Hereditary tyrosinemia type 1 from a single center in Egypt: clinical study of 22 cases

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Original article

Background: **Hereditary tyrosinemia type 1 (HT1) is an increasingly recognized inborn error of metabolism among Egyptian children. This study was undertaken to define the presenting clinical, biochemical and imaging features and outcome of 2-(2-motrp-4-trifluoro-methylbenzoyl)-1, 3-cyclohexanedione (NTBC) therapy and liver transplantation in a cohort of Egyptian children diagnosed with HT1.**

Methods: **The study was carried out at the Pediatric Hepatology Unit at Cairo University Children's Hospital. HT1 was diagnosed by quantification of succinylacetone (SA) in dry blood spots.**

Results: **Twenty-two patients were diagnosed with HT1 in a period of 3 years from August 2006 to July 2009. Infants with focal hepatic lesions and hepatomegaly (*n*=13) were younger at diagnosis than those with rickets (*n*=5) (median age: 3.25 *vs.* 10 months; *P*=0.05). Alpha fetoprotein was highly elevated in all children. Seven children died within a few weeks of diagnosis before therapy was initiated. Ten children were treated with NTBC. The response to NTBC treatment was apparent by a steep drop in serum alpha fetoprotein (AFP) and undetectable SA in urine within 2 months. Three children underwent living donor liver transplantation after treatment with NTBC for 10, 18 and 22 months respectively, despite adequate response to therapy because of financial issues. The explanted livers were all cirrhotic with no dysplasia or malignant transformation.**

Conclusions: **Focal hepatic lesions are the commonest presentation of HT1 patients and they present at an earlier age than rickets. NTBC is effective but very expensive. Liver transplantation is still considered in HT1 patients.**

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Key words: **children;**
Egypt;
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Introduction

Hereditary tyrosinemia type 1 (HT1) is an autosomal recessive inborn error of tyrosine metabolism caused by a deficiency of fumarylacetoacete hydrolase (FAH), the last enzyme in the tyrosine catabolic pathway. The human FAH cDNA has been cloned and mapped to human chromosome 15q, and the gene structure has been elucidated.[1] Biochemically, HTI is characterized by accumulation of succinylacetone (SA) and its precursors fumarylacetoacetate and maleylacetoacetate, which play a major role in the pathogenesis of clinical symptoms. [2] The natural history of HT1 is characterized by severe liver disease, which frequently results in death. Symptoms can present early in infancy with an acute rapid course, or they may progress more chronically.[3] Most patients present with failure to thrive and hepatomegaly. The liver disease is progressive, causing micro- and macronodular cirrhosis. Icterus, ascites and hemorrhage appear. Patients also display renal tubular acidosis of the Fanconi type, and typical radiographic changes of rickets are often present. Mental retardation is not a feature. Surviving patients have a high risk for developing hepatocellular carcinoma.[4]

The drug 2-(2-nitro-4-trifluoro-methylbenzoyl)-1, 3-cyclohexanedione (NTBC) is a potent inhibitor of 4-hydroxyphenylpyruvate dioxygenase, thus reducing tyrosine degradation and production of SA.[5] The

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metabolic block induced by NTBC leads to an increase in plasma tyrosine concentration and an increased excretion of urinary phenolic tyrosine metabolites. For the NTBC-treated patient, it is recommended that the plasma tyrosine level be kept to below 500 μmol/L so as to avoid adverse effects and to decrease the load on the tyrosine degradation pathway.[6]

In Egypt, the diagnosis of HT1 has been available since August 2006. Over the last 3 years 22 cases were diagnosed at the Hepatology Unit, Cairo University Children's Hospital, Cairo, Egypt. The present study aimed to define the presenting clinical, biochemical and imaging features. The outcome of cases whether they received NTBC therapy or not will be described as well as the outcome of liver transplantation.

Methods

Diagnosis of HT1 was carried out by quantification of SA in dried blood spots (DBS).[7] A positive result was considered if SA was elevated above 1 μmol/L. Testing for SA was carried out when HT1 was suspected in the following clinical settings: 1) Infants presenting with hepatomegaly or hepatosplenomegaly and abdominal ultrasound revealed a heterogenous texture of the liver parenchyma, focal hepatic lesions, nephromegaly or increased renal echogenecity; 2) Infants or children presenting with rickets with hepatomegaly or hepatosplenomegaly; 3) Infants or children presenting with liver disease with deranged synthetic functions; 4) Infants or children presenting with liver disease with markedly elevated alpha-fetoprotein.

