Liver Transplant for Children With Hepatocellular Carcinoma and Hereditary Tyrosinemia Type 1

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Abstract

Objectives: This study sought to determine the prevalence of hepatocellular carcinoma and other premalignant lesions in children with hereditary tyrosinemia type 1 who had undergone an orthotopic liver transplant at the Shiraz Transplant Center, in Shiraz, Iran.

Materials and Methods: Between September 2006, and June 2011, thirty-six patients with hereditary tyrosinemia type 1 received a liver transplant from a deceased (whole or split) or a living-related donor. Clinical records and pathologic specimens, before and after surgery, for each case were reviewed. In addition, ultrasound, abdominal computed tomographic imaging scan findings, and levels of alpha-fetoprotein were recorded.

Results: Twenty-two patients with hepatic nodules larger than 10 mm underwent a Tru-Cut needle biopsy before their liver transplant. In 2 patients, a diagnosis of hepatocellular carcinoma was made by pathologic examination; in the other 20, cirrhosis was confirmed with no evidence of malignancy. After pathologic examination of the explanted livers, the largest nodules in the 36 patients were 35 mm. Five cases had at least 1 nodule of hepatocellular carcinoma. Three of the other patients had small cell dysplasia in some of nodules. All 5 cases with hepatocellular carcinoma received pretransplant nitisinone treatment. All patients with hepatocellular carcinoma after their liver transplant are alive at the time of this writing.

Conclusions: The prevalence of cell dysplasia and hepatocellular carcinoma in children with hereditary tyrosinemia type 1 in our study is not as high as that reported previously, so it appears that patients older than 2 years of age require a liver transplant.

Key words: Hereditary tyrosinemia type 1, Liver transplantation, Hepatocellular carcinoma

Introduction

Hereditary tyrosinemia type 1 (HT-1) is an autosomal recessive metabolic disorder characterized by deficiency of fumarylacetoacetate hydrolase, the last enzyme in the tyrosine catabolic pathway. The clinical spectrum of the disease is extremely wide, and ranges from death from hepatic failure in the first months of life, to chronic complications, such as hepatocellular carcinoma (HCC), renal tubular dysfunction, renal failure, and episodes of peripheral neuropathy during childhood and early adulthood that are like intermittent acute porphyria.1

Accumulated fumarylacetoacetate is mutagenic and carries with it a high risk for HCC in the children with HT-1.2 The reported incidence of HCC in these patients ranges up to 50%.3 Early treatment with NTBC [2-(2-nitro-4-trifluoromethylbenzoil)-1,3 cyclohexanedione] before the age of 2 years has been suggested to prevent HCC.3

An early diagnosis, and the advent of a liver transplant, have been curative for these children. Fear of occurrence of HCC has pushed surgeons to perform a liver transplant in small children. Although liver transplant in infants has provided
good long-term outcomes in some centers, there are surgical technical difficulties in this group of children, so the exact timing of a liver transplant must be investigated. This study sought to determine the prevalence of the dysplasia, HCC, and timing of liver transplant among the children with HT-1 in Shiraz Transplant Center in Shiraz, Iran.

Materials and Methods

From 2006 until 2011, two hundred eighty-six pediatric liver transplants were performed at Shiraz Transplant Center in Shiraz, Iran. Thirty-six patients with HT-1 (17 boys and 19 girls) received the transplant, 11 of which were from deceased donors (6 whole organ and 5 split livers), and 25 received their graft from living-related donors (mother 14, father 10, and uncle 1). In each case, the diagnosis of HT-1 was confirmed by the presence of characteristic clinical findings, high serum alpha-fetoprotein (AFP) and positive serum succinylacetone.

All patients had complete hematologic, liver, and kidney work-up including serum concentrations of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, serum bilirubin, and plasma proteins, AFP, serum tyrosin, and succinylacetone levels. They also underwent imaging studies including ultrasonography and computed tomography (CT) of the abdomen. All patients with hepatic nodules greater than 10 mm in size underwent an ultrasound- or CT scan-guided Tru-Cut needle biopsy, after correction of coagulopathy.

