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Case Report (Pages: 20353-20371)

Porphyria-like Neurological Crises and Fanconi Syndrome-Type Renal Tubular Disorder in An Undiagnosed Case of Chronic Tyrosinemia Type 1: A Case Report and Review of the Literature

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Abstract

Background: Tyrosinemia type 1 (TYRSN1) is an autosomal recessive metabolic disease that occurs due to a defect in the enzyme fumarylacetoacetate hydroxylase. In the case of a defect in this enzyme, toxic metabolites resulting from the breakdown of tyrosine accumulate in vital organs, leading to various symptoms and problems in these patients.

Case Presentation: A 3-year-old boy was admitted to the hospital with confusion, constipation, vomiting, abdominal pain, fever, oliguria, and anorexia. On examination, hypertension, genu varum, abnormal gait, and urinary retention were observed. Laboratory tests revealed hypoglycemia, glucosuria, metabolic acidosis, anemia, hypokalemia, and hypocalcemia. Ultrasound and CT scans revealed large kidneys and a heterogeneous liver with multiple nodules. Additional tests revealed elevated alkaline phosphatase, a high alpha-fetoprotein level, hypophosphatemia, and increased urinary excretion of phosphorus and potassium. Hand radiography also revealed rickets. Due to suspicion of hereditary diseases of amino acid metabolism, blood and urine chromatography revealed a marked accumulation of tyrosine. The diagnosis of chronic TYRSN1 was confirmed by measuring high urinary excretion of succinylacetone. The patient was treated with nitisinone and a restricted diet of tyrosine and phenylalanine, and within 1 week, he showed a dramatic response to treatment.

Conclusion: Our patient was a case of chronic TYRSN1 who, owing to a lack of timely diagnosis, had symptoms of neurological crises similar to acute porphyria, as well as symptoms of Fanconi syndrome-type renal tubular disorder and rickets. Due to the rarity of this disease and its diverse clinical manifestations, its diagnosis is challenging in countries such as Iran, where screening for this disease is not routinely performed, and most patients are diagnosed when they have severe complications.

Key Words: Fumarylacetoacetate deficiency, Neurological crises, Tyrosinemia type 1.

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1- INTRODUCTION

Hereditary tyrosinemia type 1 (TYRSN1, OMIM 27670), or hepatorenal tyrosinosis, is an autosomal recessive metabolic disease (aminoacidopathy) that occurs due to a defect in the enzyme fumarylacetoacetate hydroxylase (FAH, EC.3.7.1.2) and is marked by the accumulation of tyrosine derivatives in body fluids and significant excretion into the urine (1, 2). In 1977, FAH was recognized as the deficient enzyme responsible for TYRSN1 (3). This enzyme is encoded by the FAH gene, which is located on chromosome 15 (15q25.1) and contains 14 exons (4); approximately 100 mutations associated with TYRSN1 have also been identified (5). The amino acid tyrosine can be ingested through food or synthesized in the human body from phenylalanine through the activity of phenylalanine hydroxylase (PAH). Tyrosine undergoes degradation through the action of five enzymes located in the cytosol of liver cells, and in the final step of this process, the FAH enzyme breaks down fumarylacetoacetate (FAA), a toxic metabolite, into fumarate and acetoacetate. With a deficiency in the FAH enzyme, toxic intermediate metabolites resulting from the breakdown of tyrosine, such as FAA, succinyl acetoacetate (SAA), succinyl acetone (SA), and maleylacetoacetate (MAA), accumulate in the liver, kidney, and central nervous system (CNS) cells (6-8). These metabolites are thought to be genotoxic and carcinogenic, causing cellular oxidative stress, leading to cell and organ damage, and they can cause severe disruption of intracellular metabolism (1). Notably, the main cause of elevated tyrosine in body fluids is not due to a deficiency in FAH. This is because FAH is five steps away from the initial catabolic stage in the degradation of tyrosine, and the increase in blood tyrosine is most likely due to secondary inhibition of the proximal stages of metabolism and tyrosine breakdown, and not a deficiency of FAH (6, 9).

In TYRSN1 patients, the liver, kidney, and nervous system are most affected. The clinical presentation of TYRSN1 is heterogeneous and involves failure to thrive (FTT), hepatosplenomegaly, jaundice, vomiting, diarrhea, fever, coagulopathy, cardiomyopathy, neurological crises resembling acute intermittent porphyria (AIP), and a Fanconi syndrome-type renal tubular disorder with subsequent hypophosphatemic rickets, which may also occur in these patients (10-13).

2- CASE PRESENTATION

A 3-year-old boy was referred to the emergency department of our hospital with complaints of confusion, constipation, vomiting, periumbilical abdominal pain, fever, oliguria, and anorexia, which had started 5 days prior. The patient had a history of multiple hospitalizations due to similar symptoms and multiple episodes of hypoglycemia of unknown cause since the age of 1. These issues had not been further investigated and had been treated only symptomatically. According to the patient's parents, this episode of the patient's symptoms was much more severe than previous episodes. The patient was the third child in his family and was born to a 25-year-old mother at 39 weeks of gestation by cesarean section without any problems. His brother and sister had no history of problems similar to those of our patient and were healthy. His parents were also cousins who did not mention a history of similar diseases in themselves or their families. The patient had lost approximately 2 kg in weight in the last 2 months, and his current weight was 10 kg (percentile below 10%). His height was also measured as 95 cm (percentile 25%). The respiratory rate was 22 breaths per minute, and the pulse rate was 110 beats per minute. The rectal body temperature

was 38 degrees Celsius. Blood pressure was taken from both arms and was 130/75 mmHg, which was above the 95th percentile for this age. This measurement was repeated, yielding similar results, which confirmed the presence of hypertension (HTN). His vomiting was non-bloody and non-bilious, consisting only of food and water, and occurred immediately after consuming these substances. Abdominal pain was mostly in the periumbilical region and did not radiate to any specific body location. Abdominal palpation did not reveal any organomegaly or tenderness, but the bladder was completely distended due to urinary retention. Heart and lung auscultation were normal, with no pathological sounds heard. In the lower limbs, his legs exhibited a condition similar to genu varum, and he had an abnormal gait. His parents also stated that the child had dysuria and a foul odor in the urine for a long time. He was vaccinated according to the national vaccination program and had no postvaccination reactions in previous years. The patient was very ill and had difficulty staying awake and speaking. For this reason, with the history as mentioned above, he was immediately admitted to the pediatric intensive care unit (PICU) so that additional examinations could be started as soon as possible. To initially improve the patient's general condition, a urinary catheter was inserted to drain the patient's distended bladder, and the patient was also given serum therapy and intravenous nutrition, which led to a significant improvement in his general condition. Initial tests, including hematological, serological, and biochemical assessments, as well as urine analysis (U/A) with blood and urine culture, were ordered. The test results are detailed in Tables 1 and 2.