All patients were subjected to the following examinations:

1. Full history taking: including age at the onset of first symptom, history of abdominal distention, jaundice, edema, bleeding, bone disease, growth and developmental milestones;

2. Family history included consanguinity and history of other sibs suffering from the same condition;

3. Anthropometric measurements and clinical examination for presence of pallor, jaundice, edema, abdominal distention, abdominal wall veins, hepatomegaly, splenomegaly, ascites, palmar erythema, bleeding tendency, ecchymosis and rachitic manifestations;

4. Laboratory investigations including: complete blood count; liver functions: total and direct serum bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP), gamma glutamyl transpeptidase (GGT), serum albumin, prothrombin time and concentration; serum alpha fetoprotein (AFP); kidney function: urea, creatinine; serum calcium and phosphorus; extended metabolic screening of DBS by liquid chromatography tandem mass spectrometry (LC-MS/MS) particularly for methionine, tyrosine and phenylalanine; determination of SA in DBS or urine by LC-MS/MS;

5. Imaging studies: abdominal ultrasonography performed using Fukuda Denshi FF Sonic, Model UF-4100 scanner with 5.5 MHz transducer; X-ray ends of long bones for active rickets (when indicated); triphasic CT for hepatic focal lesions.

Outcome and treatment

Seven children died within a few weeks of diagnosis before therapy was initiated. Ten patients were treated with NTBC at a dose ranging 0.55-0.7 mg/kg per day in two divided doses. No special diets or formulas were provided to the patients; mothers were consulted to avoid high protein diets. Three children underwent living related liver transplantation after treatment with NTBC for 10, 18 and 22 months, respectively. At the time of writing this manuscript 5 children have not yet received treatment because NTBC is extremely expensive and not readily available. Untreated patients are supplemented with renal replacement therapy in the form of 1-OH vitamin D and phosphate containing solutions.

Follow-up was carried out for 3 months for both treated and untreated patients and included anthropometric measurements, clinical examination, complete blood counts, full liver function tests, AFP levels, renal function tests, serum calcium and phosphorus and urinary SA for treated patients for dose adjustment. Serum tyrosine was not regularly followed up for economic reasons, particularly that no special formulae were offered to the patients.

Statistical analysis

Statistical analysis was performed using the SPSS program, version 14 (SPSS Inc, Chicago, IL). The nonparametric Mann-Whitney *U* test was used for abnormally distributed data. $P<0.05$ was considered statistically significant. Results were expressed as medians and ranges.

Results

From August 2006 to July 2009, 22 children were diagnosed with HT1 at the Hepatology Unit, Cairo University Children's Hospital. These children were born between 2004 and 2008, 4-5 children each year. These 22 children came from 20 families. Sixteen couples were consanguineous (80.0%). One of the non-consanguineous couples had 2 children diagnosed

with HT1. The median age of onset of symptoms was 4 months (range: 1-24 months) and the median age of presentation to our unit was 12 months (range: 1-66 months) and the median interval from the first symptom to diagnosis was 6 months (range: 0.5-42 months).

According to the presenting symptoms and initial physical findings at first visit, the patients were grouped into the following: 1) Thirteen patients presented with abdominal distention and an abdominal ultrasound and/ or a triphasic CT scan revealed focal hepatic lesions or heterogeneous hepatic parenchyma; 2) Five patients presented with rickets and hepatomegaly; 3) Two patients presented with jaundice and hepatosplenomegaly; 4) One patient presented with failure to thrive and hepatomegaly; 5) One patient was diagnosed by screening at one month of age because his older sister had HT1.

The demographic, clinical and laboratory data of the 22 children are shown in Tables 1 and 2. When the age at the first symptom was compared between the group presenting with focal hepatic lesions (n=13) and those presenting with rickets (n=5), it was found that patients presenting with focal hepatic lesions were significantly younger than those with rickets [median age: 3.25 (range: 1-14) *vs.* 10 (range: 3-24) months, P=0.05]. When the interval between the first symptom and diagnosis was compared between the aforementioned groups, those presenting with rickets had a significant delay in diagnosis (median interval: 5.5 (range: 1-18) *vs.* 26 (range: 12-42) months, P=0.001).

