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The Case | A challenging case of severe rickets

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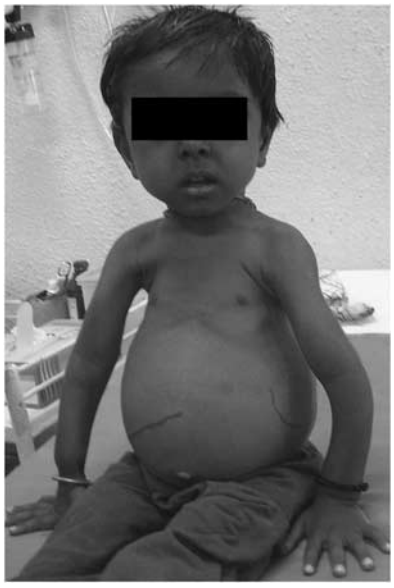

Figure 1 | Clinical photograph showing hepatosplenomegaly and rickets.

A 2-year-old boy born of a non-consanguineous marriage was admitted with a history of failure to thrive and motor-development delay since birth. He had polyuria, polydipsia, and constipation. On examination, his weight and height were below the third centile for age. He had a widely open anterior fontanelle with clinical features of rickets including gross bony deformities and bony tenderness. Abdominal examination revealed nodular hepatomegaly, with a liver span of 8 cm and splenomegaly of 3 cm below the left costal margin (Figure 1).

Investigations revealed hyperchloremic metabolic acidosis with normal anion gap and hypokalemia. Urinalysis revealed aminoaciduria, phosphaturia, and glycosuria. Liver functions were within normal limits. X-ray of the limbs showed multiple healing fractures. Ultrasound showed normal-sized kidneys without nephrocalcinosis and hepatomegaly with multiple hyperechoic nodules in the liver. Computed tomography of the abdomen showed enlarged liver with multiple non-enhancing lesions. His alpha-feto-protein levels were elevated (935 ng/ml).

Liver biopsy was done, which showed loss of architecture of the liver with pseudolobules separated by fibrous septae. The hepatocytes showed microvesicular fatty change. The fibrous septae showed a chronic inflammation infiltrate with piecemeal necrosis. Ductular proliferation was prominent. Kupffer cells were unremarkable.

What is your diagnosis?
How will you confirm the diagnosis?

SEE NEXT PAGE FOR ANSWERS

The Diagnosis | Tyrosinemia, type I

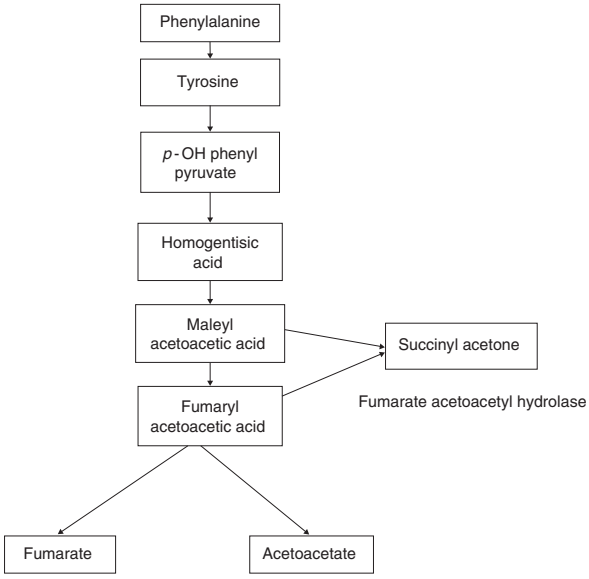

Figure 2 | Pathway showing defect in metabolism of tyrosine in tyrosinemia type 1.

Tandem mass spectrometry showed low blood-free and acyl carnitines. Amino-acid qualitative analysis of urine showed significantly elevated levels of tyrosine. Analysis of plasma showed a tyrosine level of 232 μmol/l (normal 30–100 μmol/l). Urine succinylacetone level was 8.2 μmol/l (normal <1 μmol/l). A diagnosis of tyrosinemia type I was established.

Tyrosinemias are characterized by the accumulation of tyrosine in the body. The most severe form, type I, is a disorder that causes liver failure, painful neurologic crises, Fanconi's syndrome, and hepatocellular carcinoma. It is caused by a deficiency of fumarylacetoacetate hydrolase (Figure 2). Oculocutaneous tyrosinemia, type II, is caused by a deficiency of tyrosine aminotransferase. Tyrosinemia type III is a rare disorder caused by a deficiency of 4-hydroxyphenylpyruvic dioxygenase and presents with ataxia and mental retardation.[1] These disorders are diagnosed by the presence of elevated tyrosine by plasma amino-acid chromatography and tyrosine metabolites by urine organic acid analysis. Urine shows elevated *p*-hydroxy-phenyl organic acids in all types of tyrosinemia, and the pathognomic succinylacetone in tyrosinemia type I.[2] Diagnosis can be confirmed by enzyme or molecular studies in tyrosinemia type I. Therapy consists of a diet low in phenylalanine and tyrosine. For tyrosinemia type I, 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione can be used.[1]

Tyrosinemia type I is of autosomal recessive inheritance. It has a prevalence of about 1 in 100,000 newborns. It is characterized by progressive liver disease and Fanconi's syndrome. It occurs in an acute and a chronic form. Hepatocellular carcinoma is frequently encountered in the chronic form of the disorder.[2] The enzyme defect results in accumulation of fumaryl- and maleyl-acetoacetate, which cause cellular damage. Succinylacetone, derived from these metabolites, is elevated in the serum and urine of these patients. The diagnosis can be established by determination of succinylacetone in urine or serum and by assay of fumaryl acetoacetate hydrolase in lymphocytes and fibroblasts. Prenatal diagnosis is possible by analysis of succinylacetone in amniotic fluid and by fumaryl-acetoacetate hydrolase assay in cultured amniotic fluid cells or chorionic villus material. Liver transplantation is as yet the only definite treatment for this disorder.[3]

In a child who presents with features of proximal renal tubular acidosis along with hepatosplenomegaly, inborn errors of metabolism need to be considered. Glycogen storage disorders like Von Gierke's and Fanconi–Bickel syndrome along with tyrosinemia are the important differential diagnosis. Hypoglycemia and hyperlipidemia are important markers of Von Gierke's and Fanconi–Bickel syndrome. These glycogen storage disorders show glycogen deposits on liver biopsy.

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