Table-1. Hematology data.

Hematology parameters	Result	Normal Range
WBC (mm*3) with diff results	8100	4000 -10000
Neutrophil	42% (3402)	-
Lymphocyte	50% (4050)	-
Monocyte	6% (486)	-
Eosinophil	2% (162)	-
RBC (10 6/µL)	4.0	4.2– 5.4
HGB (g/dl)	10	12 - 16
HCT (%)	31.8	36 – 46
MCV (FL)	79	77 – 96
MCH (pg)	25	26 – 32
MCHC (g/dl)	32	26 – 36
RDW (%)	15	11.5-14.5
PDW (%)	12.9	15-17
MPV (%)	10.7	7-11
Platelets (10 3/µL)	150	150 – 450
ESR (mm/h)	12	0 – 20
PT (sec)	15.5	10.5-13.5
PTT	69	-
INR (%)	1.36	0.85-1.15

Abbreviations: WBC: White blood cell, **RBC:** Red blood cell, **HGB:** Hemoglobin, **HCT:** Hematocrit, **MCV:** Mean corpuscular volume, **MCH:** Mean corpuscular hemoglobin, **MCHC:** Mean corpuscular hemoglobin concentration, **ESR:** Erythrocyte sedimentation rate, **RDW:** Red cell distribution width, **PT:** Prothrombin time, **INR:** International normalized ratio, **PTT:** Partial thromboplastin time, **MPV:** Mean platelet volume, **PDW:** Platelet distribution width

Table-2. Biochemistry and serological data.

Biochemical parameters	Result	Normal Range
Blood Glucose (mg/dl)	55	70 – 130
Blood Urea (mg/dl)	13	15 – 45
Uric Acid (mg/dl)	1.2	3.5-7.2
Creatinine (mg/dl)	0.4	0.6 – 1.3
K (mEq/L)	2.5	3.5 – 5.5
Ca (mg/dl)	8.6	9 – 11
Na (mEq/L)	138	135-145
CRP	Negative	-

Abbreviation: K: Potassium, **Ca:** Calcium, **Na:** Sodium, **CRP:** C-Reactive Protein

Urine and blood cultures were normal. In the U/A, severe glycosuria was reported. Arterial blood gas (ABG) also revealed metabolic acidosis, with pH=7.20, PCO2=28, and HCO3=15. A chest X-ray (CXR) was also taken, which revealed normal heart and mediastinal sizes, with no specific active pulmonary opacities noted. Additionally, cupping, fraying, and splaying were observed bilaterally on both sides of the proximal humerus, and widening was observed at the ends of the anterior ribs at the costochondral junction. These findings, along with genu varum in the lower limbs, increased the suspicion of rickets in him (Figure 1).

The patient's laboratory results revealed mild anemia, hypoglycemia, hypokalemia, and mild hypocalcemia. His blood glucose level was corrected with dextrose serum, and his serum potassium and calcium levels were also corrected. Following the correction of potassium, the patient's urinary retention improved, and urine flow was restored, so the urinary catheter was removed. However, the patient's abdominal pain, constipation, vomiting, and anorexia continued. Therefore, an abdominal and pelvic ultrasound was performed, which revealed a normal liver shape and size, with a span of 99 mm at the midclavicular line.

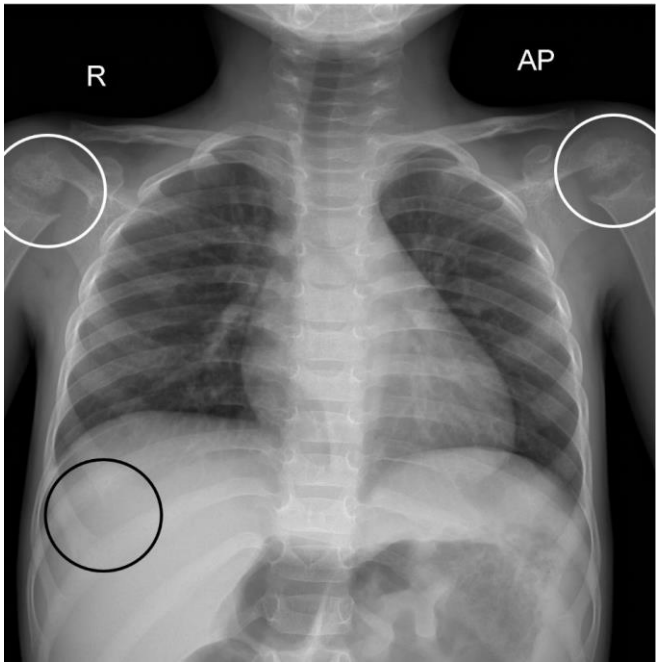

Figure-1: The patient's chest X-ray image shows widening of the anterior rib ends at the costochondral junctions (black circle), and cupping, fraying, and splaying on both sides of the proximal humerus (white circle).

The echogenicity of the liver parenchyma was heterogeneous, with hypoechoic, mass-shaped areas with a diameter of 3-15 mm scattered throughout the liver lobe parenchyma. The kidneys were larger than normal. The longitudinal diameter of the right kidney was 111 mm (normal range: 70- 80 mm), and the longitudinal diameter of the left kidney was 117 mm. Parenchymal echogenicity was increased, and corticomedullary differentiation was reduced. Other abdominal and pelvic organs had normal size and shape, and no other pathological findings were observed. Based on the results obtained from the ultrasound and to further examine the patient's liver and kidneys, a CT scan was ordered. On the CT scan, the liver was heterogeneous and contained multiple nodules and small hypodense foci throughout the liver (Figure 2). The kidneys were larger than normal and were free of stones or hydronephrosis (Figure 3). Other abdominal and pelvic organs appeared normal, and no free fluid was observed in the abdomen or pelvis. The heart and mediastinum appeared normal, and no specific pathology was detected in the lung or pleural fields.

