

# Etiology and Complications of Liver Cirrhosis in Children: Report of a Single Center from Southern Iran

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## ABSTRACT

### BACKGROUND

Liver cirrhosis is one of the major causes of hospitalization and mortality in children. A wide spectrum of disorders including developmental abnormalities, infections, metabolic and genetic disorders can lead to liver cirrhosis in pediatric patients. Determination of its etiology is important for treatment, prevention of progressive liver damage, family counseling and prioritizing liver transplantation. The aim of this study is to evaluate causes of liver cirrhosis in children in Southern Iran.

### METHODS

We included all cirrhotic children aged less than 18 years who referred to an outpatient pediatric gastroenterology clinic affiliated with Shiraz University of Medical Sciences between March 2009 and September 2010 in this cross-sectional study. The etiology of cirrhosis was determined according to clinical findings, laboratory tests, imaging studies such as ultrasonography or computed tomography scan, hepatobiliary scintigraphy and histopathologic examination of the liver biopsy. Cirrhosis with unknown etiology was considered as cryptogenic.

### RESULTS

A total of 106 cirrhotic children aged between 5 months to 18 years with a mean age of  $8.24 \pm 6.12$  years that included 60 boys (56.6%) and 46 girls (43.4%) were enrolled in the study. The most common causes of liver cirrhosis were Wilson disease (n=22; 20.7%), biliary atresia (n=19; 17.9%), and cryptogenic cirrhosis (n=14; 13.2%). Other causes were autoimmune hepatitis (n=12; 11.3%), idiopathic neonatal hepatitis (n=10; 9.4%), hepatorenal tyrosinemia (n=9; 8.5%), glycogen storage disease (n=6; 5.7%), and progressive familial intrahepatic cholestasis (n=4; 3.8%).

### CONCLUSION

Considering the most common etiology of liver cirrhosis in children in this part of Iran we suggest testing for Wilson disease in all cirrhotic children.

### KEYWORDS

Cirrhosis; Children; Wilson disease; Biliary atresia

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## INTRODUCTION

Cirrhosis is a diffuse process characterized by progressive hepatic

fibrosis, distortion of the hepatic architecture and formation of regenerative nodules,<sup>1,2</sup> that is relatively uncommon in the pediatric age group.<sup>3,4</sup> The characteristic feature of cirrhosis in children is ascendancy of biliary cirrhosis and cirrhosis due to inborn errors of metabolism.

Chronic cholestasis, inborn errors of metabolism and chronic hepatitis are the main causes of cirrhosis in children.<sup>5</sup> In a previous study on 83 children we reported the most common causes of cirrhosis in children waiting for liver transplantation as biliary atresia (27.7%) and cryptogenic cirrhosis (24.1%).<sup>6</sup> In another study in our center cryptogenic cirrhosis and autoimmune hepatitis related cirrhosis were reported as the main indications for liver transplantation in children.<sup>7</sup>

Complications of cirrhosis include jaundice, ascites, gastrointestinal variceal bleeding, and hepatic encephalopathy, whose presence is indicative of decompensated disease.<sup>8-10</sup> Other reported complications include edema,<sup>11</sup> spontaneous bacterial peritonitis,<sup>12</sup> and hepatopulmonary<sup>13</sup> and hepatorenal syndromes.<sup>14</sup>

For suitable treatment of liver cirrhosis the need for early diagnosis and etiological definition should be emphasized.<sup>15</sup> Thus, the aim of this study is to report the causes of liver cirrhosis and evaluate its complications in children from Southern Iran.

## MATERIALS AND METHODS

All cirrhotic children aged less than 18 years who referred to an outpatient pediatric gastroenterology clinic affiliated with Shiraz University of Medical Sciences between March 2009 and September 2010 were enrolled in this cross-sectional study. Cirrhosis was diagnosed according to clinical, radiological, or histological criteria.

