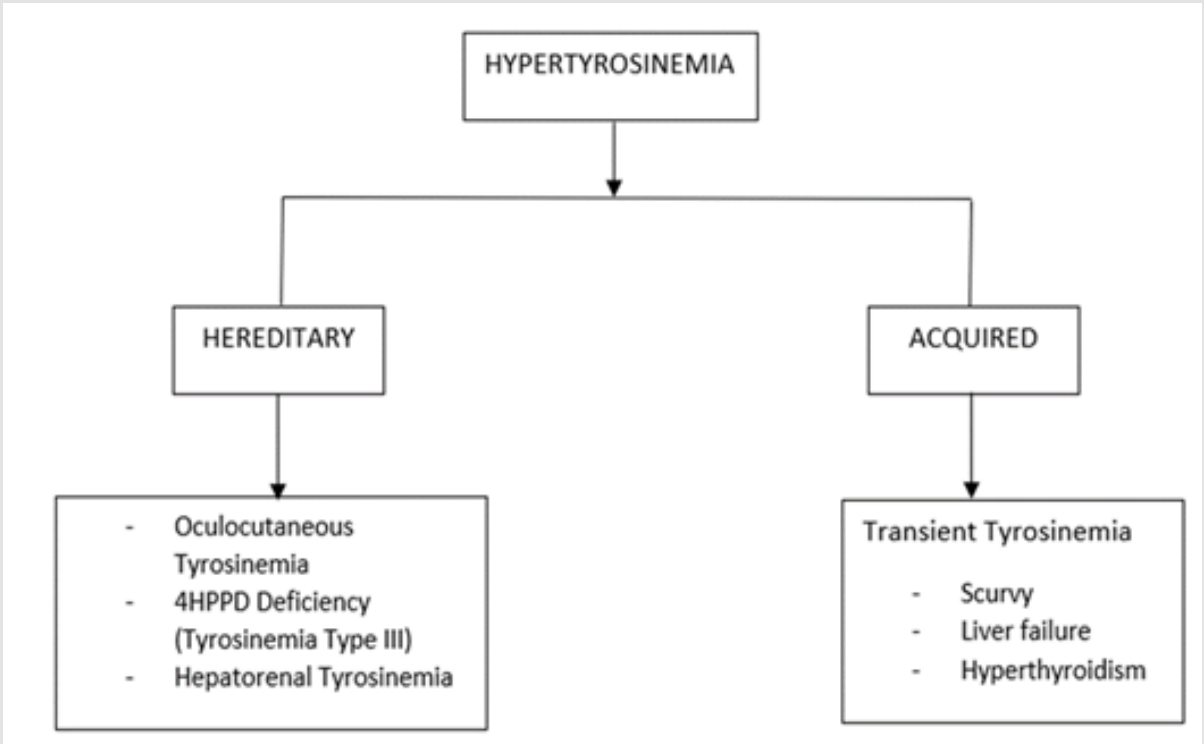

Figure 3: Causes of Tyrosinemia.