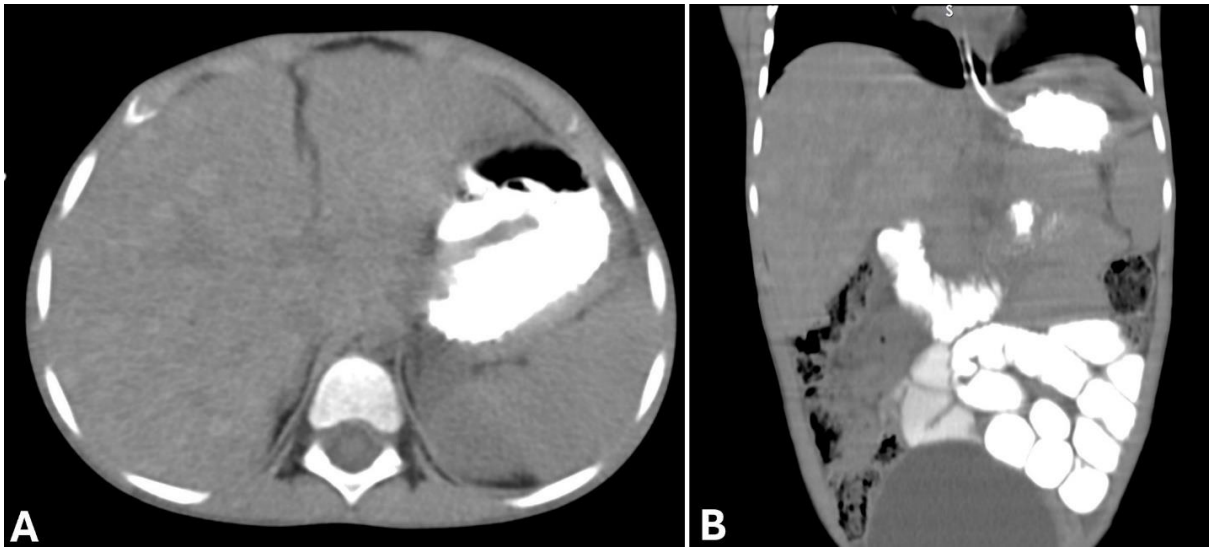

Figure-2: CT scan of abdominal organs in transverse (A) and coronal (B) views. The liver is heterogeneous and contains multiple nodules throughout the liver and small hypodense foci.

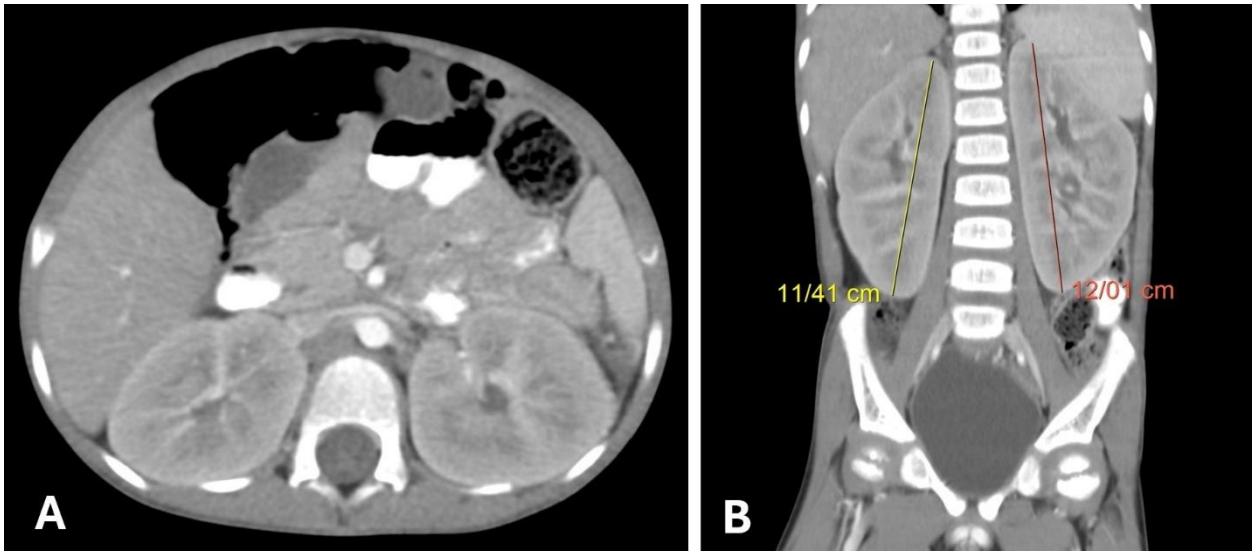

Figure-3: CT scan of abdominal organs in transverse (A) and coronal (B) views. The kidneys are larger than normal and are free of stones or hydronephrosis.

Due to the presence of multiple liver nodules, the patient underwent liver function tests along with additional tests, the results of which are listed in Table 3. Alkaline phosphatase (Alk.P) was increased, and alpha-fetoprotein was also measured at over 1000. Hypophosphatemia was also reported. Other liver tests were normal or only slightly increased. Given the patient's hypophosphatemic condition, suspicious findings on the patient's CXR (Figure 1), and genu varum in the lower limbs, the possibility of hypophosphatemic rickets was also increased. Therefore, an X-ray of the patient's hand was performed, which revealed cupping, fraying, and splaying of the distal ends of the radius and ulna, suggesting rickets secondary to hypophosphatemia in the patient (Figure 4).

After 3 days of hospitalization, the patient's abdominal pain, constipation, and vomiting improved somewhat, and he was able to start oral feeding. It was thought that the cause of the patient's hypokalemia was vomiting, but after resolving these symptoms, his hypokalemia recurred several times, and his serum potassium level decreased to less than 3.5, which indicated that vomiting was not the cause of this potassium excretion. Suspecting that the urinary excretion of potassium had increased. The patient's urinary ion excretion was examined, revealing phosphaturia (excretory fraction = 27%; normal range: <15%), explaining the patient's hypophosphatemia. Additionally, the urinary potassium/creatinine ratio was measured at 24.4 (normal range: <15-20), which indicated urinary potassium excretion and was the cause of the patient's hypokalemia.

The patient continued to have HTN during his hospitalization, with all of the readings above the 95th percentile for this age group, and the highest pressure measured was 130/70 mmHg, which did not respond to conventional drug treatment. For this reason, HTN-related tests were performed, in which renin, aldosterone, Adrenocorticotropic hormone (ACTH), and OH-17 progesterone levels were reported to be normal (Table 3).

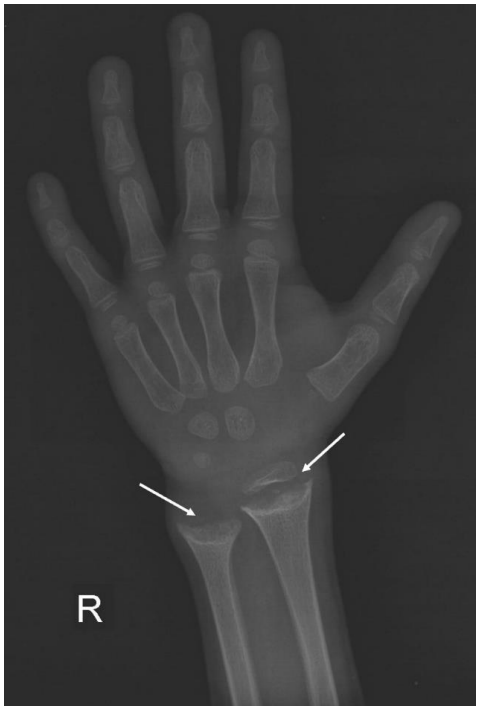

Figure-4: Cupping, fraying, and splaying of the distal ends of the radius and ulna (arrows), suggesting rickets secondary to hypophosphatemia**.**

Table-3. Biochemistry data.