All patients were clinically examined and a data gathering form was completed that contained demographic, clinical and paraclinical data. The etiology of cirrhosis was identified according to clinical findings; laboratory tests such as serum ceruloplasmin, 24-hour urine for copper, anti-nu-

clear, anti-smooth muscle, and anti-liver kidney microsomal type 1 antibodies, HBs antigen, anti-HBc antibody, anti-HCV antibody, sweat chloride test, alfa-1 antitrypsin genotyping, serum succinylacetone and other relevant investigations; radiographic evaluation such as ultrasonography or computed tomography scan; hepatobiliary scintigraphy; and histopathologic examination of the liver biopsy. Cirrhosis with unknown etiology was categorized as cryptogenic. Of these 106 patients, 94 cases had liver biopsy-proven cirrhosis and in another 12 cases liver biopsy was not done due to coagulopathy. Cirrhosis was diagnosed according to ultrasonography findings of heterogeneous liver with coarse echo with or without nodule formation and irregular borders. Patients with acute hepatitis and those whose cirrhotic livers were not definitively established were excluded from the study. Totally, we analyzed 106 children with documented liver cirrhosis for etiologies and complications of cirrhosis.

Severity of liver disease was evaluated by Child-Pugh classification, "Pediatric End-stage Liver Disease (PELD)" score for those under the age of 12 years and "Model for End-stage Liver Disease (MELD)" score for those over the age of 12 years. The PELD/MELD scores were calculated according to standard formulas and analyzed using the [www.unos.org](http://www.unos.org) website.

Complications of cirrhosis were diagnosed as follows. Jaundice was diagnosed clinically as yellowish discoloration of sclera and skin. Ascites was diagnosed according to physical findings such as abdominal flank bulge with fluid, fluid wave, shifting dullness, a ballotable liver and spleen, umbilical and inguinal hernia and ultrasonographic evidence of ascites. Hepatic encephalopathy was diagnosed clinically as irritability, lethargy, acute change in mental status, neurodevelopmental delay, school problems, sleep reversal, ataxia, and tremors. Esophageal varices were diagnosed endoscopically. Abdominal paracentesis with polymorphonuclear cells more than 250/mm<sup>3</sup> was considered to be diagnostic of spontaneous bacterial peritonitis. Hepatopulmonary syndrome was diagnosed as arterial oxygen pressure of <70 mmHg in room air with

alveolar/arterial gradient of >20 mmHg.

All data were analyzed by ANOVA and the student's t-test using SPSS for Windows (version 15.0).

## RESULTS

There were 106 pediatric patients with liver cirrhosis with a mean age of  $8.24 \pm 6.12$  years (range: 5 months to 18 years). Of these, 60 cases were boys (56.6%) and 46 were girls (43.4%).

The mean PELD/MELD scores were  $14.2 \pm 11.9$  (range: 6-48) and the mean Child-Pugh score was  $8.1 \pm 2.2$  (range: 5-13). According to the Child-Pugh classification, 27% were classified as grade A, 44% as grade B and 29% as grade C.

The most common causes of liver cirrhosis were Wilson disease (n=22; 20.7%), biliary atresia (n=19; 17.9%), and cryptogenic cirrhosis (n=14; 13.2%). Other causes were autoimmune hepatitis (n=12; 11.3%), idiopathic neonatal hepatitis (n=10; 9.4%), hepatorenal tyrosinemia (n=9; 8.5%), glycogen storage disease (n=6; 5.7%), progressive familial intrahepatic cholestasis (n=4; 3.8%), paucity of bile ducts (n=3; 2.8%), cardiac cirrhosis, choledocal cyst and primary sclerosing cholangitis (2 cases for each one; 1.9%), and Caroli's disease in one child (0.9%).

In our study, none of the patients had liver cirrhosis caused by an infection. There was no statistically significant difference between boys and girls for any etiology of liver cirrhosis ( $p=0.56$ ). The characteristics of patients in different etiologic groups are shown in Table 1.

The most frequent complication of liver cirrhosis in children was jaundice (n=72; 67.9%) followed by ascites in 47 (44.3%). Non-bleeding esophageal varices were present in 32 children (30.2%) and gastrointestinal variceal bleeding was seen in 17 cases (16.1%). Other complications included hepatic encephalopathy (n=13; 12.7%), edema (n=8; 7.5%), spontaneous bacterial peritonitis (n=5; 4.7%) and hepatopulmonary syndrome (n=5; 4.7%). Hepatorenal syndrome was not present in any children with liver cirrhosis; 19 patients (17.9%) had no

complications. The results of liver function tests in children with liver cirrhosis are shown in Table 2.

