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Case Report

Type 1 Tyrosinemia with Hypophosphatemic Rickets: A Case Report

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Abstract:

Introduction:
Tyrosinemia type 1 is an autosomal recessive metabolic disorder, which typically affects liver and kidneys. It is caused by a defect in fumarylacetoacetate hydrolase (FAH) enzyme, the final enzyme in the tyrosine degradation pathway. The disease typically manifests as early onset type in early infancy with acute hepatic crisis with hepatomegaly and bleeding tendency.

Case Presentation:
Our case was a girl in mid childhood period with profound rickets and slowly progressing liver disease who presented with difficulty walking and weakness of muscles. She had an elevated serum tyrosine and urinary succinylacetone, which confirmed the diagnosis of tyrosinemia type1 and after treatment with (2-nitro-4-trifluoromethylbenzoyl)-1,3-ciclohexanedione (NTBC) significant remission, was achieved.

Key words: Hypophosphatemic rickets, Type1 Tyrosinemia.

Introduction

Tyrosinemia type 1 is an autosomal recessive metabolic disorder, which typically affects liver and kidneys (1). It is caused by a defect in fumarylacetoacetate hydrolase or fumarylacetoacetase (FAH) enzyme, the final enzyme in the tyrosine degradation pathway (2). Because of this defect, toxic metabolites like succinylacetone, maleylacetoacetate and fumarylacetoacetate are formed and they can cause severe disruption of intracellular metabolism of the kidney and liver (3). The birth incidence rate of tyrosinemia type 1 is approximately 1:100,000 but in some regions especially in Quebec, Canada it has higher frequency (4). Tyrosinemia type 1 mainly affects liver, kidney and peripheral nerves in patients. Coagulopathy, failure to thrive, hepatosplenomegaly, rickets, neurological problems, cirrhosis or other liver problems and cardiomyopathy are some of its clini presentations (2).

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Introduction

Tyrosinemia type 1 is an autosomal recessive metabolic disorder, which typically affects liver and kidneys (1). It is caused by a defect in fumarylacetoacetate hydrolase or fumarylacetoacetase (FAH) enzyme, the final enzyme in the tyrosine degradation pathway (2). Because of this defect, toxic metabolites like succinylacetone, maleylacetoacetate and fumarylacetoacetate are formed and they can cause severe disruption of intracellular metabolism of the kidney and liver (3). The birth incidence rate of tyrosinemia type 1 is approximately 1:100,000 but in some regions especially in Quebec, Canada it has higher frequency (4).

Tyrosinemia type 1 mainly affects liver, kidney and peripheral nerves in patients. Coagulopathy, failure to thrive, hepatosplenomegaly, rickets, neurological problems, cirrhosis or other liver problems and cardiomyopathy are some of its clinical presentations (2). If untreated, it can lead to hepatocellular carcinoma or liver failure (5, 6). Tyrosinemia type 1 diagnosis is based on clinical manifestations plus urine succiny-lacetone and serum tyrosine ranges (6).

The treatment for tyrosinemia type 1 consists of a low tyrosine and phenylalanine diet along with nitisinone (NTBC)[1], a compound that prevents production of toxic metabolites. The treatment should be started as soon as the diagnosis is confirmed (7-9).

In this study, we report a 6-year-old patient with tyrosinemia type 1 who was admitted due to muscle weakness and difficulty walking and finally after treatment significant remission was achieved.

Case presentation

A six years old girl presented with difficulty in walking and weakness of muscles so she was admitted in neurology ward in Qaem Hospital in Mashhad-Iran. Her height and her weight were 101 cm (Z score:-2.8) and 15.5 kg (Z score:-2) respectively, according to 2007 WHO[2] references.

On her physical examination, widening of wrists, marked rachitic rosary and hepatomegaly was observed (the liver was palpable 4 cm below the costal margin) and after initial testing and the low level of serum Phosphorous and vitamin D, the probability of rickets was considered. Therefore skeletal survey was taken. In her wrist radiograph osteopenia, reduction in size and number of ossification centers, fraying, flaring, cupping and multiple fractures was noted (Figure.1).

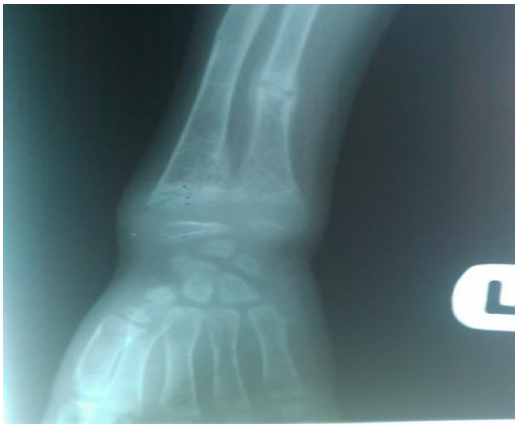

Fig. 1: Left hand radiologic signs of rickets along diaphyseal fracture before treatment

Her chest radiograph also showed classic view of dirty lung and rachitic rosary in rickets (Figure.2).