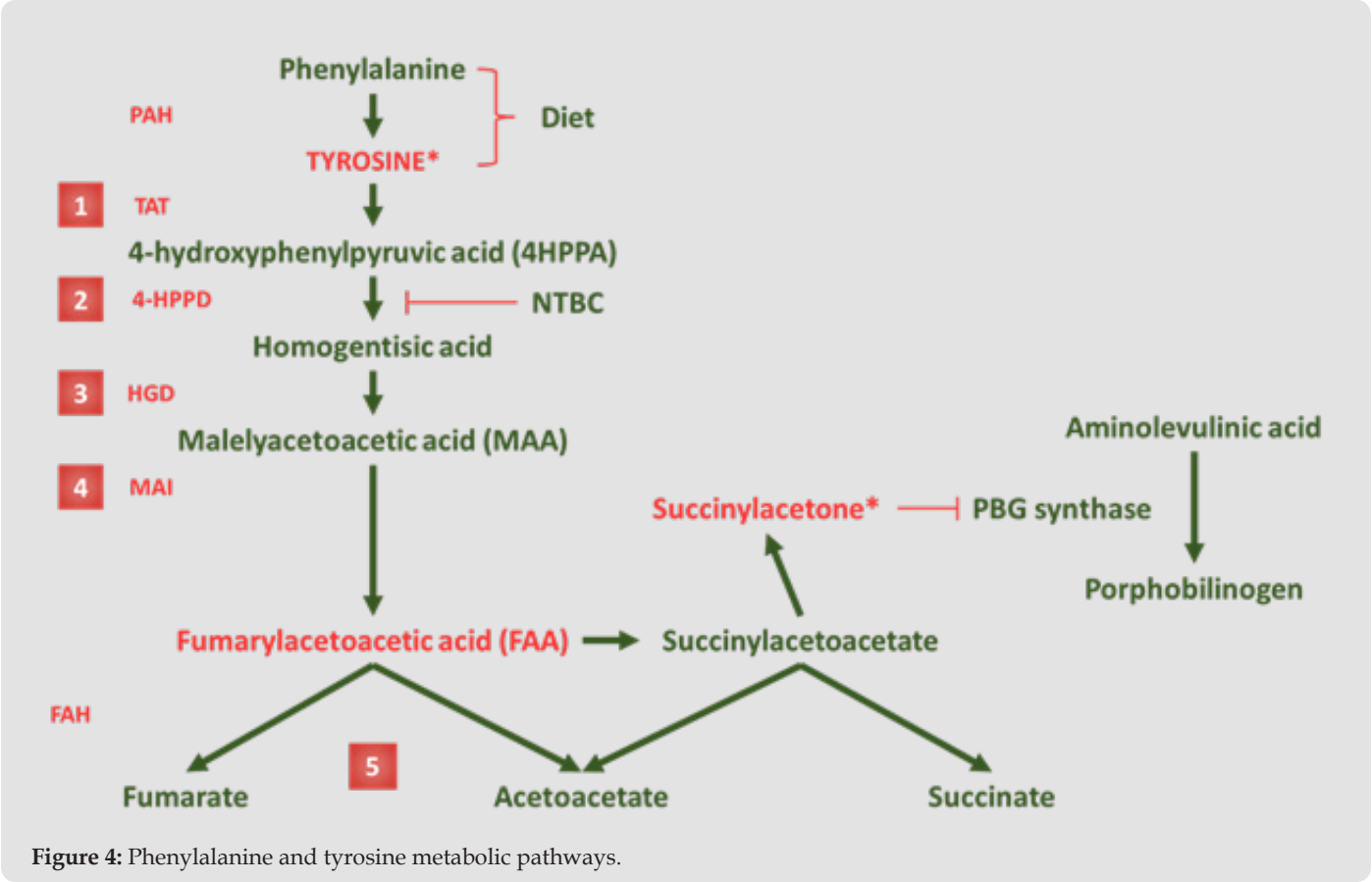

Figure 4: Phenylalanine and tyrosine metabolic pathways.

Transient Tyrosinemia of the newborn is the most common disorder of amino acid metabolism in humans. Risk factors for the development of transient tyrosinemia include prematurity, a high protein intake, and vitamin C (cofactor of 4HPPD) deficiency. Patients are usually asymptomatic and respond to ascorbate administration or resolve spontaneously on a normal diet, together with the absence of liver, renal, or cutaneous signs, distinguishes transient Tyrosinemia from other diseases. [3] Also, unlike in our patient, the liver is not affected in transient Tyrosinemia. Lastly, mutation in FAH gene results in hereditary Tyrosinemia type I. This enzyme is the terminal step in the tyrosine catabolic pathway. The abnormally accumulated products due to FAH deficiency are indicated along with their clinical effects. Toxic metabolites produced are the fumarylacetoacetate (FAA) and maleylacetoacetate (MAA) which in turn are converted to the toxic succinyl acetoacetate (SAA) and succinylacetone (SA). Succinylacetone is derived from accumulated succinyl acetate and is directly associated with renal and neurologic effects (Fanconi renal tubular syndrome, porphyric type crises) and directly inhibits the pathway for heme synthesis at the porphobilinogen synthase activity step. The accumulation of increased levels of δ-aminolevulinic acid is associated with the neurologic (porphyric-like) crises observed in untreated HT-1. Fumarylacetoacetate accumulation is directly associated with the observed ongoing hepatic and renal damage [3,4]. Like our patient, it presents hepatic involvement as shown by laboratory results of elevated AFP, alkaline phosphatase with deranged bleeding parameters, thus our final diagnosis is Tyrosinemia Type 1. Worldwide, Tyrosinemia type I affects about 1 in 100,000 individuals. This type is more common in Norway where 1 in 60,000 to 74,000 individuals are affected. Tyrosinemia type I is even more common in Quebec, Canada where it occurs in about 1 in 16,000 individuals. In the Saguenay-Lac St. Jean region of Quebec, Tyrosinemia type I affects 1 in 1,846 people [5].