	Result	Normal Range
AST (IU/L)	44	5-37
ALT (IU/L)	25	5-41
Alk.P (IU/L)	1717	180-1200
Bill Total	0.3	0.2-1.2
Bill Direct	0.2	0-0.4
Gamma-GT (U/L)	51	5-50
Albumin (g/dl)	3.8	3.5-5.5
Alpha-Fetoprotein (ng/ml)	1000 <	Less than 8.1
Beta-HCG (mIU/mL)	2 >	5.3 >
Cholesterol (mg/dl)	109	< 200 Desirable
Triglyceride (mg/dl)	74	Normal: < 150
Inorganic Phosphate (mg/dl)	1.6	3-6
Magnesium (mg/dl)	2.2	1.5-2.3
Phosphorus (mg/dl)	6	3.1-6
LDH (U/l)	488	225-500
25OH Vitamin D3 (U)	38	30-70
Ferritin (ng/mL)	5	30-300
OH Progesterone-17 (ng/ml)	0.8	0.2-0.8
ACTH (pg/ml)	20	7.2 - 63.6
Renin (ng/mL)	2	1.5-3.5
Aldosterone (ng/dL)	30	< = 40 (supine)
Anti-TTG (IgA)	3.7	18<
PTH (pg/mL)	30	10-65
TSH (mIU/L)	1.54	0.4-6
Free T4 (ng/dL)	1.5	0.8-2

Abbreviations: K: Potassium, **Ca:** Calcium, Na: Sodium, **CRP:** C-Reactive protein, **AST:** Aspartate transaminase, **ALT:** Alanine transaminase, **Bili:** Bilirubin, **Alk.P:** Alkaline phosphatase, **HCG:** Human chorionic gonadotropin, **LDH:** Lactate dehydrogenase, **ACTH:** Adrenocorticotropic hormone, **TTG:** Tissue transglutaminase, **PTH:** Parathyroid hormone, **TSH:** Thyroid-stimulating hormone.

Finally, by putting together the findings, including increased AFP, Alk.P, frequent hypokalemia, hypocalcemia, and hypophosphatemia in the context of phosphaturia and potassiumuria, metabolic acidosis, hypoglycemia, HTN, constipation, vomiting, abdominal pain, bad urine odor, fever, FTT, the family relationship of the parents, and liver and kidney involvement in the imaging studies, the suspicion of hereditary diseases of amino acid metabolism increased sharply. Therefore, in consultation with other pediatric specialists, High-Performance Liquid Chromatography (HPLC) analysis of blood and urine amino acids and urine succinylacetone (SA) excretion was performed for the patient. The results obtained are written in Tables 4 and 5. Figure 5 shows the results of HPLC analysis of blood amino acids.

Finally, due to the elevated blood tyrosine level, its very high urinary excretion, and elevated urinary SA excretion (1560 nmol/mmol creatinine, normal range: < 28), a diagnosis of tyrosinemia was confirmed. Since the patient's liver and kidneys are involved, the patient's tyrosinemia is very likely type 1 because liver and kidney disease have not been reported in tyrosinemia types 2 and 3, and our patient did not have symptoms associated with these two types (12).

Additionally, the onset of symptoms in this patient was gradual, and he had been experiencing symptoms since the age of 1; therefore, the chronic form of tyrosinemia

type 1 (TYRSN1) was considered for this patient. Immediately after diagnosis, empirical treatment was initiated with a dose of 10 mg Nitisinone (NTBC) per day (1 mg/kg/day) was started for the patient, and foods rich in phenylalanine and tyrosine were restricted from the diet. After one week of PICU hospitalization, he was transferred to the general pediatric ward.

Table-4. Blood amino acids high-performance liquid chromatography (HPLC) analysis.

Amino Acid	Result (µmol/L)	Reference (2-10 years)	Amino Acid	Result (µmol/L)	Reference (2-10 years)
Aspartic Acid	9	3-15	Alanine	398	158-314
Glutamic Acid	64	11-51	Tyrosine	493	34-82
Serine	154	77-169	Tryptophane	57	5-57
Glutamine	331	373-709	Valine	175	133-273
Histidine	68	54-106	Phenylalanine	88	35-67
Glycine	297	113-361	Isoleucine	46	31-83
Threonine	151	48-140	Leucine	95	64-164
Citrulline	20	18-50	Ornithine	110	24-64
Arginine	105	38-98	Lysine	181	77-181
Asparagine	65	24-64	Methionine	33	11-27

Table-5. Urinary amino acids high-performance liquid chromatography (HPLC) analysis.

Amino Acid	Result (mmol/mol Creatinine)	Reference (3-8 years)	Amino Acid	Result (mmol/mol Creatinine)	Reference (3-8 years)
Aspartic Acid	16	9-59	Alanine	600	15-97
Glutamic Acid	40	18-53	Tyrosine	1077	8-32
Serine	1207	40-94	Tryptophane	228	2-27
Glutamine	1917	45-165	Valine	37	2-12
Histidine	521	61-259	Phenylalanine	101	5-25
Glycine	7916	100-280	Isoleucine	18	1-7
Threonine	724	10-67	Leucine	47	3-22
Citrulline	72	1-23	Ornithine	24	1-8
Arginine	101	0-11	Lysine	1865	5-51
Asparagine	413	13-73	Methionine	5	2-8