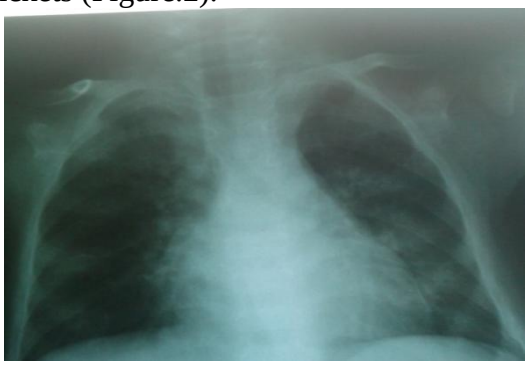

Fig. 2: Chest x-ray of rachitic patient

[1] (2-nitro-4-trifluoro-methylbenzyol)-1,3 cyclohexanedione

[2] World Health Organization

In laboratory tests, Alkaline phosphatase was significantly higher than normal (Alk-p:7815 , nl: to 1200). The liver echo was completely non homogen and the vision of diffuse hypo and hyper echoic nodules was observed, the largest nodule had a diameter of 15 mm throughout the liver parenchyma. So she was considered a rachitic case and after consultation with a pediatric endocrinologist, she assumed as secondary hypophosphatemic rickets. Further laboratory tests (Table.1) shows proteinuria , high level of serum tyrosine and elevated level of succinylacetone so the diagnosis of late onset tyrosinemia type 1 with Fanconi syndrome and hypophosphatemic rickets was confirmed.

Table 1: Laboratory data of the patient normal ranges.

Bs	93	mg/dl	70-100 mg/dl
Urea	25	mg/dl	to 20 mg/dl
Creatinine	0.6	mg/dl	0.5-1 mg/dl
Cholesterol	186	mg/dl	100-200 mg/dl
Triglyceride	105	mg/dl	80-150 mg/dl
Sodium	139	meq/lit	135-150 meq/lit
Potassium	4	meq/lit	3-5 meq/lit
Calcium	9.5	mg/dl	8.5-10.5 mg/dl
Phosphorous	1.1	mg/dl	3.5-5.5 mg/dl
Total protein	7.1	gr/dl	
Albumin			4.9 gr/dl
Protein urine (random)	25		26 mg/dl
Calcium urine (random)			13.5 mg/dl
Creatinin urine random			26 mg/dl
Ca/cr ratio			0.2
25 (OH) vitamin D			22.2 ng/ml
Tyrosine micromol/lit			290 micromol/lit
Methionine micromol/lit			23micromol/lit
Succinylacetone micromol/lit			5.7 micromol/lit

So she was managed for one year and in her last visit, significant remission was achieved. (Figure.3).

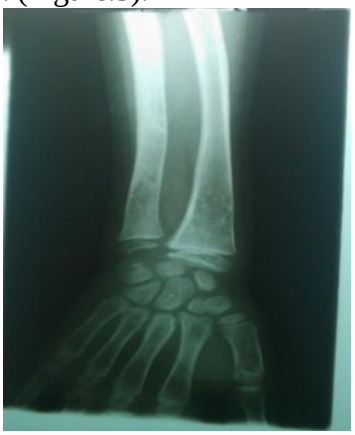

Fig. 3: The same Left hand 1 year after medication

Discussion

The first case of typical hepatorenal tyrosinemia was described by sakai et al. in 1957 (6) beyond this time more than 100 cases reported in literatures , but limited number of cases from Iran was reported probably due to problems in diagnosis and treatment of this disease in our country (10). The disease typically manifests as early onset type in early infancy with acute hepatic crisis with hepatomegaly and bleeding tendency. The acute crisis may resolve spontaneously but hepatomegaly and failure to thrive persist (10). In a few cases disease may persist later in childhood with a chronic form, which frequently manifests as rickets (11).

Our case was in middle childhood period with profound rickets and slowly progressing liver disease.

In countries which screening of tyrosinemia is not available diagnosis of type 1 tyrosinemia is based on the presence of liver disease, kidney disease and/or rickets, increased tyrosine and methionine in plasma, and presence of Salicylic Acid (SA) in urine and blood and serum amyloid A (SAA) in urine along with presence of 4-oxo-6 hydroxy- hepatonic acid in the urine (12, 13). However, diagnosis can be

suspected on the basis of persistent asymptomatic firm hepatomegaly, mildly deranged liver functions, very high alfa fito protein levels and high tyrosine levels in plasma with urinary aminoaciduria (4). Similarly our patient has mild acidosis (Hco3:12.2 mmol/lit) and proteinuria, elevated serum tyrosine (5.7 micromol/lit) but normal methionine, hypophosphatemic rickets and firm hepatomegaly.

Other cause of hypophosphatemic rickets like fructose intolerance, galactosemia, cystinosis etc. were suspected and ruled out.

Diagnosis of type 1 tyrosinemia is confirmed by measurement of urinary succinylacetone but more confirmatory tests (enzymatic and genetics) could not be done in our patient.

Historically tyrosinemia type 1 was treated with a tyrosine and phenylalanine restricted diet with and without liver transplantation.

In 1992 a new drug orfadin (NTBC, Nitisinone) which is a potent inhibitor of 4 hydroxy phenyl pyruvate dioxygenase has revolutionized the treatment of tyrosinemia type 1 and is now the ministry of therapy (8,14,15). In our patient about 1 year after beginning of especial diet and medication, rickets was cured and problems related to liver and kidney regressed.

Conclusions

According to the case presentation, in approach to rickets, first of all type of rickets should be determined and if hypopho-sphatemic rickets is proposed, it is essential to evaluate related condition so if tyrosinemia is the underlying cause appropriate management will cure the signs.

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