According to the data from Center of Human Genetics, in the Philippines we have an incident of 1 in 397,395 live births. As of July 2022, we have a total of 13 patients diagnosed with Tyrosinemia Type 1 who are alive. Out of 13, 6 were from Visayas, 3 from Luzon and 4 from Mindanao and 1 of them is our patient. Tyrosinemia type 1 is in inherited in autosomal recessive manner. At conception, each sibling of an affected individual has a 25% chance of being affected, a 50% chance of being asymptomatic carrier, and a 25% chance of being unaffected. It involves the mutation in FAH gene located in long arm chromosome 15q25.1. In our patient, her DNA analysis showed a homozygous L41P missense mutation in the FAH gene. This type of mutation is not yet reported in any literature [5]. Clinically, Tyrosinemia type I may be classified based on the age of onset of symptoms. The acute form manifests before 6 months of age

(but rarely in the first 2 weeks of life) with acute liver failure. The subacute form presents between 6 months and 1 year of age with liver disease, failure to thrive, coagulopathy, hepatosplenomegaly, rickets and hypotonia. The chronic form of Tyrosinemia type 1 presents after the first year of life with chronic liver disease, renal disease, rickets, cardiomyopathy and porphyria-like syndrome. The patient in this case was classified as having the acute form of Tyrosinemia type I because of the presence of liver failure during the first month of life. Tyrosinemia type 1 is diagnosed through expanded newborn screening with succinylacetone (SA) assay. The presence of succinylacetone in blood and urine is pathognomonic.

Definitive diagnosis of the disorder is done by FAH enzyme assay and molecular testing of the FAH gene. Newborn screening is an essential public health strategy that enables the early detection and management of several congenital disorders, which if left untreated, may lead to mental retardation and/or death. Early diagnosis and initiation of treatment, along with appropriate long-term care help ensure normal growth and development of the affected individual. It has been an integral part of routine newborn care in most countries for seven decades now, either as a health directive or mandated by law. In the Philippines, it is a service available since 1996 and has been integrated into the public health delivery system with the enactment of Republic Act 9288 or the Newborn Screening Act of 2004. This NBS law has ensured

(1) That every baby born in the Philippines is offered NBS,

(2) The establishment and integration of a sustainable NBS system within the public health delivery system,

(3) That all health practitioners are aware of the benefits of NBS and of their responsibilities in offering it;

(4) That all parents are aware of NBS and their responsibility in protecting their child from any of the disorders in the panel.

In 1996, the panel of disorders included the following five disorders:

(1) Congenital Hypothyroidism (CH)

(2) Congenital Adrenal Hyperplasia (CAH)

(3) Galactosemia (GAL),

(4) Phenylketonuria (PKU)

(5) Homocystinuria (HCY)

In 2000, screening for HCY was discontinued due to lack of case finding. Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency and Maple Syrup Urine Disease (MSUD) was added in 2000 and 2012, respectively. In 2014, the Philippine NBS program expanded and increased the screening panel from 6 to 29 disorders, including Biotinidase deficiency, Cystic Fibrosis, Hemoglobinopathies, and selected amino acid disorders (including Tyrosinemia types 1,2 and 3), organic acid disorders and fatty acid oxidation defects (Padilla, et al, [6]). Under the expanded newborn screening program, confirmatory testing of the additional disorders shall be included in the ENBS fee of Php 1750.00. Additionally, medical metabolic milk formula shall be provided for free to all confirmed cases. Prior to introduction of newborn screening, diagnosis of Tyrosinemia type 1 was based on clinical findings. In retrospect, patient SA had ENBS with Succinylacetone assay, which revealed elevated succinylacetone and tyrosine levels. Urine organic acid analysis showed elevated N-acetyltyrosine and plasma amino acid analysis revealed elevated plasma tyrosine levels. The DNA analysis of this case showed a pathogenic variant in the FAH gene. Other diagnostic tests that are helpful in the diagnosis of Tyrosinemia type I include elevated AFP, increased serum transaminases, bilirubin studies, hypoglycemia, coagulation defects, and presence aminolevulinic acid in urine. The accumulation of toxic metabolites in Tyrosinemia type1 produces a number of severe clinical complications owing to their effects on multiple organs. The first attempt of treatment was diet restriction of phenylalanine (PHE) and tyrosine (TYR) to prevent accumulation of toxic metabolites.