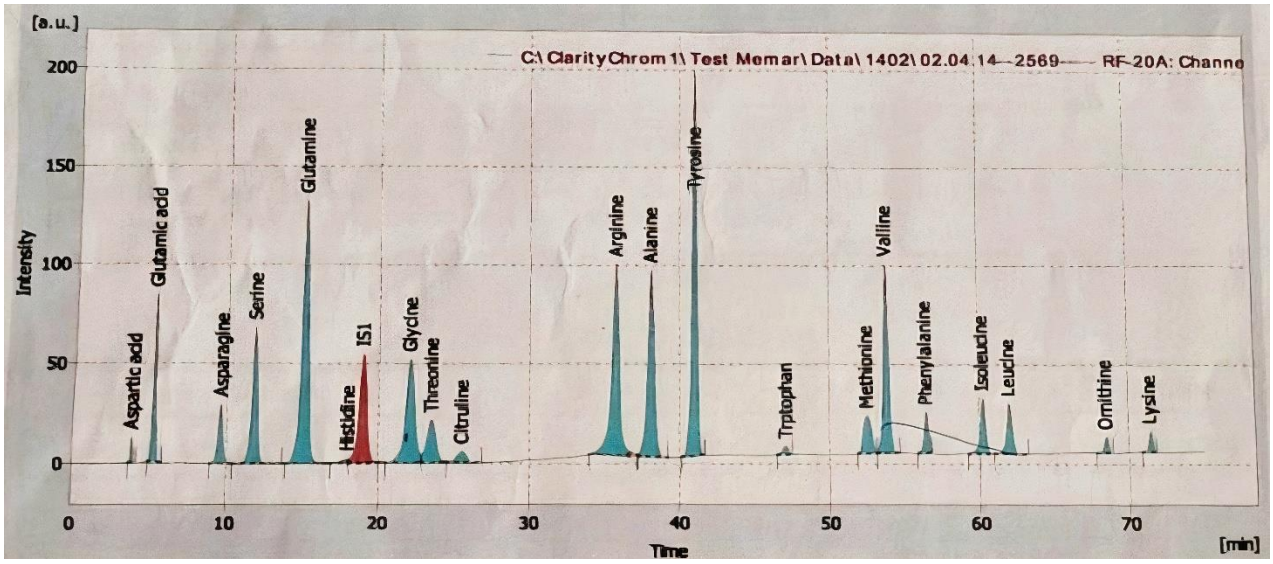

Figure-5: Blood amino acid chromatography.

One week after the start of treatment, he responded dramatically to the treatment, and HTN, constipation, vomiting, anorexia, metabolic acidosis, bad urine odor, hypokalemia, and other symptoms largely improved. Also, due to the high AFP, suspicion of hepatocellular carcinoma (HCC) in the context of tyrosinemia increased. Therefore, a liver biopsy was performed with parental consent, which was negative for HCC. The patient was discharged from the hospital after 15 days of hospitalization in good general condition. His parents were advised to take NTBC regularly and to follow a diet free of tyrosine and phenylalanine. They were also advised to return to the pediatric clinic within 1 month to reassess the patient's condition. Iron tablets were prescribed to improve the child's mild anemia, as well as phosphate, calcium, and vitamin D tablets to improve the patient's rickets. In addition to improving the child's developmental status and compensating for his FTT, powdered milk rich in organic and mineral substances and free of tyrosine and phenylalanine was added to the patient's medications. Molecular genetic testing to identify mutations in the FAH gene and ensure a definitive diagnosis of TYRSN1 was suggested to the patient's parents. On the patient's next visit to the pediatric clinic, he responded very well to treatment and was in good general condition. His anorexia, HTN, vomiting, constipation, and other symptoms had largely resolved, and the patient had gained 300 grams of weight in the past 1 month. Molecular genetic testing was performed at an outside center, which confirmed the mutation in the FAH gene and the definitive diagnosis of TYRSN1. The AFP level had fallen below 100 ng/ml. However, frequent follow-ups were emphasized. Additionally, due to the possible cognitive and neurodevelopmental effects of TYRSN1, his parents were advised to screen their child for possible problems by visiting the relevant centers. Finally, they were again advised not to discontinue the patient's treatment under any circumstances and to continue it for the remainder of his life to prevent the occurrence of irreversible and life-threatening complications.

3- DISCUSSION

In geographic areas without newborn screening, the prevalence of TYRSN1 is estimated to be approximately 1 case per 100,000 to 120,000 live births (14). There is significant variation in the prevalence of TYRSN1 in different parts of the world. Notably, across many countries, including Iran, there are no accurate statistics on the prevalence of TYRSN1. However, the highest prevalence reported is in a region of the province of Quebec, Canada, where the incidence of TYRSN1 in that region is 1 case for every 1,800 live births (10). TYRSN1 is classified as an autosomal recessive disorder, which results in an equal distribution across genders, affecting both men and women similarly (15). This disorder can be classified as acute, subacute, and chronic. However, clear boundaries between them are not defined. The acute type is considered the most common and severe form of TYRSN1, and patients are diagnosed before 2 months of age. In most cases, the initial manifestations of TYRSN1 appear within the first month of life, and infants present with symptoms such as FTT, jaundice, hepatomegaly, elevated liver enzymes, diarrhea, and vomiting due to difficulty in digesting high-protein foods, a tendency to bleed, and an odor similar to boiled cabbage. In the subacute form, the disease is diagnosed between 2 and 6 months of age, and the chronic form is diagnosed after 6 months of age and even in childhood, with complications of organ failure, such as liver failure, hypophosphatemic rickets, renal failure, and neurologic crisis, which include changes in mental status (6, 12, 16, 17).

In FAH deficiency, the main and important metabolite of tyrosine catabolism, FAA, accumulates in liver cells and leads to cell damage and apoptosis. It is also converted into SAA and SA. SA is directly associated with renal and neurological effects, such as Fanconi syndrome-type renal tubular disorder and acute porphyria-like crises. SA also interferes with the activity of various liver enzymes. This metabolite interferes with parahydroxyphenylpyruvic acid dioxygenase (p-HPPD) and leads to an increase in plasma tyrosine concentration. It also inhibits the second stage of heme biosynthesis by competitively inhibiting porphobilinogen (PBG) synthase, which leads to the accumulation of the amino acid δ-aminolevulinic acid (δ-ALA) in plasma and its increased urinary excretion. The accumulation of elevated levels of ALA is associated with the neurological crises observed in patients with untreated or poorly treated TYRSN1, which may occur at any age. Given the clinical and biochemical similarity of the neurological crises caused by TYRSN1 to acute AIP, this group of symptoms in patients is sometimes known as porphyria-like neurological crises (6, 10, 18). This is caused by axonal degeneration, secondary demyelination, and perhaps direct CNS neuronal/synaptic dysfunction (6). During severe crises, untreated or poorly treated children, like our patient, may experience recurrent neurologic crises lasting one to seven days, characterized by altered mental status, seizures, confusion, paralytic ileus with vomiting and constipation, extremity dysfunction, recurrent abdominal pain, peripheral neuropathy (acute neuropathic pain) with hypertonia, associated with HTN, hyponatremia (which at times is associated with seizures), autonomic dysfunction, painful paresthesia, self-mutilation, and muscle paralysis that may mimic the progressive ascending paralysis seen in Guillain–Barre syndrome, ultimately lead to respiratory muscle paralysis, which ultimately leads to mechanical ventilation-dependent respiratory and even death (2, 17, 19). Management of neurological crises primarily involves ensuring sufficient caloric intake, providing respiratory support if necessary, and addressing pain (20). Patients with TYRSN1, like our patient, may also experience multiple episodes of hypoglycemia, which could be due to hyperinsulinism or acute liver dysfunction (6).