Clinical rickets was detected in 14 patients (63.6%), of whom 5 had complaints. Biochemical evidences of bone disease included high AP in all patients, of whom one was diagnosed at one month of age by screening. Hypophosphatemia was found in 20 patients (90.9%) and hypocalcemia in 13 (59.1%).

Ultrasound findings are shown in Table 3. Hepatic echogenicity was abnormal in 20 of the 22 patients (heterogenous, bright, focal or cystic lesions). The results of renal ultrasound were abnormal in 17 out of the 22 patients (nephromegaly and/or increased renal echogenicity).

Liver biopsy was performed in 5 patients, of whom one had neonatal hepatitis and 4 had active liver cirrhosis. One patient was diagnosed as having HT1 at 2.5 months of age and presented with hepatic focal lesions that were highly suspicious of malignancy. Triphasic CT of the patient confirmed the diagnosis of

Table 1. Demographic and clinical data of the 22 patients with hereditary tyrosinemia type 1

Variables	Patients, *n* (%)
Sex	
Males	8 (36.4)
Females	14 (63.6)
Residence	
Cairo	11 (50.0)
Outside Cairo	11 (50.0)
Consanguinity (in 20 couples)	16 (80.0)
Age of first symptom [median (range)] in mon	4 (1-24)
Age at presentation [median (range)] in mon	12 (1-66)
Interval between first symptom and diagnosis in mon	6 (0.5-42)
Abdominal distention	13 (59.1)
Jaundice	8 (36.4)
Bleeding tendency (epistaxis)	3 (13.6)
Edema	2 (9.1)
Hepatomegaly	21 (95.5)
Splenomegaly	21 (95.5)
Clinical ascites	1 (4.5)
Rickets	14 (63.6)

Table 2. Laboratory data of the 22 patients

Variables	Patients, *n* (%)
Anemia (Hb <10 g/dL)	17 (77.3)
Thrombocytopenia (platelets <150 000/μL)	10 (45.5)
Total bilirubin (>1.2 mg/dL)	15 (68.2)
Direct bilirubin (>0.2 mg/dL)	14 (63.6)
AST (folds above the upper limit of normal)	
Within normal	2 (9.1)
One fold increase	19 (86.4)
Two folds increase	1 (4.6)
ALT (folds above the upper limit of normal)	
Within normal	18 (81.8)
One fold increase	4 (18.2)
AP (folds above the upper limit of normal)	
Within normal	0 (0.0)
One fold increase	3 (13.6)
Two folds increase	4 (18.2)
Three folds increase or more	15 (68.2)
Serum albumin (g/L)	
Normal	15 (68.2)
Hypoalbuminemia (<32 g/L)	7 (31.6)
Prothrombin concentration (%)	
Normal	2 (9.1)
<70%	20 (90.9)
Serum calcium (8.8-10.8 mg/dL)	
Normal	10 (45.5)
Hypocalcemic (<8.8 mg/dL)	12 (54.5)
Serum phosphate (4.5-6.7 mg/dL)	
Normal	2 (9.1)
Hypophosphatemia (<4.5 mg/dL)	20 (90.9)
AFP (ng/mL)	
Elevated	22 (100.0)
Median (range)	43 785 (4504-175 000)
SA (μmol/L)	
Elevated >1 μmol/L (%)	22 (100.0)
Median (range)	68 (12-465)

Hb: hemoglobin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; AP: alkaline phosphatase; AFP: alpha fetoprotein; SA: succinylacetone.

malignant focal lesions, and AFP was 175 000 ng/mL. Open biopsy revealed a picture of neonatal hepatitis with focal steatosis and no dysplasia or malignant transformation (Fig. 1).

