Clinical Spectrum of Hereditary Tyrosinemia Type 1 in a Cohort of Pakistani Children

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ABSTRACT

BACKGROUND: Hereditary Tyrosinemia Type 1 (HT1), a rare autosomal recessive metabolic disorder, arises from fumarylacetoacetate (FAH) enzyme deficiency, resulting in toxic metabolite buildup. It manifests in acute, subacute, and chronic forms, with early diagnosis and Nitisinone treatment being vital.

OBJECTIVES: The study aims to highlight the different clinical presentations of Hereditary Tyrosinemia type 1 in a cohort of Pakistani children.

DESIGN: Retrospective observational study.

METHODOLOGY: All patients diagnosed with HT1 at Shifa International Hospital, Islamabad and Pak Emirates Military Hospital, Rawalpindi between 2010 and 2023 were included. Information was collected regarding age, gender, symptoms, physical signs, and laboratory results.

RESULTS: The study identified 6 cases of HT1. The average age at presentation was 8 months, with a mean delay in diagnosis of 26.8 months. Males were 4 (66.7%) and 2 (33.3%) were females. All patients had underlying liver disease presenting as abdominal distension with hepatosplenomegaly and accompanying growth failure. Four cases presented with rickets, 2 of which had hypophosphatemic rickets. Urine for succinylacetone was raised in all patients. Alpha fetoprotein was raised but hepatocellular carcinoma was diagnosed in 1 patient only. Low protein diet, and vitamin supplements were used for management. Five of the 6 patients died within 2 years of diagnosis.

CONCLUSION: Delayed referrals and unavailability of Nitisinone are the major challenges in diagnosing and treating HT1 in Pakistan.

KEYWORDS: Hereditary tyrosinemia type 1, Pakistan, rickets, hepatosplenomegaly, fumaryl acetoacetate hydrolase, liver failure

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Introduction

Hereditary tyrosinemia type 1 (HT1), also referred to as hepatorenal tyrosinemia, results from a shortage of the enzyme fumarylacetoacetate hydrolase (FAH), which is the final enzyme in the degradation pathway of tyrosine.[1] This enzyme's stability is critical for its function, as it predominantly exists in an active dimeric form while its monomeric state remains inactive and prone to aggregate formation.[2] It is an autosomal recessive condition, and is confirmed by documenting elevated plasma or urinary concentration of succinylacetone.[3] Deficiency of FAH causes toxic intermediary metabolites succinylacetone, maleylacetoacetate, and fumarylacetoacetate to accumulate.[1] The genetic mutations responsible for this disease occur in the FAH gene, with previously known as well as novel mutations being reported in Pakistan.[4]

The global prevalence of HT1 is estimated to be around 1 in 100 000 individuals. In certain regions where the occurrence of HT1 is notably greater, the projected occurrence of individuals carrying a particular mutation can be up to 1 out of 14 adults.[5] HT 1 is a metabolic disorder that can manifest in different forms.[6] The acute form, which presents within the first 6 months of life, is linked with features of acute liver failure. The subacute form, which presents between 6 and 12 months, is characterized by failure to thrive, developmental delay, melena, jaundice, hepatosplenomegaly, and coagulopathy. The chronic form has a gradual onset and less severe features. It can lead to hypophosphatemic rickets secondary to renal Fanconi syndrome, as well as neurological symptoms such as polyneuropathy and porphyria-like crises.[7,8] Fanconi syndrome has defects of proximal tubular transport function, including impaired resorption of glucose, phosphate, amino acids, bicarbonate, uric acid, water, potassium, and sodium. This can result in hypophosphatemic rickets, hypokalemia, polyuria, and polydipsia, which usually appear in infancy. Hypertrophic cardiomyopathy and hyperinsulinemia leading to hypoglycemia are less common manifestations.[9,10]

Laboratory findings include markedly elevated serum alpha-fetoprotein levels, prolonged prothrombin, and partial thromboplastin times in the presence of normal or mildly elevated transaminases and serum bilirubin, as well as elevated plasma concentrations of tyrosine, methionine, and phenylalanine.[4] Patients of HT1 are managed with Nitisinone, which is

2-(2-nitro-4-trifluoro-methylbenzoyl)-1,3 cyclohexanedione, a drug that inhibits 4-hydroxyphenylpyruvate dioxygenase, preventing the accumulation of fumarylacetoacetate and its conversion to succinylacetone.[11] It was approved by the Food and Drug Administration in 2002 and has been shown to control liver failure in 90% of patients.[12] Failure to treat the acute form of this condition can result in hepatic failure, renal dysfunction, neurological crisis, and potentially fatal consequences.[13]

Early diagnosis and treatment can save lives. HT1 is less studied and reported from Pakistan. The study aims to report the clinical spectrum of HT1 as reported in a cohort of Pakistani children.