## DISCUSSION

Liver cirrhosis is the most common hepatic cause for hospitalization in adults' gastroenterology and hepatology wards and also the third leading gastrointestinal causes of death in Iran.<sup>16</sup> Although rather uncommon and multifactorial in etiology, liver cirrhosis is a severe and often rapidly fatal disease in pediatric patients. There is little epidemiological information regarding etiology of liver cirrhosis in children and its change over time.

The most common causes of liver cirrhosis in this study were Wilson disease (20.7%), biliary atresia (17.9%), cryptogenic cirrhosis (13.2%), and autoimmune hepatitis (11.3%). Recently this center has become an active pediatric liver transplant center in the Middle East region with more than 70 pediatric liver transplants annually, thus the high number of subjects with Wilson disease might be attributed to referrals from other parts of the country. In a recent study from Iran the most common hepatic diseases among inpatients were hepatitis B virus (HBV) and cryptogenic or non-alcoholic fatty liver disease induced cirrhosis.<sup>17</sup> In another study from Southern Iran HBV infection was the major cause for cirrhosis and ascites was the most common complication in adult patients.<sup>18</sup> The mean PELD/MELD scores in this study was 14.2 that is comparable with 15.5 in the Behroozian R et al series.<sup>19</sup>

Patients with cirrhosis are susceptible to a variety of complications and their life expectancy is markedly reduced.<sup>20</sup> The most frequent complications of liver cirrhosis in children in the present study were jaundice (67.9%), ascites (44.3%), gastrointestinal variceal bleeding (16.1%), and hepatic encephalopathy (12.7%).

In a Tunisian study on 36 girls and 35 boys with cirrhosis, jaundice and hepatomegaly were the most frequent clinical signs. Regarding the etiology of cirrhosis, biliary causes (including biliary atresia, choledocal cysts, and progressive familial intrahepatic cholestasis) were diagnosed as the

**Table 1:** Characteristics of patients with liver cirrhosis according to etiology

Underlying diseases	No.(%)	Male/female	Mean age (yrs)	Age range (yrs)	Child A	Child B	Child C	Mean PELD/ MELD	Mean Child score
Wilson disease	22 (20.7)	14/8	12.1±3.3	6-18	2	8	12	23.4±12.9	9.6±2.2
Biliary atresia	19 (17.9)	8/11	1.1±0.9	0.5-4	1	12	6	15.5±10.7	8.1±1.3
Cryptogenic	14 (13.2)	9/5	11.2±4.8	2-18	8	4	2	6.6±9	6.8±2.4
Autoimmune	12 (11.3)	5/7	15.5±3.3	8-18	1	4	7	20.6±10.8	9.4±2.3
INH	10 (9.5)	5/5	2.8±2.1	1-6	1	5	4	16.9±11.4	8.5±1.7
Tyrosinemia	9 (8.5)	6/3	4±6	0.7-10	3	4	2	8±5.5	7.7±2.5
GSD	6 (5.7)	4/2	8.6±3	4-12	6	0	0	6.1±4.3	5.3±0.5
PFIC	4 (3.8)	2/2	3±3.2	1-8	0	4	0	11±7.3	7.7±9.5
Paucity of bile ducts	3 (2.8)	3/0	3±2.3	1-5	1	1	1	15.3±12.5	7.6±2
Cardiac cirrhosis	2 (1.9)	1/1	5.2±2.4	4-7	1	1	0	1	7±1.4
Choledochal cyst	2 (1.9)	1/1	7±2.8	5-9	0	2	0	13.5±3.6	9
PSC	2 (1.9)	2/0	12.5±7.7	7-18	2	0	0	5±5.6	6
Caroli's disease	1 (0.9)	0/1	11	11	1	0	0	8	6

INH: Idiopathic Neonatal Hepatitis; GSD: Glycogen Storage Diseases; PFIC: Progressive Familial Intrahepatic Cholestasis; PSC: Primary Sclerosing Cholangitis; PELD: Pediatric End-stage Liver Disease; MELD: Model for End-stage Liver Disease.