Table 4 shows a comparison between some laboratory parameters of the 10 patients treated with NTBC before and after therapy. The duration of NTBC treatment was less than 6 months in 2/10 (20%) and between 9 and 26 months in 8/10 (80%) patients. The median age at initiation of NTBC was 11 (range: 1-32) months and the median dose was 0.57 (range: 0.55-0.7) mg/kg per day. We used the lower dose, for economic reasons, and found it sufficient to improve growth, normalize impaired synthetic liver functions, heal bone disease secondary to renal tubular impairment, and maintain a continuous drop in AFP levels. Doses less than 0.55 mg/kg per day were associated with detectable succinylacetone in DBS or urine and required dose increase.[8]

The response to NTBC treatment was evidenced by a steep drop in serum AFP and undetectable SA in urine within 3 months. Six months after the therapy, alkaline phosphatase normalized in all patients except one; serum phosphate normalized in all but two patients.

In patient 1, triphasic CT showed intensely enhanced focal hepatic lesions (Fig. 2A), with bilaterally symetrically swollen kidneys (Fig. 3A). Six months after treatment with NTBC, the enhanced focal lesions were replaced by innumerable non-enhanced cirrhotic nodules (Fig. 2B) and the kidneys almost normalized (Fig. 3B).

Three patients (patients 1, 3 and 5) underwent living donor liver transplantation after 22, 18 and 10 months of NTBC treatment respectively despite adequate response to the therapy because of financial issues. The explanted livers were all cirrhotic with no dysplasia or malignant transformation. The 3 transplanted patients are surviving until writing this manuscript for 13, 11 and 4 months respectively. One of the 3 patients had biliary stricture for which a biliary stent was inserted and removed 5 months later with good biliary drainage. The other 2 patients did not experience any

Table 3. Ultrasound finding in the 22 patients with hereditary tyrosinemia type 1

Variables	Patients, *n* (%)
Hepatomegaly	21 (95.5)
Liver echopattern	
Heterogenous	16 (72.7)
Bright	2 (9.1)
Focal	10 (45.5)
Cystic	1 (4.5)
Normal	2 (9.1)
Splenomegaly	21 (95.5)
Kidneys	
Nephromegaly	8 (36.4)
Increased echogenicity	12 (54.5)
Normal	5 (22.7)
Ascites	6 (27.3)

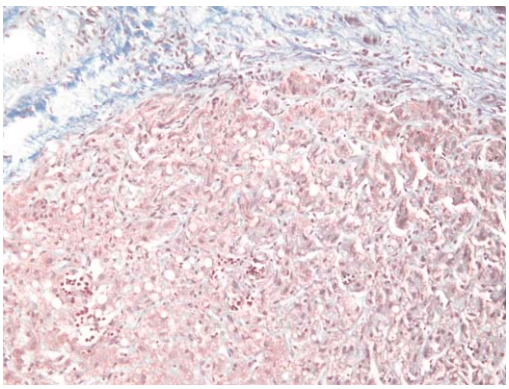

Fig. 1. Photomicrograph of a liver biopsy of a 2-month-old female patient with hereditary tyrosinemia type 1 showing neonatal hepatitis associated with focal steatosis, portal and pericellular fibrosis (Gomori trichrome stain × 200).

Table 4. Comparison of some laboratory data before and after NTBC therapy

Patient No.	Patients at diagnosis					Treatment			Last follow up on treatment				
	S. albumin (g/L)	AFP (ng/mL)	PC (%)	AP (IU/L)	SP (mg/dL)	Age at start of therapy (mon)	Duration of treatment (mon)	NTBC dose (mg/kg/d)	S. albumin (g/L)	AFP (ng/mL)	PC (%)	AP (IU/mL)	SP (mg/dL)
1	28	175 000	10	1416	4.5	6	22	0.55	41	13	100	340	5.6
2	34	74 900	24	1450	2.8	12	12	0.57	36	22	85	180	5.1
3	22	69 600	60	1360	2.2	30	18	0.65	44	395	90	170	5.9
4	31	57 800	70	1161	3.1	32	26	0.63	38	16	98	200	4.4
5	35	61 600	31	370	2.9	10	10	0.57	46	59	93	285	5.1
6	4	84 600	100	675	5.2	1	12	0.55	46	8	80	265	4.5
7	27	143 000	20	999	2.1	5	12	0.57	39	44	78	283	4.6
8	39	97 600	16	1406	4.1	6	9	0.61	42	826	68	310	5.3
9	33	53 900	29	491	2.3	21	5	0.70	33	1001	67	350	3.0
10	41	1 000	61	1490	1.5	28	2	0.55	36	460	83	1315	1.9

AFP: alpha fetoprotein; PC: prothrombin concentration; AP: alkaline phosphatase (normal value: 120-360 IU/mL); SP: serum phosphate (normal value: 4.5-6.7 mg/dL); NTBC: 2-(2-nitro-4-trifluoro-methylbenzoyl)-1, 3-cyclohexanedione.