The goal of nutrition management is twofold:

(i) Restrict the amino acids phenylalanine and tyrosine to maintain plasma amino acid concentrations within treatment range

(ii) Support normal growth and development. However, it is clear that hepatic disease may progress despite dietary treatment [5].

Therapy of Tyrosinemia type 1 consists of nitisinone in order to decrease levels of the toxic compounds. Nitisinone, was formerly known as NTBC (2-(2-nitro-4-trifluoromethylbenzol) cyclohexane 1-3, dione) and is the medical treatment of choice (Angilere, et al. [7]). It blocks para hydroxyphenylpyruvic acid dioxygenase (pHPPD), the second step in the tyrosine degradation pathway, preventing the accumulation of fumarylacetoacetate and its conversion to succinylacetone. It is generally prescribed at 1.0 mg/kg/day given in two divided doses. However, because of the long half-life (50-60 hours), affected individuals who are older than one year and stable may maintain adequate therapy with once-a-day dosing. Dosage should be adjusted to maintain blood nitisinone levels between 40 and 60 μmol/L, which theoretically blocks more than 99% of p-HPPD activity. As long as blood concentration of nitisinone is within the therapeutic range, urine succinylacetone does not need to be measured. Gladly, this medication is freely given to confirmed Tyrosinemia type 1 cases in the Philippines. Patient S.A was able to avail of this free nitisinone which she started taking at the age of 1 month. At the present, SA has good compliance with the medication. The natural history in children who are treated with nitisinone is different from that in untreated

children. Affected children younger than age two years who are treated with a combination of nitisinone and low-tyrosine diet are markedly improved compared to those children treated with low-tyrosine diet alone. The combined nitisinone and low-tyrosine diet treatment has resulted in a greater than 90% survival rate, normal growth, improved liver function, prevention of cirrhosis, correction of renal tubular acidosis, and improvement in secondary rickets.

Low-Tyrosine Diet

Nitisinone increases blood concentration of tyrosine, necessitating a low-tyrosine diet to prevent tyrosine crystals from forming in the cornea. Dietary management should be started immediately upon diagnosis and should provide a nutritionally complete diet with controlled intakes of phenylalanine and tyrosine using a vegetarian diet with low-protein foods and a medical formula such as Tyrex or Tyros. This special formula milk is also provided for free to confirmed Tyrosinemia cases in the country. The patient has good compliance with the medications, metabolic diet and regular clinical follow up at the newborn screening continuity clinic of SPMC. Her metabolic diet is prepared by the SPMC dietician. The meal plan fulfills the goal of total protein intake of 2.5 grams per kilo per day and a total caloric intake of approximately 110 calories per kilogram per day. Figure 16 shows the meal plan for the whole day at the age of 14 months. This meal plan consists of a total protein intake of 2.5g.kg/day, total caloric intake of ~1100 cal/day (110cal/kg/day), natural protein intake of 1.2g/kg/day. The Tyros milk can be given at a minimum of 17 scoops/day. SA is also supplemented with vitamins and minerals.

Liver Transplantation

Prior to the availability of nitisinone for the treatment of Tyrosinemia type I, the only definitive therapy was liver transplantation. It should be reserved for those children who (1) have severe liver failure at clinical presentation and fail to respond to nitisinone therapy or (2) have documented evidence of malignant changes in hepatic tissue.