**Table 2:** Results of liver function tests in children with liver cirrhosis

Laboratory test	Maximum	Minimum	Mean ± SD
Total protein	10.1	3.4	7 ± 1.1
Albumin	5.8	1.7	3.5 ± 0.8
Globulin	7	1	3.4 ± 1
AST	848	12	166.2 ± 131.3
ALT	545	16	122.7 ± 101
Alkaline phosphatase	4201	54	939.7 ± 729.7
Total bilirubin	60	0.2	8.6 ± 11.7
Direct bilirubin	28.2	0.1	3.4 ± 4.9
INR	5	1	1.8 ± 0.9

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; INR: International normalized ratio

most frequent (40%), causes followed by metabolic diseases that included hepatorenal tyrosinemia, Wilson disease (17%) and post-hepatitis cirrhosis (17%). In 27% of cases, no etiology was found.<sup>21</sup> The authors concluded that etiological diagnosis in children with cirrhosis was a problem in their country because of the lack of availability of some specific tests.<sup>21</sup> In Iran, the main indications for liver transplantation in children were reported as Wilson disease (20.3%), cryptogenic cirrhosis (16.7%)

and autoimmune cirrhosis (14.5%),<sup>22</sup> which agreed with the results of this study.

Bernard, in a review article has reported that chronic cholestasis starting in early infancy, chronic hepatitis, and metabolic disorders are the main causes of cirrhosis in children. He recommended that precise identification of the cause is very important because effective therapy is available for many causes. Close follow-up is necessary for prolonging life and to prevent, diagnose and manage

complications on time as well as to consider liver transplantation when no effective therapy is available.<sup>5</sup>

In a study from Northern India on 235 children with hepatobiliary disorders, acute hepatitis (28%), chronic liver disease (36%) and neonatal cholestasis syndrome (26%) were presented as the most common causes of liver disease. Chronic liver diseases included post-hepatitic cirrhosis (13%), Wilson disease (21%), autoimmune (4%), and non-Wilsonian metabolic diseases (16%).<sup>23</sup>

In Brazil the most common causes of pediatric cirrhosis were biliary atresia (50%), autoimmune disorders (20.5%) and cryptogenic (17.6%).<sup>24</sup>

The most common indications for liver transplantation in children in Argentina were biliary atresia (30%), fulminant hepatic failure (27%) and autoimmune cirrhosis (16%).<sup>25</sup>

In Oman, progressive familial intrahepatic cholestasis (30%) as well as fibrocystic diseases of the liver and kidneys (21%) were the most common causes of liver cirrhosis.<sup>26</sup>

These reports from developing countries recognized that metabolic disorders, cholestatic syndromes and autoimmune hepatitis were the most common causes of cirrhosis in children in these countries.

Also, in Japan the main causes of liver cirrhosis in children who underwent liver transplantation were biliary atresia (72.9%), cryptogenic (8.1%), Budd Chiari syndrome (5.4%), progressive familial intrahepatic cholestasis (5.4%), and Wilson disease (2.7%).<sup>27</sup>

In a nationwide survey in Japan to evaluate the etiology of liver cirrhosis, the data from 33379 patients with liver cirrhosis were analyzed at 58 hospitals. The most common causes of cirrhosis were hepatitis B virus (13.9%), hepatitis C virus (60.9%), alcohol (13.6%), primary biliary cirrhosis (2.4%) and autoimmune hepatitis (1.9%).<sup>28</sup>

In our center, Saberifiroozi et al. in a study on 480 adult patients (mean age: 39 ± 13 years; 68.1% men) on the liver transplantation list reported that the most common causes of cirrhosis were cryptogenic (143; 29.9%) and hepatitis B virus (127; 26.5%).<sup>29</sup>

These studies have shown completely different causes of liver cirrhosis in children and adults, as the most common cause of liver cirrhosis in adults in our center were viral hepatitis. In the current study, there were no cases of viral hepatitis.

Liver cirrhosis has several complications, of which some cause mortality. Ascites, gastrointestinal variceal bleeding, hepatic encephalopathy and jaundice are the most frequent decompensating events that result from liver cirrhosis.<sup>30-32</sup> Bacterial infections may occur during the entire course of cirrhosis but they are far more frequent in patients who have ascites and bleeding.<sup>33</sup>

This study concluded that metabolic disorders (Wilson disease, hepatorenal tyrosinemia), cholestatic syndromes (biliary atresia, idiopathic neonatal hepatitis, progressive familial intrahepatic cholestasis), and autoimmune hepatitis are the most common causes of cirrhosis in children in our area. Early diagnosis and determining the common causes of cirrhosis in different geographical areas are important for effective treatment and decreasing the rate of complications and mortality.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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