All patients were on relatively restricted tyrosine and phenylalanine diet; only 12 of them were given nitisinone treatment (NTBC) before liver transplant, for duration between 2 months and 1.5 years (mean, 7.3 ± 4.8 months). In 2 patients NTBC was started before 2 year of age and another 10 cases were taken it after 2 year of age due to delayed diagnosis. Explanted livers were studied in 10-mm serial sections to find any small nodules of HCC.

Results

The mean age of the patients was 3.9 year (range, 9 mo to 14 y). The PELD scores were between 14 and 36. Alpha-fetoprotein levels before liver transplant were 7 to 3532 μg/L (normal, up to 5 μg/L).

Abdominal ultrasonography and CT scan showed hepatic nodules in all 36 patients before liver transplant. The reported size of the nodules by CT scan before the transplant was 9 to 34 mm.

Twenty-two patients with hepatic nodules larger than 10 mm underwent a Tru-Cut needle biopsy before the liver transplant. In only 2 patients HCC was diagnosed by pathologic examination; in the others, only cirrhosis was confirmed without evidence of malignancy.

After pathologic examination of the explanted livers, the largest nodules in the 36 patients were 35 mm. Five cases where found with at least 1 HCC nodule. Three of the other patients had small cell dysplasia in some of nodules; however, after a thorough examination of the explanted liver, no HCC nodule was found in these 3 patients.

Table 1 shows the results of pathologic examination of the explanted livers of the 5 patients with HCC regarding age, maximum size, number of the HCC nodules, AFP levels, and prior NTBC treatment. The mean AFP levels in patients with and without HCC were 650.2 ± 336.6 μg/L and 424.7 ± 667.1 μg/L (P = .399).

### Table 1. Demographics and Clinical Findings of Patients with HT-1 and HCC (n=5)

<table>
<thead>
<tr>
<th>Age of the Patient (y)</th>
<th>AFP Level (μg/L)</th>
<th>No. of the HCC Nodules</th>
<th>Largest Size of HCC Nodules (mm)</th>
<th>Prior NTBC Treatment</th>
<th>Dietary Restriction</th>
</tr>
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<tr>
<td>2</td>
<td>980</td>
<td>1</td>
<td>35</td>
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<td>Relative</td>
</tr>
<tr>
<td>4</td>
<td>989</td>
<td>1</td>
<td>15</td>
<td>Yes</td>
<td>Relative</td>
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<tr>
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<td>1</td>
<td>20</td>
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<tr>
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<td>Relative</td>
</tr>
</tbody>
</table>

Abbreviations: AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; HT-1, hereditary tyrosinemia type 1; NTBC, nitisinone

None the patients younger than 2 years of age (17 cases) had liver cell dysplasia or HCC nodules. All 5 cases with HCC nodules were among the patients older than 2 years of age (19 patients). All of our patients with HCC were treated with NTBC before the transplant. At the time of this writing, all of the patients with HCC after liver transplant are alive.

Discussion

Hereditary tyrosinemia type 1 is an inborn error of metabolism caused by a deficiency of fumaryl-acetoacetate, which is the last enzyme in the pathway of tyrosine metabolism. It causes accumulation of a toxic and mutagenic substance, that is, succinylacetone. Chronic liver disease manifested
by cirrhosis is the most common liver disorder in patients with HT-1, and it is most commonly macro-micronodular, with a varying degree of steatosis.3

There is high risk of HCC in patients with HT-1, with a reported risk from different centers of 15% to 50%. Medical treatment for patients with NTBC reduces the risk of HCC development but it does not eliminate it.6 Nitisinone decreases serum concentrations of AFP, but its effect on the risk of HCC is unclear.2 In 1 retrospective study of long-term outcomes of 46 patients treated with NTBC, 15 cases had persistently elevated levels of AFP, and 2 patients developed HCC.7 All our cases with HCC were among the patients who received NTBC, so apparently this treatment did not prevent the development of HCC.