Genetic Counseling

Part of the overall management of every genetic disorder is to conduct genetic counseling. It is a process of helping people understand and adapt to the medical, psychological and familial implications of genetic contribution to disease. As for our patient, at 1 month old, she was referred for genetic counseling due to diagnosis of Tyrosinemia Type I. Genetic counseling via videoconferencing was done with both parents and the following concerns were discussed: Limited financial resources in the family; Parents were unfamiliar of the condition, felt isolated and anxious as they described the condition as "rare" and something that requires a lot of attention; Recurrence Risk / Future Pregnancy Plans; Concerns on the access and availability of treatment. Families receiving a diagnosis of rare genetic conditions may experience isolation and anxiety. Hence, networking or connecting parents to support groups is highly encouraged. The family was endorsed to the TYR1 Philippines support group in facebook application and to the Philippine Society of Orphan Disorders (PSOD) for an opportunity to share personal experiences and feelings, coping strategies or firsthand information about the disorder or treatment.

Long-Term Follow Up

Frequent evaluation of the following parameters is typical in the management of individuals with Tyrosinemia type I. (Figures 5 & 6) shows the table from a study conducted by King et. Al, which shows the recommended monitoring schedule for Tyrosinemia type 1cases. Monitoring of the Growth and development of our patient is also a part of the monitoring of all patients diagnosed with a metabolic disorder. For patient SA, her length, weight, and head circumference were all normal for age. In October 2014, the Department of Health (DOH) ordered for an establishment of newborn screening continuity clinics (NBSCC) in each region of the country to facilitate continuity of care of confirmed patients in its area of coverage. The clinic is based in a tertiary hospital identified by the DOH to be part of the National Comprehensive Newborn Screening System Treatment Network. The clinic is equipped to facilitate the continuity care of confirmed NBS cases in their area of coverage. Each clinic is run by a full-time nurse and pediatrician. Currently, there are 15 continuity clinics handling the long-term care of confirmed cases in the country. The NBSCC in the Davao region is hosted by SPMC and this is the clinic that handles the long-term follow-up care of SA. She has regular tyrosine level monitoring which is free of charge. (Figures 6 & 7) shows the monthly tyrosine and succinylacetone monitoring during the first year of life. This graph above showed her monthly levels of tyrosine. Since diagnosis, the patient's tyrosine levels were within normal limits except in August 2021 where the patient had infection and was in a high catabolic state explaining the elevated result at 642. The graph above shows her monthly levels of Succinylacetone which were maintained within normal limits. The graph above shows her monthly monitoring of Phenylalanine (PHE) levels with normal values of 20-80umol/L. There were 4 instances that Phenylalanine levels were below the normal limits, which were addressed by adjusting the diet and medications accordingly (Figure 8).

DOI: 10.26717/BJSTR.2023.48.007606

Evaluation	Initiation of therapy (baseline)	First year of life		From 1 year to 5 years of age			After 5 years of age
		Monthly	Every 3 months	Every 3 months	Every 6 months	Yearly	
HT-1 markers							
Blood succinylacetone[a] (plasma/ blood on filter paper)	x	x[b]		x			Every 6 months
Urine succinylacetone (only if blood is not available)	x	x		x			Every 6 months
Blood NTBC concentration[a]		x		x			Every 6 months
Plasma amino acids (plasma/ blood on filter paper)	x	x[b]		x			Every 6 months[c]
Laboratories for HT-1 monitoring							
CBC: hemoglobin, hematocrit, WBC, platelet count	x		x			x	Yearly
Liver evaluation							
Serum AFP concentration	x	x			x		Every 6 months[d]
PT	x	x[e]				x	Yearly
PTT	x	x[e]				x	Yearly
ALT/AST	x		x[e]			x	Yearly
Imaging: CT or MRI (with contrast) or ultrasound[f,g]	x					x[c]	Yearly[c]
Renal studies							
Renal imaging (ultrasound)[h]	x						
Blood chemistries: bicarbonate, BUN, creatinine	x					x	Yearly
Blood calcium and phosphate	x					x	Yearly
Urine analysis	x						
Standard dietary management laboratories: if not included above, see text for more information							
Developmental evaluation/ neuropsychology assessment							Before school age
Ophthalmology: slit-lamp examination	When symptomatic or at increased risk (see text for more information)						

Figure 5: Evaluation and follow-up of HT-1 patients identified by newborn screening.