A Fanconi syndrome-type renal tubular disorder in untreated TYRSN1 patients presents with aminoaciduria, glucosuria, phosphaturia, and renal tubular acidosis (RTA). The onset and severity vary among patients, but patients become symptomatic by 6 months of age (6, 21). FAA in proximal renal tubular cells, similar to hepatocytes, can cause oxidative stress, apoptosis, and cell death. Furthermore, it has also been demonstrated that SA can cause renal Fanconi syndrome by reducing the absorption of glucose and amino acids in the proximal renal tubules (22, 23). Long-term complications of renal tubulopathy in these patients include glomerulosclerosis, nephromegaly, nephrocalcinosis, chronic renal failure, and HTN. Initiation of treatment in patients with renal tubular dysfunction usually leads to improvement in renal function within 1 month (24, 25). Additionally, in patients with TYRSN1, hypophosphatemia follows phosphaturia, which may lead to secondary hypophosphatemic rickets. This condition is associated with bone softening and weakness and is treated by initiating standard treatment for tyrosinemia, as well as correcting acidosis, restoring calcium and phosphate balance, and administering vitamin D (15, 26). A study regarding renal involvement in TYRSN1 by Forget et al., involving 32 patients, reported findings such as aminoaciduria (82%), hypercalciuria (67%), tubular acidosis

(59%), nephromegaly (47%), renal hyperechogenicity (47%), nephrocalcinosis (16%), and reduced glomerular filtration rate (GFR) (48%) (24). Another study by Paradis et al. on eight TYRSN1 patients observed nephromegaly (50%), tubulopathy (80%), and vitamin D-resistant rickets (50%) (27). Bone marrow function may also be impaired in some TYRSN1 patients, such as our patient, leading to hematological disorders such as anemia, leukopenia, and thrombocytopenia (10).

Clinical symptoms typically begin before 2 years of age, but most patients show symptoms of the disease before 6 months of age. However, if the disease is not properly diagnosed and treatment is not started on time, and if the child reaches an older age, the risk of organ failure increases, as does the risk of developing liver nodules that have a high risk of progressing to HCC in 17–37% of affected children (6, 28, 29), and many of them die years later due to liver failure, episodes of metabolic crisis, HCC, or respiratory failure caused by porphyria-like neurological crises, which results in a life expectancy of less than 10 years for untreated patients (25, 30).

Significant progress in both diagnostic and therapeutic fields has markedly improved the prognosis of patients with TYRSN1. In 1992, the drug Nitisinone (2-[2-nitro-4-trifluoromethylbenzyol] 1,3-cyclohexanedione, NTBC) was introduced, becoming a viable treatment option for TYRSN1, before which orthotopic liver transplantation and dietary management were the only treatment options (31). In 1999, a clinical trial on the effect of NTBC in patients with TYRSN1 showed significant results (32). NTBC blocks the degradation of tyrosine at the early stages of its metabolic pathway by inhibiting the enzyme 4-hydroxyphenylpyruvate dioxygenase (HPPD), minimizes the formation of the toxic metabolites FAA, SAA, MAA, and SA, and improves the clinical condition of patients. NTBC at a dosage of 1 mg/kg/day should be initiated upon suspicion of TYRSN1, and the response to this drug is typically rapid, with clinical improvement occurring within one week (6, 33). Additionally, the risk of HCC and the development of severe liver disease can be reduced to less than 1% if NTBC treatment is initiated in early infancy and continues without interruption (6). Owing to the extended half-life of NTBC, a single daily dose is adequate for maintaining HPPD inhibition. However, there are no evidence-based guidelines for therapeutic targets, and the recommended plasma concentration of NTBC varies from 30 to 70 μmol/L. Some suggest that the lowest dose that completely suppresses urinary and plasma SA and results in biochemical control should be administered (34, 35). It has been reported that low plasma NTBC concentration is associated with a high risk of severe complications such as FTT, an increased likelihood of needing liver transplantation, and cognitive problems, despite undetectable urinary SA levels; therefore, monitoring plasma NTBC concentration and ensuring adequate dosage and treatment in these patients is essential (36). Some researchers propose that liver transplantation should be considered in cases where there is no response to NTBC therapy and a restricted diet after about one week, or when the disease is very severe and when the patient has severe liver complications, such as coagulopathy, develops HCC, and severe neurological issues, such as encephalopathy (6). Early treatment with NTBC reduces the need for liver transplantation in patients and improves kidney function after liver transplantation in those who require liver transplantation despite the use of NTBC (15). Treatment of TYRSN1 with NTBC should be accompanied by a phenylalanine- and tyrosine-restricted diet (21, 23, 31)

because a side effect of treatment with NTBC is the accumulation of tyrosine, whose crystals can be deposited in various tissues, which can produce ophthalmologic complications (including keratitis and corneal ulcerations), hyperkeratosis of palms and soles, and neurological symptoms (6, 10, 11). The reason for limiting phenylalanine intake in TYRSN1 is that approximately 75% of dietary phenylalanine is hydroxylated to form tyrosine by the enzyme PAH. Therefore, these patients should also limit phenylalanine intake in addition to limiting tyrosine (6). Experts in this field recommend that dietary tyrosine intake be limited to maintain plasma tyrosine concentrations in the range of 200–600 μmol/L. However, it is unclear whether there is a relationship between reduced tyrosine levels and the absence of clinical complications in TYRSN1 patients (6, 7, 10, 13). This combination therapy resulted in over 90% survival, normal growth, enhanced liver function, prevention of HCC, corrected RTA, and improvement of hypophosphatemic rickets (10). Despite the success of this treatment method in significantly improving patients, research shows that neurocognitive outcomes in these patients are unfavorable when they are managed with good metabolic control. Neurodevelopmental impairment includes reports of decreased IQ (intelligence quotient), learning disabilities at school, and impaired motor control (37). Garcia et al. reported a significant correlation between the phenylalanine-to-tyrosine ratio and IQ in school-age patients with TYRSN 1 (38). In a study by Bendadi et al. on ten TYRSN1 patients receiving nitisinone, the average total IQ score was significantly lower compared with that of their unaffected siblings. Also, no significant association was found between IQ score and either plasma tyrosine or phenylalanine concentration (39).

It is well known that TYRSN1 is associated with neurologic crises, and treatment with NTBC effectively reduces this risk. However, when patients discontinue the drug or take it irregularly, the risk of neurologic crises increases (18). A crucial aspect of treating TYRSN1 patients is the need for frequent follow-ups to monitor adherence to NTBC and dietary supplements. There are few studies on adherence to treatment in these patients, which have shown that treatment adherence, especially adherence to dietary guidelines, is usually less than optimal. González-Lamuño, Domingo, et al. In an observational study of 69 HT1 patients (7 adults and 62 children) who were treated with NTBC and a low-tyrosine, low-phenylalanine diet, the authors reported that adherence to both pharmacological and, in particular, dietary treatment was poor, and their data showed that NTBC levels were lower than recommended in more than one-third of patients (11). Patients and their parents should understand the treatment they are prescribed and the need for it, to be able to organize and take the medication as needed, tolerate some of the possible foreseeable side effects, and adhere to their treatment regimen in the long term (11, 40). We must keep in mind that there is no mild phenotype of this disease that does not require treatment, and timely diagnosis and treatment of this disease can prevent its irreversible complications to a large extent (12).

