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A Challenging Case of Hereditary Tyrosinemia Type -1 Presenting as Refractory Rickets

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Abstract

Background: Hereditary tyrosinemia type 1 (HT-1) is a rare metabolic and genetic disorder due to deficiency of enzyme fumarylacetoacetate hydrolase (FAH) and impaired tyrosine break down resulting in accumulation of tyrosine and succinyl acetone with consequent damage to tissue and organs. Delay in diagnosis results in liver and kidney failure, abnormalities of the nervous system and increased risk of liver cancer.

Clinical Description: A child treated multiple times as hypophosphatemic /refractory rickets elsewhere; presented with frequent fractures, significant involvement of liver and kidney, raised Alfa-fetoprotein levels, elevated urine Succinyl acetone levels was finally diagnosed as chronic HT-1 with features of advanced disease at the age of 2 yr and 5 months. Evaluation of growth failure further revealed raised tTG IgA levels. Neonatal screening with serum or urine succinyl acetone could diagnose him early and the multiple fractures and growth failure prevented.

Management: Genetic counselling, dietary advice, non-availability of Nitisinone, management of fractures, confirmation of Celiac disease in a child with coagulopathy are challenging issues.

Conclusion: Algorithm for diagnosis and management of HT-1 should evolve. Refractory Rickets needs to be evaluated carefully and associated hepatorenal involvement should be given special consideration.

Keywords: Hereditary Tyrosinemia Type 1; Celiac Disease; Fumarylacetoacetate Hydrolase; Newborn Screening

Abbreviations

HT-1: Hereditary Tyrosinemia Type 1; FAH: Fumarylacetoacetate Hydrolase; AFP: Alfa-Fetoprotein; HBsAg: Hepatitis B Surface Antigen; SGOT: Serum Glutamic Oxaloacetic Transaminase; SGPT: Serum Glutamic Pyruvic Transaminase; VDDR: Vitamin D–Dependent Rickets; XLH: X-linked Hypophosphatemic Rickets; tTG: t-Transglutaminase; RD: Relatively Decreased; ADHR: Autosomal Dominant Hypophosphatemic Rickets; HHRH: Hereditary Hypophosphatemic Rickets with Hypercalciuria; N: Normal; Pi: Inorganic Phosphorus; PTH: Parathyroid Hormone.

Introduction

Hereditary tyrosinemia type 1 (HT-1) is a rare metabolic and genetic disorder with a global incidence of about 1 in 100,000 (M=F). It is caused by lack/ deficiency of enzyme fumarylacetoacetate hydrolase (FAH), resulting in impaired break down of tyrosine and its metabolites with accumulation of tyrosine and succinyl acetone and damage to tissue and organs leading to liver and kidney failure, abnormalities of the nervous system and increased risk of liver cancer. Its incidence or prevalence in India is unknown [1].

This genetic disorder has autosomal recessive trait and the patient must inherit the same defective gene from each parent to manifest the disease. Risk of transmitting the disease to a child if both parents are carriers is 25%. Undiagnosed tyrosinemia type I is usually fatal before the age of 10. Type I (HT-1) is the most severe form caused by deficiency of the enzyme fumarylacetoacetate hydrolase (FAH) [2]. Type II, caused by a deficiency of the enzyme tyrosine aminotransferase is associated with some degree of intellectual disability in 50 percent of individuals. Type III, caused by a deficiency of the enzyme 4-hydroxyphenylpyruvate dioxygenase has typical features like intellectual disabilities, seizures, and periodic loss of balance and coordination [3]. HT-1 is further subdivided in three types on the basis of presentation:

A. **Acute:** most severe form; with symptoms like poor weight gain, enlarged liver and spleen, distended abdomen, swelling of the legs, increased tendency to bleeding/GI bleeding, nosebleeds, jaundice and lethargy starting in the first few months of life.
B. **Sub-Acute:** less severe form; with symptoms starting in the 2nd half of the 1st year of life; with symptoms of frequent vomiting and diarrhoea “Boiled cabbage” or “rotten mushroom” odor to the body and urine, Rickets and growth failure in addition and
C. **Chronic:** in which Symptoms of renal disease, rickets, cardiomyopathy, cirrhosis and developmental delays develop after the 1st year of life [4].