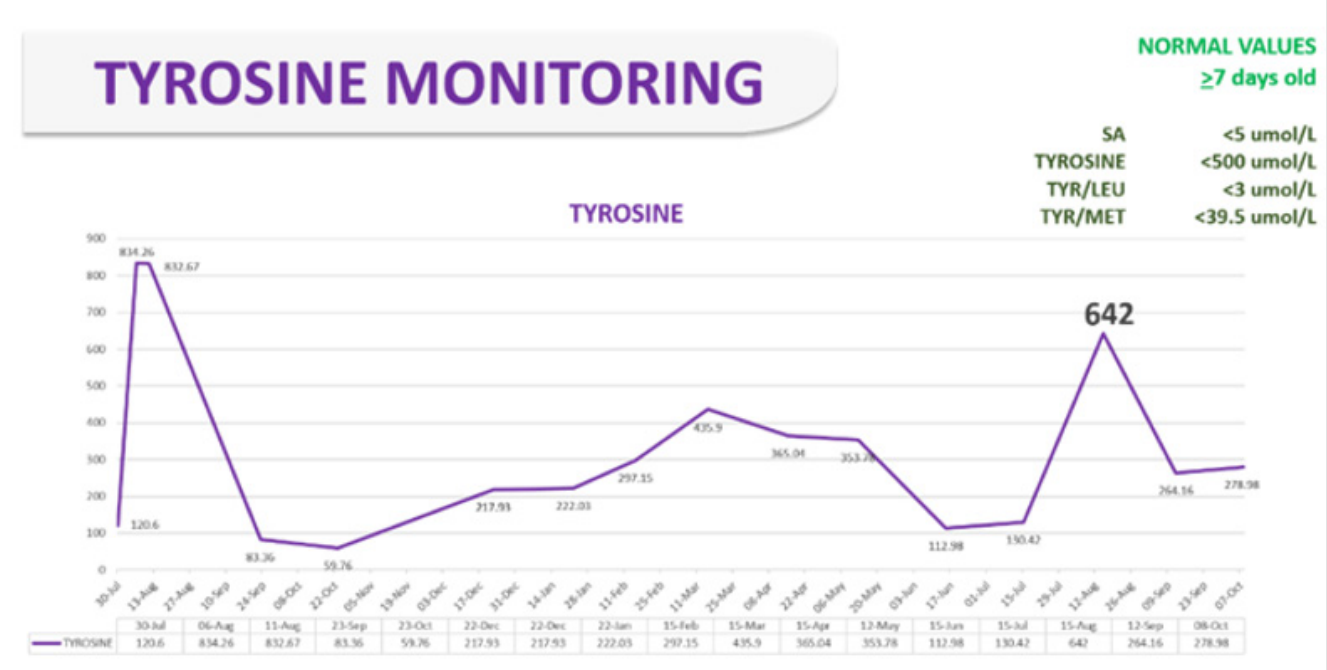

Figure 6: Monthly monitoring of Tyrosine levels.

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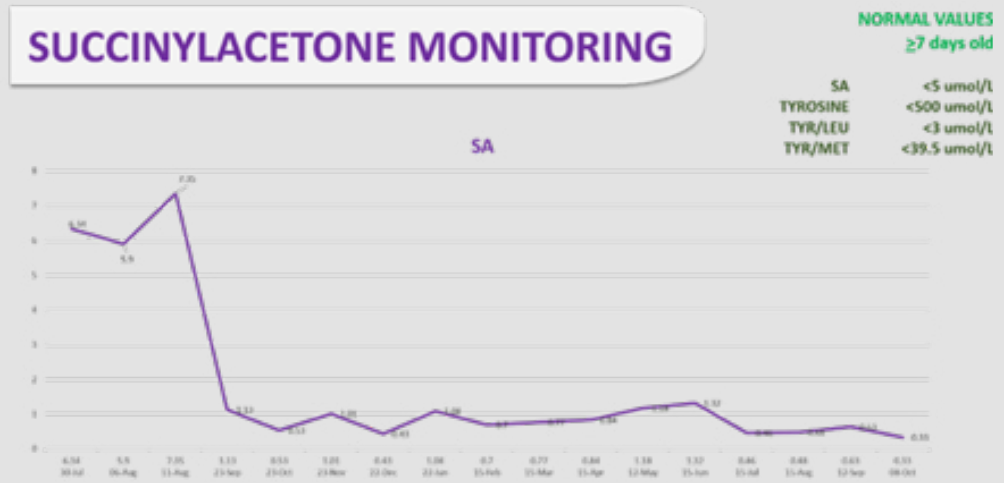

Figure 7: Monthly monitoring of SA levels.