Methods

Retrospective analysis of pediatric patients with HT1 was done at Shifa International Hospital, Islamabad and Pak Emirates Military Hospital, Rawalpindi from 2010 to 2023. Ethics approval and consent to participate was taken from the Institutional Review Board of Shifa International Hospital with IRB # 0120-23 and written informed consent was taken. A total of 6 patients were diagnosed during this time period on the basis of clinical signs and symptoms and elevated urinary succinylacetone levels measured using Gas Chromatography-Mass Spectrometry (GC-MS). Medical records were checked for detailed history, age, examination findings like growth parameters, signs of rickets, and liver failure. Laboratory investigations including liver function tests, coagulation profiles, bone profiles, urinary succinylacetone, and alpha fetoprotein levels were recorded. We also reviewed the patient's family history of tyrosinemia in siblings and first-degree relatives.

Statistical Analysis

Results were analyzed using SPSS version 23. Qualitative data was analyzed as mean and standard deviation and quantitative data as frequency and percentages.

Results

A total of 6 cases, 4 male (66.6%) and 2 female (33.3%), of HT1 were identified. All were born to consanguineous parents, with no family history of similar disease. Prenatal testing and neonatal metabolic screening of the patients was not done due to the absence of these services in the country. The average age of onset of symptoms was 8 months and the average age at diagnosis was 34.7 months, making the average time elapsed till diagnosis 26.8 months. All of our patients were below the fifth percentile of height and weight for age.

Abdominal distension accompanied with hepatosplenomegaly was the most common presenting complaint, seen in all patients. Jaundice was seen in 2 patients. Two patients (33%) were admitted because of gastrointestinal bleeding with melena and hematemesis. Other common clinical presentations are shown in Figure 1. Four cases presented with bowing of legs

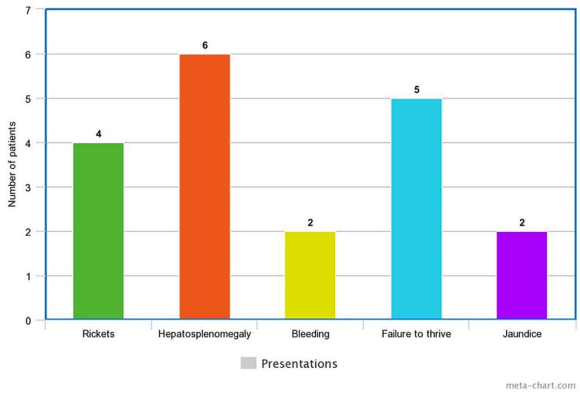

Figure 1. Common presentations of children with tyrosinemia.

and rachitic changes evidenced on wrist X-rays, while 2 were diagnosed with hypophosphatemic rickets.

As shown in Table 1, all patients had raised alkaline phosphatase levels (260-6551 IU/L), while 5 patients (83.3%) had raised ALT (31-470) and AST (43-631). Total and Direct Bilirubin was only raised in the 2 patients who presented with jaundice. Coagulation studies were deranged in every patient, with raised PT and INR. On abdominal ultrasound, 4 (66.7%) patients exhibited renal parenchymal disease, with normal renal function tests.

Due to the unavailability of Nitisinone, those with hypophosphatemic rickets were managed with Joulie's solution, fat-soluble vitamin supplements, and were advised to consume a low phenylalanine and tyrosine diet. Counseling regarding liver transplant was done. Five out of the 6 patients died within 2 years of diagnosis, while the sixth patient (Case 5) is alive and was diagnosed a month ago. Case 1 developed hepatocellular carcinoma, for which he received palliative chemotherapy, and eventually died due to intraoperative complications during liver transplant. One patient (Case 2) died of coagulopathy resulting in significant intracranial bleeding and subarachnoid hemorrhage. Liver failure was the cause of death in the remaining 3 children.

Discussion

This is the first study highlighting the various manifestations of HT1 in the pediatric population of Pakistan. We identified 6 patients, with a higher proportion of males (66.7%) than females (33.3%). In a prior Indian study, the gender distribution was equal.[14] Male gender predominance has been observed in research conducted in the United Kingdom, where 47% of the total patients were identified as having Pakistani origin.[15] The exact incidence rate of HT1 in Pakistan remains uncertain, but it's expected to be elevated due to the prevalence of consanguineous marriages. All our patients were born to first-degree consanguineous parents without any family history. In a Spanish study involving 34 patients, 35.3% had first-degree consanguinity, and 26.5% had a family history of HT1.[16] In a study performed in Libya, a consanguinity rate of 81.2% was recorded, while a study in Palestine documented a consanguinity rate of 92%.[17,18] This suggests a potential association

Table 1. Laboratory findings of children with tyrosinemia.