The diagnosis of TYRSN1 is based on the presence of the aforementioned clinical symptoms, increased plasma tyrosine, methionine, and phenylalanine, and increased levels of tyrosine metabolites, such as the presence of SA in urine and blood, SAA in urine, and aminoaciduria. It has also been described that the presence of 4-oxo-6-hydroxyheptanoic acid in urine can be pathognomonic for TYRSN1. The definitive diagnosis is confirmed through

molecular genetic testing aimed at identifying mutations in the FAH gene (2, 10, 41). In the evaluation of liver enzymes in patients with TYRSN1, increased levels of gamma-glutamyl transpeptidase (GGT) and AFP are usually observed. However, other liver enzymes (such as AST and ALT), as well as the serum bilirubin concentration, may remain normal or only slightly increased, similar to what was observed in our patient. In patients diagnosed with acute TYRSN1, the plasma concentration of AFP is often significantly elevated, and in patients with chronic TYRSN1, the AFP levels are often within the normal range. However, normal or high plasma AFP concentrations alone cannot be used to determine the acute or chronic course of the disease. In our patient, although the course of TYRSN1 was chronic, the plasma AFP concentration was high (7, 10, 41). The long-term risk of HCC is strongly associated with elevated serum AFP levels. Therefore, consistent measurement of AFP is highly important when following up patients with TYRSN1. However, normal serum AFP levels do not guarantee the absence of HCC, and imaging studies such as a CT scan or an MRI should also be performed. Additionally, elevated AFP levels should decrease continuously throughout the first year of treatment, and if AFP does not decrease consistently or if it increases, imaging should be performed immediately (6, 42). Prenatal diagnosis of TYRSN1 is possible by analysis of SA in amniotic fluid and by assaying FAH in cultured amniotic fluid cells or chorionic villus material (15).

In addition to TYRSN1, there are two other types of tyrosinemia. Type 2 tyrosinemia (Richner-Hanhardt Syndrome or oculocutaneous tyrosinemia) is caused by a deficiency of the enzyme tyrosine aminotransferase (TAT), which leads to increased plasma tyrosine levels and subsequent skin, eye, and neurodevelopmental problems in patients. It typically manifests in early childhood, and affected individuals have thickened, scaly, hyperkeratotic plaques on the skin of the palms of the hands and significant yellowish thickening and hyperkeratosis on the plantar surfaces of their digits. Ocular involvement has been observed in the form of keratitis, eye pain, redness, and photophobia. Also, mental and motor retardation have been observed in these patients (30). Tyrosinemia type 3 is the rarest type of tyrosinemia and is caused by a defect in the enzyme HPPD, an enzyme primarily expressed in neurons, neutrophils, the kidney, and liver cells. Few patients have been identified and reported, and therefore, their clinical phenotype is not yet well defined. However, these patients also have very high blood tyrosine levels and have neurological (such as ataxia and seizures, mental and motor retardation), skin, and eye symptoms, but do not present with liver disease or renal tubular dysfunction (6, 10, 30). The most prominent feature of TYRSN1, which distinguishes it from types 2 and 3 tyrosinemia, is liver and kidney involvement and increased serum SA, tyrosine, and methionine levels, which are key diagnostic signs for TYRSN1 (12).

Most published case reports support the hypothesis that porphyria-like neurological crises usually occur due to irregular or discontinued NTBC use or disease progression. Our patient presented a unique challenge in that neurological symptoms appeared as the first manifestation of the disease, and prompt diagnostic workup and administration of NTBC resulted in rapid clinical improvement in this patient. This highlights the importance of considering TYRSN1 in the differential diagnosis of unexplained neurological crises in children with abnormal liver and kidney function to ensure timely intervention and prevent fatal outcomes (17, 19, 37).

In countries where TYRSN1 is not part of their newborn screening program, TYRSN1 is usually diagnosed based on clinical symptoms along with biochemical findings and by identifying gene mutations in the FAH gene. In countries where assessment for TYRSN1 is part of the routine newborn screening program, TYRSN1 is typically diagnosed before the onset of symptoms, often at one month of age (10, 11). Starting treatment for these patients in the first months of life prevents damage to vital organs and the need for liver transplantation. However, in many countries, including Iran, where this disease is not included in the newborn screening program, TYRSN1 is most often diagnosed when clinical symptoms manifest as severe organ damage, and patients face irreversible and life-threatening complications. Therefore, having a national or global newborn screening program for the early diagnosis of TYRSN1 is very important.

Figure 6 shows the pathway of tyrosine metabolism along with its related abnormalities. A brief description of this figure is given below. The amino acids phenylalanine and tyrosine enter the human body through dietary sources, such as meat and dairy products. Additionally, phenylalanine can be converted into tyrosine by the enzyme PAH (6, 8). A deficiency in this enzyme may lead to the condition known as phenylketonuria (PKU) (25). Tyrosine is converted to 4-hydroxyphenylpyruvate by the enzyme TAT, and a deficiency in this enzyme leads to tyrosinemia type 2 (30). 4-hydroxyphenylpyruvate is converted to homogentisic acid by the enzyme 4-hydroxyphenylpyruvate dehydrogenase (HPPD). A deficiency in this enzyme results in tyrosinemia type 3 and hawkinsinuria (20, 25). This enzyme is also a key enzyme inhibited by NTBC. Keratitis is not observed in untreated TYRSN1 patients; however, the administration of NTBC therapy results in increased blood tyrosine levels, potentially causing ophthalmologic issues such as keratitis (6). Homogentisic acid is converted to MAA by the enzyme homogentisic acid dioxygenase (HGD), and a deficiency in this enzyme leads to alkaptonuria (AKU). MAA is converted to FAA by the enzyme maleylacetoacetate isomerase (MAI), and a deficiency in this enzyme leads to maleylacetoacetate isomerase deficiency (MAAID) (25). FAA is converted to fumarate and acetoacetate by the enzyme FAH, and a deficiency in this enzyme leads to TYRSN1. Following a deficiency in the FAH enzyme, FAA and MAA accumulate in the body and lead to symptoms related to tyrosinemia. FAA and MAA are also converted to SAA, which in turn is converted to SA and succinate (1, 6, 7). SA is an extremely potent competitive inhibitor that interferes with various liver enzymes. This metabolite interferes with the enzyme HPPD and leads to increased plasma tyrosine. This metabolite also inhibits the second stage of heme biosynthesis by inhibiting the enzyme PBG synthetase, which leads to the accumulation of the amino acid δ-ALA in plasma and its increased urinary excretion. The accumulation of elevated levels of ALA is associated with neurological crises similar to acute intermittent porphyria observed in patients with untreated or poorly treated TYRSN1. It has also been shown that SA can cause Fanconi syndrome-type renal tubular disorder by reducing the absorption of glucose and amino acids in the proximal renal tubules (10, 18).