1.1. Clinical Description

A 2- year-5-month-old boy uneventful birth history and immunizations as per age; presented with complaints of weakness, history of frequent fractures and abdominal distension since last 1 year. This sixth child of parents had 4 sisters and history of death of elder sibling by per oral bleeding at 2 months of age. He started walking at 1 year of age with a normal developmental history. He was consulted at a private hospital for complaints of limping at the age of 1 year 5 months and was diagnosed having Rickets with fracture of right fibula. The S. Calcium was 8.6 mg/dl, phosphorus 1.6 mg/dl and vitamin D 25-OH - 41.5ng/ml. He was treated with vitamin D and calcium and a below knee cast was also applied.

He again had fracture of left fibula after 3 months (Figure 1). He also developed distension of abdomen, and was given albendazole and iron folic acid. The child received treatment from various doctors (Allopathic, Ayurvedic) and received various medicines including Vitamin D3, Calcium, multivitamins and lactulose.

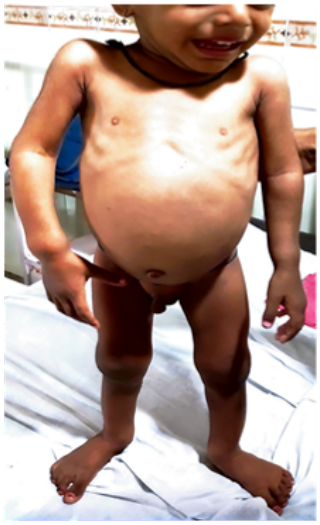

Figure 1: Fracture of left fibula.

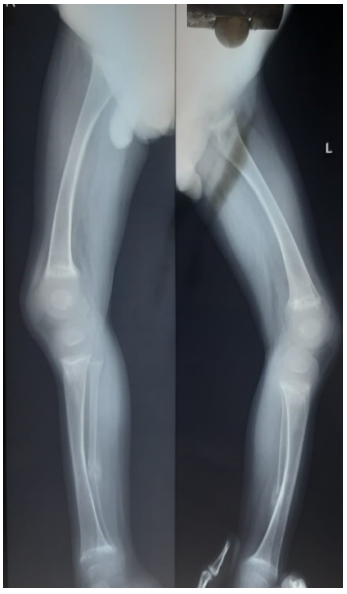

Figure 2: Fracture fibula.

His weight was 8 kg (-4 Z) with growth failure with height 77 cm (-4 Z) and head circumference 48.5 cm. No pallor, icterus cyanosis, lymphadenopathy, or edema was noted. Clinical

signs of rickets, like widening of bilateral wrist, elbow joint, double malleoli and bowing of legs were noted during general physical examinations (Figure 2). Lab investigations are summarized in Table 1. Reticulocyte counts were 0.3% and PBF was normal. HBsAg and Anti HCV were negative. Thyroid profile was normal. Coagulation profile was severely deranged (PT - 24.9 sec, with INR 1.95), suggesting Coagulopathy. Injection vitamin K and one unit of fresh frozen plasma were transfused.

Albumin /Globulin Ratio were high (2.7 -ref range 1-2.1 g/dl). Mean plasma glucose was 115 mg/dl & HbA1c was normal. Total lipid was 487 mg /dl, and phospholipids, triglycerides& total cholesterol were 176, 141 &109 mg/dl respectively. Urine examination was negative for ketones, glucose, bilirubin, urobilinogen, protein, with PH 7.0 and specific gravity 1.030, spot urine phosphorus estimation suggested phosphaturia (Table 1).