PATIENT NUMBER	1	2	3	4	5	6
Calcium (mg/dL)	9.0	8.8	10.0	4.6	9.1	8.7
Phosphorus (mg/dL)	2.75	4.55	4.5	4.0	1.7	4.9
Prothrombin time (s)	18	21	40	30	14	14
International normalized ratio	1.3	1.5	2.9	2.1	1.36	1.36
Alkaline Phosphatase (IU/L)	2310	2000	6551	2168	1811	260
Alanine transaminase (IU/L)	78	63	83	145	31	470
Aspartate transaminase (IU/L)	55	59	61	127	43	631
Alpha fetoprotein (IU/mL)	10860	7288	10288	11905	243	6418
Total bilirubin (mg/dL)	75	0.5	0.9	1.1	0.22	6.53
Direct bilirubin (mg/dL)	21	0.1	0.15	0.2	0.13	4.7
Urine succinylacetone (mmol/mol Cr)	20.4	217	338.6	113.1	717.55	156

between the high prevalence of HT1 in countries or among individual families with high rates of consanguineous marriages. This is also evident by the high consanguinity (100%) as seen in our cohort.

The average age at diagnosis was 34.7 months, which was earlier than a study conducted in Spain, where the average age at diagnosis was 52 months.[16] Our study also found that the average delay in diagnosis was 26.8 months, mainly due to delayed referrals and low suspicion for HT1. Delay in diagnosis and unavailability of Nitisinone are major factors in early mortality, as seen in 83.3% of our patients.[19] Three of our patients had acute form of the disease, 2 sub-acute and 1 patient had chronic form of the disease.

Although limited data has been published about the disease in the region, a study published from Turkey showed similar findings where abdominal distension was also the primary clinical finding.[20] Early onset type of the disease usually manifests during infancy, presenting with hepatomegaly, acute hepatic crisis, and coagulopathy.[21] This is evidenced in our study by the presence of hepatosplenomegaly in all of the patients, and coagulopathy in 2 patients. In some instances, the disease may continue into childhood and become chronic, which often results in the development of rickets.[22] Hypophosphatemic rickets is a common consequence due to renal Fanconi Syndrome, as seen in 2 of our patients. This is in contrast to research performed in Jordan, which showed that 42.9% of the patients had rickets as an initial presentation.[23] Skin color changes and rashes have also been reported from Japan as an initial presentation, contributing to the wide range of presentations of the disease.[24] These patients were treated with Joulie's solution and Calcitriol. Literature shows hypophosphatemic rickets as a key presenting feature in patients of HT1.[25] Jaundice was the presenting complaint of only 16.7% of our cases, which is in contrast to a previous study conducted in Lebanon where jaundice was one of the most common complaints.[26] Neurological crises have been previously reported in the absence of Nitisinone,[27] which does not align with our results, where neurological manifestations were not seen. One patient developed hepatocellular carcinoma, which is a well-known complication of tyrosinemia.[28]

The disease is confirmed by documenting elevated plasma or urinary concentration of succinylacetone; all of our patients were diagnosed by elevated urinary levels of succinylacetone.[29] Our study also noted a significant elevation of alpha-fetoprotein in all patients, a characteristic feature of this disease in newly diagnosed patients even in the absence of hepatocellular carcinoma.[30]

At present, treatment of this disease involves 2 main approaches: inhibiting the formation of harmful metabolites with Nitisinone, and lowering tyrosine levels through dietary interventions. Nitisinone has been shown to significantly enhance survival rates and effectively lower admission rates for patients.[31] While Nitisinone has been demonstrated to significantly decrease the necessity for liver transplantation in patients, its unavailability in Pakistan and the high cost associated with importing the medication makes it an unfeasible option for most families.[32]

All patients were advised a diet low in phenylalanine and tyrosine, and were told to avoid meat, eggs, nuts, dried beans, lentils, milk, and cheese. This was not found to be helpful in the absence of Nitisinone. Liver transplant is a definitive treatment option, but the high cost of the procedure makes it inaccessible to most. Previously, liver transplant has shown 1 and 5 year patient survival in HT1 of up to 90.4% each in patients with HT1.[33]

Genetic counseling was provided to the parents explaining the disease's nature and the potential risk of having another affected child, but formal genetic testing for the patients and their families could not be conducted due to unavailability. Additionally, the inaccessibility of Nitisinone in Pakistan

prevented us from documenting patient outcomes with its use. However, the limitations of our study, including a small sample size, must be acknowledged.

Conclusion

This study highlights the clinical spectrum of Hereditary Tyrosinemia Type 1 (HT1) in a cohort of Pakistani children. The findings highlight the challenges in diagnosing and managing HT1 in Pakistan, particularly due to delayed referrals and the unavailability of the crucial drug, Nitisinone. The predominance of consanguineous marriages and the absence of genetic testing further complicate the landscape.

Declarations

Ethics Approval and Consent to Participate

The local Institutional Review Board has given approval with IRB Number 0120-23.

Consent for Publication

Informed consent was obtained from all individuals included in this study.

Author Contributions

Sabeen Abid Khan: Conceptualization; Writing—review & editing. Misbah Fakih: Investigation; Writing—original draft; Writing—review & editing. Nida Taufiq: Conceptualization; Visualization; Writing—review & editing. Afaaf Ahmerin: Data curation; Methodology; Writing—original draft. Asfand Bangash: Formal analysis; Investigation; Methodology; Writing—review & editing. Munir Iqbal Malik: Conceptualization; Project administration; Supervision; Writing—review & editing.

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Competing Interests

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Availability of Data and Materials

Will be available when required

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