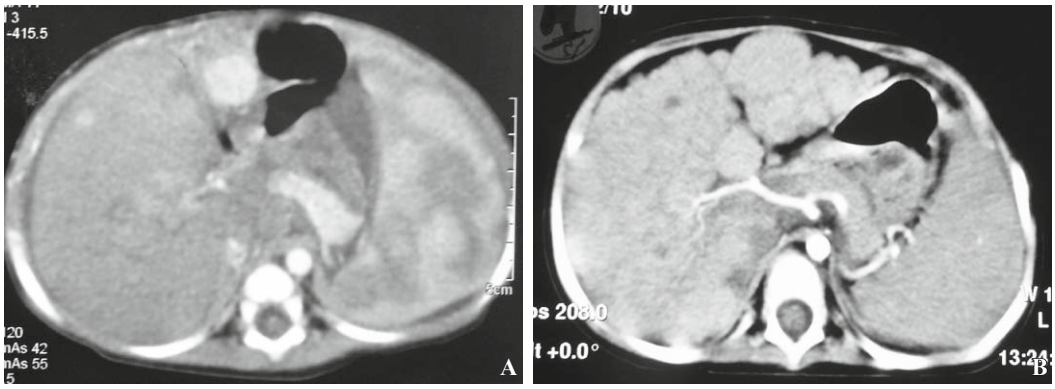

Fig. 2. A: CT scan of the abdomen of a 4-month-old female patient with hereditary tyrosinemia type 1 showing mild hepatomegaly with smooth outline and few intensely enhanced focal lesions in both hepatic lobes; **B:** Follow-up CT scan at the same level 6 months after treatment with NTBC showing marked cirrhotic changes with innumerable non-enhanced cirrhotic nodules.

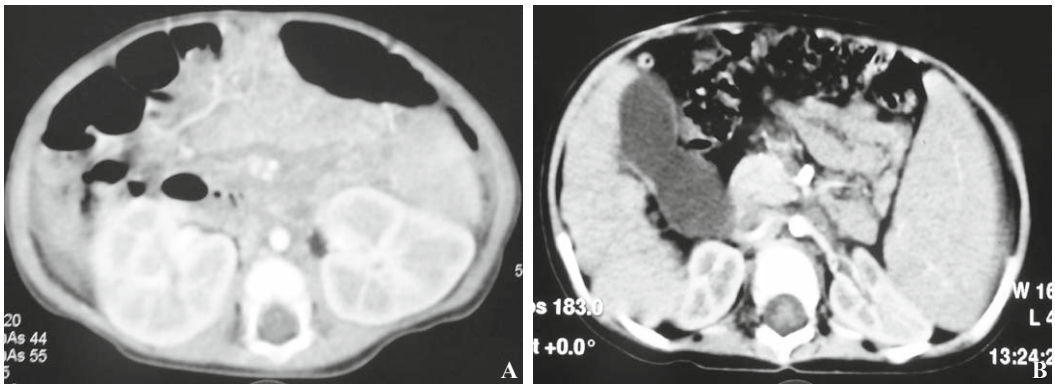

Fig. 3. A: CT scan of both kidneys of a 4-month-old female patient with hereditary tyrosinemia type 1 showing bilateral symmetrical nephromegaly; **B:** Follow-up CT scan 6 months after NTBC treatment showing an appreciable decrease in the degree of the bilateral nephromegaly with almost normal kidney size.

complications to the present. Immunosuppressive agent used post-transplantation at our center is tacrolimus in addition to a short course of steroids with gradual tapering in the first 3 months.