Investigations								
Parameter	**Value**	**Normal Range**	**Parameter**	**Value**	**Normal Range**	**Parameter**	**Value**	**Normal Range**
Hemoglobin	13.1 g/dL	10.0–14.0 mg/mL	Total bilirubin	3.23 mg/dL	0.2–1.2 mg/dL	Prothrombin time	24.9 sec	9.5–13.5 s
Total leucocyte count	10460/mL (N-28%, L-66%, E-2.4%, M-2.3%)	4,000–11,000/Ml	Conjugated bilirubin	1.84 mg/dL	0.1–0.3 mg/dL	INR	1.95	
Platelets	196,000/Ml	150,000–400,000/ Ml	Total serum proteins	6.3 mg/dL	6.0–8.0 mg/dL	Spot urine Phosphorus	53.27 mg/dl	29–42 mg/L
Serum sodium	138 mmol/L	136–145 mmol/L	Serum albumin	4.6 mg/dL	3.8–5.5 mg/dL	Spot urine Calcium-quantitative	5.2 mg/dl	
Serum potassium	3.5 mmol/L	3.8–5.5 mmol/L	Serum globulin	1.7 mg/dL	2.1-3.5 mg/dL	Parathyroid hormone	(14.4 pg/ml)	
Serum magnesium	1.7 mg/L	1.7–2.4 mg/L	Serum SGOT	50 IU/L	8.0–40.0 IU/L	Alfa-fetoprotein	4183.6 IU/ml	0.0–8..0 IU/mL
Serum alkaline phosphatase	983 IU/L	60.0–270.0 IU/L	Serum SGPT	38 IU/L	8.0–40.0 IU/L	TTG IgA	41.7 AU/ml	>11 U/ml positive
Serum calcium	9.9 mg/L	9.0–11.0 mg/L	Serum Urea	21		Serum LDH	179.6 U/L	7-50 U/L
Serum phosphorus	2.2 mg/L	2.3–4.7 mg/L	Serum creatinine	0.58 mg/dL	0.5–1.3 mg/Dl	Serum GGT	10.6 IU/L	13-45 IU/L
25-OH vitamin D	118.48 ng/ml.	upper safety limit->100	S. NH3 -107 umol/L		PH in ABG-7.34, Lactate-1.3 mmol/L			

Table 1: Lab Investigations.

Vitamin D Resistant Rickets was suspected initially. Classical features of Rickets like wrist widening, malleolar prominence, genu valgum were noted & X-ray B/L wrists revealed typical fraying, splaying, and cupping of bilateral distal femoral, radial, and ulnar metaphysis (Figures 1 & 3). X-ray bilateral knees suggested expansion of metaphyseal ends of lower end of B/L femur and upper and lower end of B/L tibia and fibula. Fracture of mid diaphysis and B/L fibula with poor callus formation seen. X ray skull was grossly normal with no lytic lesion (Figure 2). In Chest radiograph AP view, expansion of anterior ends of ribs was noted, consistent with rachitic rosary.

On further evaluation, liver was palpable 6 cm below right costal margin with sharp leaf like border; no splenomegaly was present, as visible in X-Ray FPA (Figure 2). Ultrasound abdomen suggested multiple micro and macronodular hypoechoic lesions of various sizes in both lobes of liver suggesting liver parenchymal disease- cirrhotic liver. Left Kidney measured 89x35 mm and right kidney 75x38 mm & B/L kidneys were bright with loss of corticomedullary differentiation with medical renal disease. Kidney

parenchyma thickness on both sides was 22 mm with normal outline & right undescended testis. CECT whole abdomen suggested bilateral kidneys enlarged in size, with right kidney-92x 39 mm and left kidney- 88x 52 mm. VBG suggested PH -7.37 with bicarbonate 22.5. AFP level was 4183 IU/ml.

Investigation-Succinylacetone Urine	Observed value	Biological Reference Interval
Succinylacetone Medical Remarks: Elevation Factor :12.93%	12.93	REF. RANGE IN %: 0
4-Hydroxyphenyllactic Acid Medical Remarks: Elevation Factor :215.00%	387	REF. RANGE IN %: 1.8
4-Hydroxyphenylpyruvic Acid Medical Remarks: Elevation Factor: 0.00%	0	REF. RANGE IN %: 0.2
N-Acetyltyrosine Medical Remarks: Elevation Factor: 0.00%	0	REF. RANGE IN %: 0
Impression: Elevated levels of Succinylacetone (4- Hydroxyphenyllactic acid observed suggestive of Tyrosinemia Type -1)		

Table 2: Succinylacetone Urine Estimation Report.