In Iran, neonatal screening for HT-1 is not done routinely, so most cases are diagnosed after 1 month of age. However, if NTBC were started before 1 month, it could prevent liver disease.8 By treating infants with NTBC, HT-1 evolves into a nonprogressive disease, with normal liver function; however, toxic metabolites continue to be produced, so the risk of HCC is not completely eliminated.9 Increases in the levels of AFP, or slow decreases in their levels, or non-normalizing concentrations of AFP after NTBC treatment are important predictors of HCC development.10 In a study on 12 patients with HT-1, lectin-reactive AFP is an additional marker that may help distinguish HCC from benign liver disease.11

There is no consensus between the transplant centers on the precise time a child with HT-1 should receive a liver transplant. Also, younger age and lower weight are associated with increased mortality after liver transplant.2,12 Mieles and associates13 published their experiences with 10 cases of HT-1 from the University of Pittsburgh. In their study, 5 of 10 patients (50%) with HCC were older than 2 years. 9 of 10 cases showed cell dysplasia (90%). The authors suggest that liver transplant should be considered for children with HT-1 older than 2 years, because beyond this age, the incidence of HCC increases substantially.14

Dehner and associates reviewed the native liver pathology of 5 children with HT-1 after liver transplant, by comparing the biopsies of 2 of them performed several years before transplant. They observed a morphologic change from the initial micronodular cirrhosis to mixed and macronodular cirrhosis. In that study, focal hepatocellular dysplasia was seen in the mixed cirrhosis. Macronodular cirrhosis accompanied 2 cases of HCC. The authors concluded that liver transplant is necessary before age of 2 years.14

Early liver transplant has been recommended as the curative treatment of HT-1 before 1 year of age in many previous reports.13,15,16 Contrary to these studies, Luks and associates concluded that the incidence of HCC is less than 10%, and close monitoring of appearance or increase in size of the hepatic nodule is a guide to transplant, and early transplant is not supported.17

Nineteen of our patients (52.8%) were older than 2 years. If cell dysplasia is considered a premalignant condition, the prevalence of malignancy and dysplasia was 22.2% in our patients. The overall incidence of HCC in HT-1 in our center has been lower than that of previous reports, that is, 13.8% versus 15% to 50%.2 Esquivel and associates reported their experience with 10 cases of HT-1, and 5 of them had HCC (50%), and all were more than 2 years old.18 Also, Weinberg and associates reported 37% of HCC in patients who survived beyond age of 2 years old.19

The yield from Tru-Cut biopsies for preoperative diagnosis of cell dysplasia and HCC was 25% (2 of 8 patients). Dubois and associates studied the imaging (ultrasonography or CT) of 30 patients with HT-1, and were unable to discern the cancerous nodules. These authors concluded that CT and ultrasonography are unreliable for detecting HCC early, and transplant is advised as soon as the liver nodule is imaged.20

Although in massive HCC, AFP levels show a distinct increase, but this is not a good indicator detecting HCC early. Also in our patients, the highest concentration of AFP was not in the patients with dysplasia or HCC.21 We also confirmed prior observations, which found that neither the concentration of AFP, nor imaging findings, can be used to detect HCC early.

None of our patients had dysplasia or HCC before age 2 year, in contrast to others reports that...
state that beyond age of 2 years, the risk of HCC was 37.5% to 50%.

The prevalence of cell dysplasia and HCC in children with HT-1 in our study was not as high as previously reported, so these patients may need a liver transplant after 2 years old. Also, preoperative liver biopsy has relatively low yield (25%) for detecting dysplasia and HCC, and the ultrasonography, CT finding, and AFP concentration cannot detect early HCC.

References