Discussion

Within the last 3 years, 22 patients with HT1 were diagnosed at the Pediatric Hepatology Unit at Cairo University Children's Hospital, Egypt. These patients were born over the last 5 years. This is a considerable number of patients presenting to a single center, in consideration that testing for HT1 became available in Egypt druing the 3 years. HT1 may be considered as not uncommon autosomal recessive metabolic disorder in Egypt. This may be attributed to a high rate of consanguineous marriages in Egypt.[9,10] The rate of consanguinity in our cohort was 80%. Multi-center studies in Egypt should be encouraged and national registry of HT1 cases has to be considered in order to report the annual incidence of the disease. The incidence of HT1 worldwide is 1:100 000-1:120 000 with most of the reported cases clustering in 2 regions, Scandanavia and the province of Quebec, where the incidence is estimated about 1: 20 000.[11]

In our cohort, 16 patients had a hepatic manifestation. The liver was affected in patients with HT1, with symptoms ranging from severe hepatic insufficiency to cirrhosis and hepatocellular carcinoma. Three of our cohort had overt bleeding in the form of epistaxis, and 91% had a prothrombin level below 75%. Hypoalbuminemia was also observed in 32% of the patients. Despite these derangements in synthetic liver functions, the level of plasma transaminase was slightly increased or even normal in most patients. The plasma transaminase level may be mildly elevated and is in disproportion to the degree of coagulopathy.[12] In the present study, 59% of the patients had focal hepatic lesions as a presenting symptom; of whom, except two, were younger than one year old at their first presentation.

Renal tubular dysfunction represented by aminoaciduria, glucosuria and rickets is one of the hallmarks of HT1 that can occur despite treatment,[13] and has been reported as the major clinical

manifestation in the older children.[14] Rickets was the first presentation in 23% of our patients; they were significantly older and had a significant delay in diagnosis. This may be explained by the fact that parents of rachitic children may seek medical advice at a general health facility, or they may seek advice from orthopedic surgeons or even after a prolonged delay they may present to nephrologists for late rickets. Pediatric hepatologist is more oriented with the diagnosis of HT1. In Egypt there are no special guidelines for vitamin D supplementation to infants as for vitamin A. With the increasing number of cases of HT1, pediatric nephrologists and orthopedic surgeons should be aware of the possibility of HT1 as a possible diagnosis in an infant or child with hypophosphatemic rickets.

None of our patients presented with porphyria-like neurologic crises which are common in poorly controlled HT1 and can be a major cause of morbidity and mortality.[15] This may be explained by the fact that all patients presented to a pediatric hepatology unit. However, even our patients who were not yet started on NTBC did not develop such crisis.

High AFP levels were observed in our cohort. One patient had an AFP level of 175 000 ng/mL. The patient underwent a liver biopsy from a suspected malignant focal hepatic lesion, which was later proved histopathologically neonatal hepatitis with steatosis. AFP may rise from liver injury induced by toxic metabolites accumulating immediately proximal to the metabolic block. These toxins are fumaryl acetoacetate and maleyl acetoacetate and their metabolites SA and succinyl acetoacetate. Fumaryl acetoacetate is known in animal studies to cause apoptosis,[16] to be mutagenic[17] and pro-oxidant.[18] Total AFP is sensitive but not specific for hepatocellular carcinoma.[6]

Detection of hepatocellular carcinoma relies on combined radiological and biochemical monitoring. It is recommended that ultrasound be carried out every six months for HT1 patients and hepatic magnetic resonance image annually. If a suspicious nodule develops this will be usually an indication for transplantation but other radiological modalities such as contrast ultrasound or MRI may be useful to help clarify the pathology.[19] AFP should be checked every month. Any rise of AFP or failure to fall is a cause of concern.[6]

In our treated patients, serum AFP showed a steep decrease after NTBC therapy. Three of the 10 treated patients started on NTBC after 24 months of age. If the treatment is started before 24 months of age, the risk of hepatocellular carcinoma can be decreased. Increase of AFP may be a reflection of insufficient metabolic control; however, further examination to exclude hepatocellular carcinoma (HCC) is usually warranted.[20,21] Patients with persistently high levels of AFP are probably at risk of developing cancer as already reported.[22]

Another long-term hepatic complication of HT1 is cirrhosis. Among the 5 patients undergoing liver biopsies in our study, 4 patients had active cirrhosis. Their ages ranged from 12 to 30 months. The metabolic derangement in HT1 is speculated to start in utero[23] as reflected by extreme AFP levels typically in newborns with tyrosinemia. Our patient, who was screened for HT1, because of a previously affected sister, had an AFP level of 84 624 ng/mL at one month of age despite normal clinical, biochemical and imaging findings. The speculation of in utero metabolic derangement was supported by the observation of advanced macro- or micronodular cirrhosis in very young infants.[23]