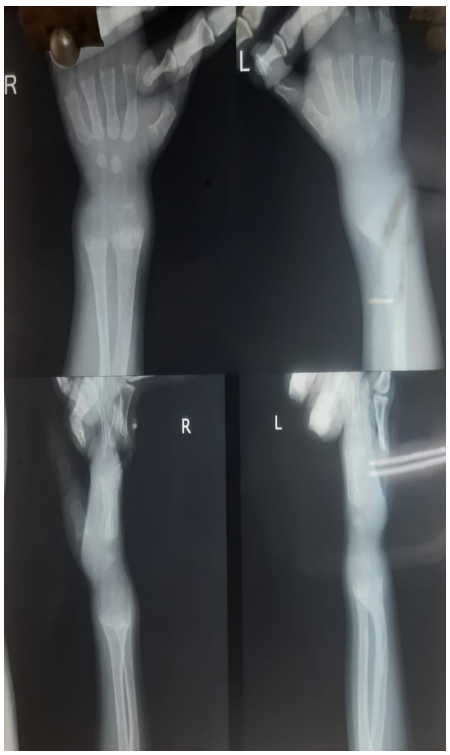

Figure 3: X Ray Wrist.

Succinylacetone urine estimation suggested elevated levels of 960 Um/L suggesting HT-1 (Table 2). t-Transglutaminase (tTG) IgA level was 41.7 U/ml. Upper GI Endoscopy showed superficial erosions in the duodenum with reduced fold height ++, and scalloping++, suggestive of Celiac disease, biopsy was not taken due to deranged liver functions and risk of bleeding.

Management

Considering above clinical findings and investigations a diagnosis of Hereditary Tyrosinemia type 1 with probable celiac disease was established. Genetic counselling was done and DNA storage and DBS sampling were planned. Drug Nitisinone was planned. Gluten free diet with restricted phenylalanine and tyrosine intake was started after consultation with nutritionist. Maintaining nutritional needs & appropriate serum tyrosine levels with gluten free diet is a challenging issue. A dietician and geneticist follow up was planned. Child was put on vitamin D3 and Calcitriol sachet along with multivitamin and calcium. LFT, PT-INR and AFP were planned at follow up after 1 month.

Discussion

Neonatal screening is a valuable tool to avoid such incidences of delayed diagnosis. Raised serum succinyl acetone levels on NBS are specific for HT-1. Elevated tyrosine levels may suggest other inborn errors of metabolism also. Early diagnosis and management is the key to success in preventing hepatic and renal failures and hepatocellular carcinoma [5]. Fumarylacetoacetate is converted to fumarate and acetoacetate by the enzyme fumarylacetoacetate hydrolase. Fumarylacetoacetate accumulation is the cause of damage to hepatocytes and renal tubule cells. It's a mutagen also [6,7].

Renal tubular injury results in aminoaciduria, glycosuria, and phosphaturia with "boiled cabbage" or "rotten mushroom" smell of urine; resultant renal tubular acidosis, hypophosphatemia, hypoproteinemia and rickets. Laboratory findings in various disorders causing Rickets [8] are depicted in Table 3.

Disorder	Ca	Pi	PTH	25-(OH)	1,25-(OH)2D	Alk Phos	Urine Ca	Urine Pi
Vitamin D deficiency	N, ↓	↓	↑	↓	↓, N, ↑	↑	↓	↑
Chronic kidney disease	N, ↓	↑	↑	N	↓	↑	N↓	↓
Dietary Pi deficiency	N	↓	N↓	N	↑	↑	↑	↓
Tumor-induced rickets	N	↓	N	N	RD	↑	↓	↑
Fanconi syndrome N ↓			N	N	RD or ↑	↑	↓	↑
Dietary Ca deficiency	N ↓	↓	↑	N	↑	↑	↓or ↑	↑