4- CONCLUSION

Due to the rarity and very low prevalence of TYRSN1, as well as its diverse clinical symptoms, this disease is rarely included in the differential diagnosis of patients with similar symptoms by physicians.

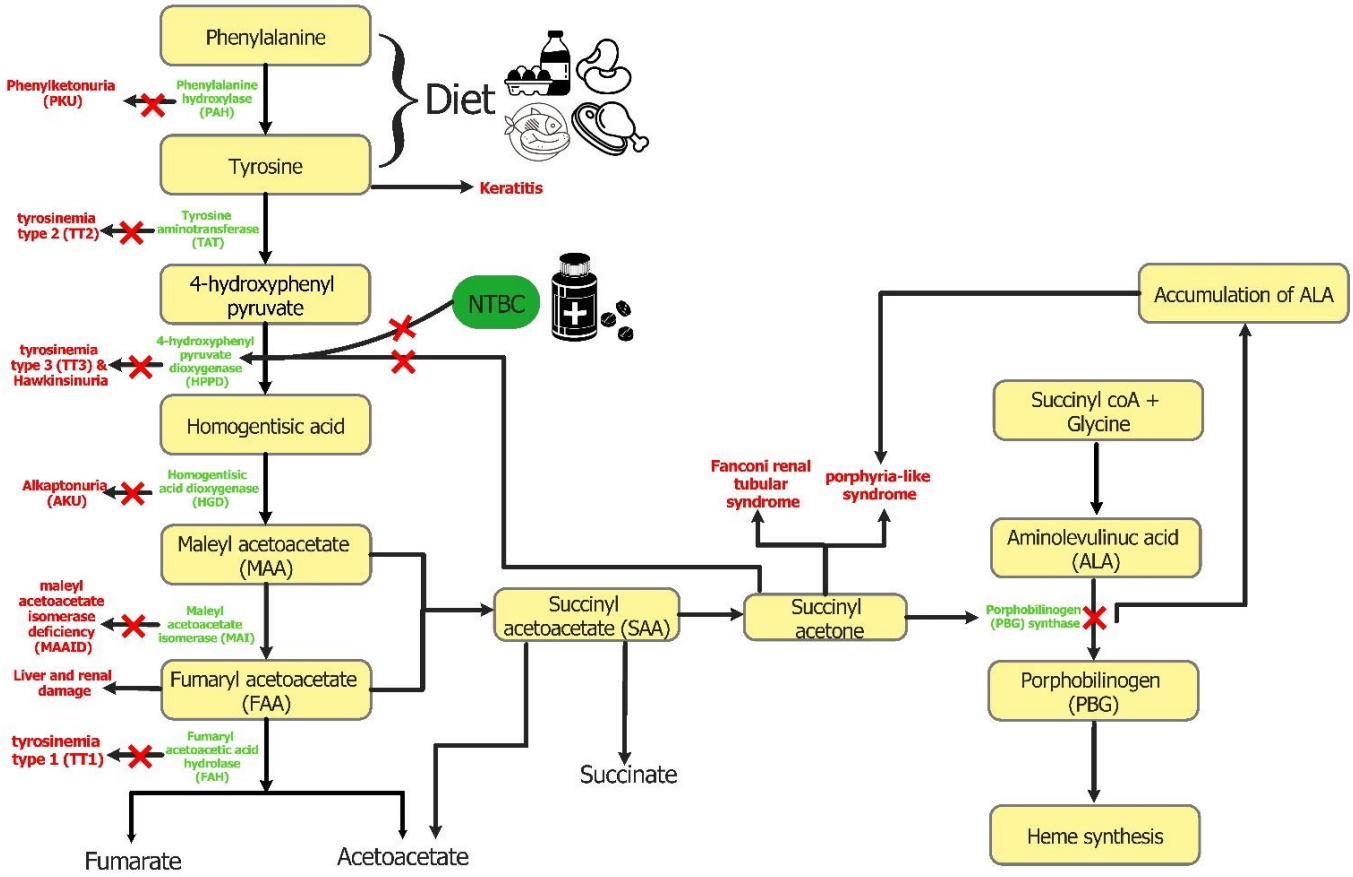

Figure-6: The tyrosine metabolism pathway and its related abnormalities.

Early diagnosis is very important for preventing various life-threatening complications of this disease. Therefore, this case report emphasizes the need for physicians to be vigilant in including TYRSN1 in their differential diagnosis of patients with similar symptoms. Additionally, countries' health care systems must understand the importance of screening children for this disease so that patients can be diagnosed at an early stage. We should also consider that in patients diagnosed with TYRSN1, treatment adherence should be routinely monitored to prevent complications resulting from discontinuation of treatment or inadequate treatment.

5- ABBREVIATIONS

TYRSN1: Tyrosinemia type 1; **FAH:** fumarylacetoacetate hydroxylase; **FAA:** fumarylacetoacetate; **SAA:** succinyl acetoacetate; **SA:** succinylacetone; **CT:** compound tomography; **PAH:** phenylalanine hydroxylase; **MAA:** maleylacetoacetate; **CNS:** central nervous system; **FTT:** failure to thrive; **AIP:** acute intermittent porphyria; **HTN:** hypertension; **PICU:** pediatric intensive care unit; **U/A:** urine analysis; **ABG:** Arterial blood gas; **CXR:** chest X-ray; **Alk.P:** alkaline phosphatase; **HIV:** Human immunodeficiency virus; **HPLC:** High Performance Liquid Chromatography; **HCC:** hepatocellular carcinoma; **AFP:** Alpha-Fetoprotein; **p-HPPD:** parahydroxyphenylpyruvic acid dioxygenase; **PBG:** porphobilinogen; δ-**ALA:** δ-aminolevulinic acid; **RTA:** renal tubular acidosis; **NTBC:** Nitisinone, (2-[2-nitro-4-trifluoro-methylbenzyol] 1,3 cyclohexanedione), **TAT:** tyrosine aminotransferase.

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8- CONFLICTS OF INTEREST

The authors have no conflicts of interest.

9- ETHICAL STATEMENT AND CONSENT TO PARTICIPANTS

The present study was approved by the Medical Ethics Committee of Biomedical Research, Ardabil University of Medical Sciences, under ethical code IR.ARUMS.REC.1404.177.

10- CONSENT FOR PUBLICATION

Written informed consent was obtained from the patient's parents for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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