Persistent cirrhosis was reported despite NTBC therapy.[24] In our treated patients, one patient had intensely enhanced focal hepatic lesions which were replaced 6 months after NTBC therapy by non-enhanced cirrhotic nodules. The 3 patients who had undergone living donor liver transplantation showed macro- and micronodular cirrhotic changes in their explanted livers despite adequate metabolic control on NTBC and continuous decline in AFP level and improvement of growth and synthetic liver function. Liver sonography may serve as a screening method for parenchymal changes and for the assessment of portal hypertension, but has limitations in the detection of HCC among the multitude of regenerative nodules in liver cirrhosis.[25]

Ultrasound examination revealed that 14 patients (63.6%) had clinical rickets associated with hypophosphatemia and 17 (77.3%) had enlarged kidney and/or echogenicity. In younger children, symmetrical nephromegaly and calcification, primary in the medulla, are frequent and constitute important radiological features.[26,27] Serum phosphorus normalized with healing of rickets in our 6 rachitic patients after treatment. Renal architecture (size and ultrasonographic echogenicity) and tubular function (aminoaciduria, hypercalciuria, phosphaturia and tubular acidosis) have been shown to be abnormal in most of children with HT1, with tubular dysfunction in the great majority and frank nephrocalcinosis in 16%-33%.[27] Renal tubular dysfunction can be successfully and persistently reversed after NTBC treatment, and early diagnosis is important to ensure the best outcome.[28]

The cost of NTBC therapy depends on the dose prescribed, which is related to the weight of the patient. For an infant weighting 6 kg, 3 capsules (2 mg each) are needed daily. Thus the cost per month will be 1680€ (2295 US dollars). The dose will be increased

according to weight gain as the baby grows. Hence this treatment imposes a significant economic burden on the family. The indication of liver transplantation in HT1 at our center is mainly the cost of the treatment. Putting in mind the financial burden of an increasingly recognized disease, and the fact that cirrhosis may develop despite NTBC treatment[24] and the fact that NTBC cannot prevent the development of HCC in some HT1 patients, when the treatment does not begin in early life,[29-31] we think that liver transplantation is not an unjustified option for our patients who underwent the procedure. NTBC does not correct the abnormal hepatic gene expression,[16] fibrogenic markers[32] or hepatic dysplasia[33] in humans with HT1. In fumaryl acetoacetate deficient knockout mice, high doses of NTBC in combination with dietary restriction of phenylalanine and tyrosine did not prevent HCC,[29,30] although a mouse model cannot be directly transferred to humans. Those aged >2 years or more when NTBC is commenced are at higher risk for HCC. Whether to offer elective transplantation to this group or to delay listing until there is evidence of HCC is liable to be discussed on a patient-to-patient basis.[19] In the present study, 6 (27%) patients were diagnosed at the age of 2 years or more.

In conclusion, HT1 is increasingly recognized among Egyptian children; this may be explained by the high rate of consanguinity among Egyptians. Hepatomegaly, early in life, with focal hepatic lesions is the commonest presentation. Diagnosis is delayed in patients with rickets. NTBC therapy is effective but very expensive. Liver transplantation may still be considered from the economic point of view and in the presence of the risk for malignant transformation particularly if treatment is started above 2 years of age.

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Competing interest: None.

Contributors: El-Karaksy H contributed to idea proposal, data collection, and writing the manuscript. Fahmy M contributed to data collection, writing the manuscript, and statistical analysis. El-Raziky M contributed to clinical follow-up of the patients and revising the manuscript. El-Koofy N contributed to ultrasound examination for the patients and revising the manuscript. El-Sayed R contributed to ultrasound examination for the patients and revising the manuscript. Rashed MS contributed to biochemical analysis and revising the manuscript. El-Kiki H contributed to imaging studies including abdominal ultrasonography, X-ray (ends of long bones for active rickets) when indicated, and triphasic CT for hepatic focal lesions. El-Hennawy A contributed to histopathological assessment of liver biopsy. Mohsen N revised the manuscript.

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