Table 3: ↓, decreased; ↑, increased; ↑↑, extremely increased; 1,25-(OH)2D, 1,25–dihydroxyvitamin D; 25-OHD, 25-hydroxyvitamin D; ADHR, autosomal dominant hypophosphatemic rickets; Alk Phos, alkaline phosphatase; ARHR, autosomal recessive hypophosphatemic rickets; Ca, calcium; HHRH, hereditary hypophosphatemic rickets with hypercalciuria; N, normal; Pi, inorganic phosphorus; PTH, parathyroid hormone; RD, relatively decreased (because it should be increased given the concurrent hypophosphatemia); VDDR, vitamin D–dependent rickets; XLH, X-linked hypophosphatemic rickets.

The hepatomegaly with deranged liver function tests raised the possibility of metabolic disorders like glycogen storage disease and Wilson's disease. Imaging findings of enlarged kidneys and rickets strongly indicated the possibility of hereditary tyrosinemia Type 1. Urinary organic acid was requested which determined high level of succinylacetone confirming the diagnosis of hereditary tyrosinemia Type 1.

Celiac disease is being diagnosed frequently in present times. Liver disorders such as auto-immune liver disease, isolated hypertransaminasaemia, non-alcoholic fatty liver disease and an association with hepatitis C virus infection have been reported in patients with coeliac disease. HT-1 with Coeliac disease has been reported previously also [9]. Approximately 97% of individuals with coeliac disease have genetic markers on chromosome 6p21, while the gene for the FAH enzyme of HT1 is mapped on chromosome 15 [10].

Treatment involves the dietary restriction of phenylalanine, methionine, and tyrosine and the use of 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione- Nitisinone) to prevent the formation of toxic metabolites. It inhibits 4-hydroxy phenyl pyruvate dioxygenase which converts 4-hydroxyphenylpyruvate to homogentisic acid. This prevents accumulation of the toxic metabolite, fumarylacetoacetate. Nitisinone is the only FDA approved treatment for HT-1 with recommended dose 1-2mg/kg/day [10]. The goal of dietary treatment is to restrict high protein foods containing tyrosine and phenylalanine, moderate protein foods need to be limited. A low-tyrosine, low-phenylalanine food pattern is necessary to maintain safe serum tyrosine levels. Target Serum tyrosine levels are less than 500µmol/L & Serum and urine succinylacetone levels below detectable levels. After achieving recommended levels, a serum tyrosine level is recommended every month for the first 6 months, and every 3 months thereafter. A combination of NTBC and dietary restriction have shown to prevent development of chronic liver disease, renal tubular damage, hepatocellular carcinoma, neurological manifestations, and avoid transplantation [10]. United States and Canadian consensus group recommends periodic screening with liver imaging and AFP levels to detect early hepatocellular carcinoma [5].

Liver transplantation may still be required in cases that fail to respond to medical therapy, have evidence of liver cancer or develop end-stage liver failure.

Conclusion

Multidisciplinary team-based approach including metabolic disease specialist, clinical biochemical geneticist, dietician, genetic counselor and clinical psychologist with pediatrician is required. This case has features of advanced disease with raised Alfa-fetoprotein levels and significant involvement of liver, kidney and frequent fractures. Preparing a diet chart, availability of Nitisinone, management of fractures, confirming Coeliac disease and counselling the parents were issues we faced. A proper algorithm for diagnosis and management was the felt need. A thorough perinatal history focused on inherited diseases and early newborn screening is helpful in early diagnosis. Rickets needs to be evaluated carefully and associated hepatorenal involvement should be given special consideration. Neonatal screening with serum or urine succinyl acetone, genetic counselling, early diagnosis and management are few of our recommendations. The patient in our follow up for 3 months and then lost to follow up.

Lessons Learnt

- Even the "Classical features of Rickets" should be evaluated cautiously if associated with hepatosplenomegaly.
- Universal newborn screening is important for early

diagnosis.

- Newer diagnostic modalities diagnose rarer diseases efficiently.
- Availability of Nitisinone, Multidisciplinary team-based approach and early diagnosis are cornerstone of management.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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