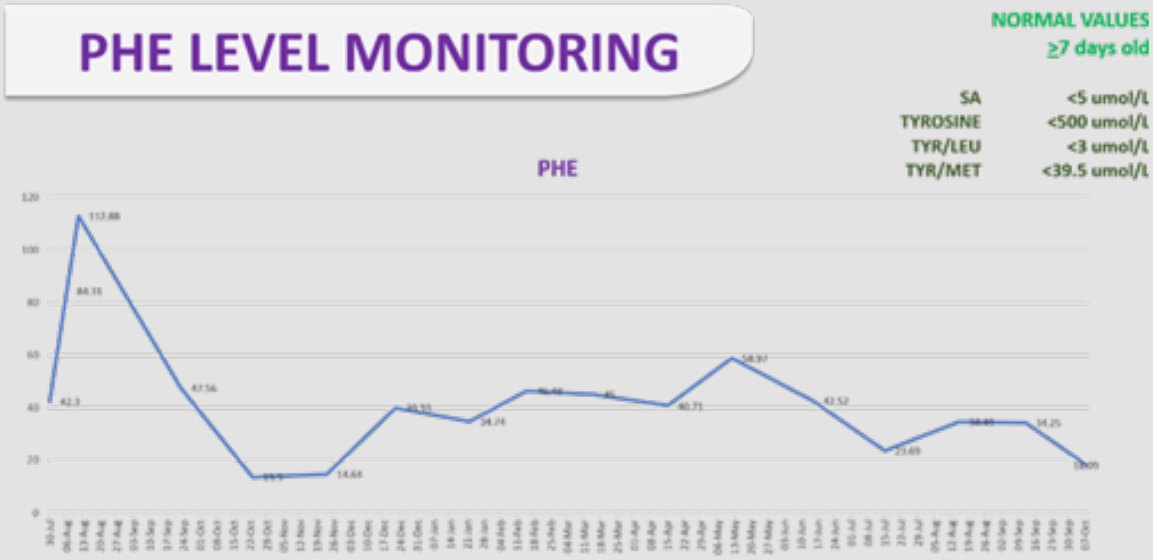

Figure 8: Monthly monitoring of Phenylalanine levels.

Prognosis

For children who were not detected by newborn screening, Tyrosinemia type I usually presents either in young infants with severe liver involvement or later in the first year with liver dysfunction and significant renal involvement, growth failure, and rickets. Growth failure results from chronic illness with poor nutritional intake, liver involvement, and/or chronic renal disease. Most patients present between 2 and 6 mo of age but rarely may become symptomatic in the 1st month or appear healthy beyond the 1st yr of life. Earlier presentation confers poorer prognosis. The 1-yr mortality of untreated children, which is approximately 60% in infants developing symptoms before 2 months of age, decreases to 4% in infants who become symptomatic after 6 months. Death in the undetected or untreated child usually occurs before age ten years, typically from liver failure, neurologic crisis, or hepatocellular carcinoma. According to a journal written by Skaricic, Et al., states that untreated, the disease eventually progresses to liver or kidney failure and generally results in a fatal outcome. Expedient diagnosis is critical because an early start of treatment can increase the likelihood of a positive outcome [8-10].

Conclusion

Tyrosinemia type 1, and its complications can be prevented by early detection through expanded newborn screening. Early institution of management following diagnosis during the newborn period is achievable since costs of confirmatory testing and treatment with special milk formula and nitisinone is already covered by the Philippine newborn screening program. The clinical course of the patient emphasizes the need for early detection of Tyrosinemia type 1 through newborn screening. The case illustrates how early diagnosis and management can improve patient outcomes and delay disease progression. The goal of saving Filipino newborns for common life-threatening heritable disorders is achieved by the continuous efforts of all stakeholders of the Philippine newborn screening program. Genetic Counseling has been helpful for parents to adapt and understand the medical, psychological and familial implications of their DNA results, most especially in understanding the recurrence risks, and the probable carrier status of other children.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2023.48.007606

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