ORIGINAL ARTICLE

Doppler assessment of children with liver cirrhosis and portal hypertension in comparison with a healthy control group: An analytical cross-sectional study

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Background: Doppler ultrasonography (Doppler US) plays an important role in evaluating patients with liver cirrhosis. This study aims to investigate the hemodynamic alterations of hepatic artery and portal vein among children with liver cirrhosis and portal hypertension (esophageal varices). **Materials and Methods:** We conducted an analytical cross-sectional study in Imam Hossein Children's Hospital, Isfahan, Iran, in 2016. A number of 33 cirrhotic children with or without esophageal varices were selected through convenience sampling method to be compared with 19 healthy children as controls using color and spectral Doppler US. **Results:** Portal vein mean velocities were 15.03 ± 7.3 cm/s in cirrhotics, 16.47 ± 6.4 cm/s in controls (P = 0.51), 11.6 ± 4.7 cm/s in patients with varices, and 17.9 ± 7.3 cm/s in patients without varices (P = 0.015). Mean diameters of caudate lobe, portal vein, and splenic vein, as well as the mean values of liver and spleen span, were significantly higher in cirrhotic children. The frequency of flow reversal (hepatofugal flow) was not detected significantly different in cirrhotics. Peak systolic velocity, end diastolic velocity, pulsatility index, and resistive index for hepatic artery as well as liver vascular index were not significantly different in cirrhotics in comparison with controls. **Conclusion:** Alterations in Doppler parameters of portal vein including diameter and velocity may be the helpful indicators of liver cirrhosis and esophageal varices in children, respectively. Parameters of hepatic artery may not differentiate children with liver cirrhosis.

Key words: Cirrhosis, Doppler ultrasonography, pediatrics, portal hypertension, portal vein

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INTRODUCTION

According to the definition of WHO, Cirrhosis is a chronic liver disease characterized by diffuse fibrosis and conversion of normal liver architecture into structurally abnormal nodules[1] and results from a complex and multifactorial process including inflammation, fibrosis, and regeneration. In this condition, intrahepatic resistance increases and results in lower compliance for portal vein flow as well as significant hemodynamic changes in hepatic vessels.[2] The underlying mechanisms for developing cirrhosis in children are often different than those in adults, although the primary management plans can be similar.[3]

Recently, several noninvasive diagnostic or prognostic modalities for evaluating patients with liver cirrhosis such as transient elastography and magnetic resonance elastography have been proposed and developed.[4] However, Doppler ultrasonography (Doppler US) examination is widely being performed for detecting early stages of liver cirrhosis. This imagery modality provides safe, noninvasive, rapid, and relatively inexpensive information about the cirrhosis-induced hemodynamic

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changes in hepatic vessels and portal vein.[5] The association of Doppler parameters with the severity of cirrhosis and portal hypertension has been investigated before.[6] Subedee *et al*. indicated that the pulsatility pattern of portal vein including pulsatility index and complete spectral widening is associated with the grade of liver damage according to Child-Pugh classification among adult patients.[7] The mean velocity of portal vein flow has been reported to be lower in patients with liver cirrhosis and portal hypertension versus controls[8] and the same findings were reported among pediatric age groups.[9]

To our knowledge and according to review of the literature, research on the value of the parameters found in Doppler examination in children with liver cirrhosis is limited worldwide. Furthermore, there is no consensus on the sensitivity and specificity of Doppler parameters in diagnosing liver cirrhosis. This study aims to investigate and compare the findings of Doppler US on hepatic vasculature and hemodynamics among a sample of the Iranian children.

METHODS

Patients and setting

This analytical cross-sectional study was conducted in Imam Hossein Children's Hospital, Isfahan, Iran, in 2016. A group of 33 children were diagnosed as patients with liver cirrhosis based on the clinical presentation and laboratory measurements as well as US findings by experienced pediatric gastroenterologist and radiologist.[6] To confirm the diagnosis, these children underwent liver biopsy. These patients were all selected to be involved in this research via convenience sampling method due to small number of cases. Another group of 19 age- and sex-matched healthy children consisted our controls via simple random sampling method for comparing with patients. Children <20 years old with the diagnosis of liver cirrhosis were enrolled in this research. Patients with severe grades of hepatic encephalopathy (III-IV) as well as those with portal vein thrombosis were excluded from the study.[7]

Study measurements

At first, demographic information including age, sex, and history of previous medication or diseases have been recorded and then children underwent a precise physical examination seeking especially for the clinical picture of liver cirrhosis such as encephalopathy, spider angiomas, jaundice, ascites, and muscle wasting. Blood samples were obtained to measure the serum levels of hepatic markers such as albumin and prothrombin time. Upper gastrointestinal endoscopy was performed for evaluating the manifestations of portal hypertension such as esophageal varices. We did not perform endoscopy for control group.

All color and spectral Doppler US examinations were done after a 4–12 h of fasting (according to the child's age) by the same radiologist. Children were assessed in supine position and with a condition of breathing quietly. Above-mentioned conditions were provided for evaluating hepatic vessels and portal vein hemodynamics with more accuracy. Doppler waveforms from hepatic vessels and portal vein were reviewed and interpreted using a color Doppler scanner with a 3.5–5 MHz convex probe considering Doppler angle <60° and placing a 2–4 mm of sample volume in the center of the vessel. We calculated the following parameters as are described below

- Pulsatility index (PI) for hepatic artery = (Peak systolic velocity [PSV] – end diastolic velocity [EDV])/mean velocity
- Resistive index (RI) for hepatic artery = (PSV – EDV)/PSV[10]
- Liver vascular index = Portal vein mean velocity/Hepatic artery pulsatility index.[8]

Statistical analysis

The IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. (Armonk, NY: IBM Corp) was used for data analysis. The Kolmogorov–Smirnov test was performed to assess the normal distribution for quantitative variables. Frequency and mean ± standard deviation (SD) were used for descriptive statistics. Obtained data were also analyzed with Chi-square, Fisher's exact and independent t tests for analytical statistics depending on the nature of the variables for comparing two study groups. $P < 0.05$ was considered statistically significant for examining hypotheses.

Ethical consideration

Ethical protocols of the current study were reviewed and approved by Isfahan University of Medical Sciences Ethics Committee. Patients were provided with sufficient information about study aims and the ways of gathering data. Written consent was obtained from all the patients before recruitment to the study. Data from the children were kept confidentially and used only for advancing research with special codes.

RESULTS

We enrolled 52 children with and without liver cirrhosis in this study. The patients group consisted of 24 boys and 9 girls aged from 9 months to 19 years while the control group consisted of 12 boys and 7 girls aged from 2 months to 17 years ($P = 0.47$, Chi-square test). Mean (SD) age was 9.5 (5.1) years for patients group and 7.4 (5.4) years for control group ($P = 0.18$, independent *t*-test).

Table 1 illustrates some qualitative variables including clinical and Doppler findings of the study sample. The esophageal

varices were only found among cirrhotic patients compared with controls ($P = 0.004$). In our cases, we found only one child with retrograde (hepatofugal) flow in portal vein. There was no significant difference between patients group and control group regard to this variable ($P > 0.99$, Fisher's exact test). Moreover, parenchymal echo patterns and surface nodularity detected by liver ultrasonography were statistically different between two groups ($P < 0.001$, Chi-square tests) so that for control group, coarse echo pattern, and nodularity were not detected while there were 29 patients with coarse echo pattern and 28 patients with nodular liver in ultrasonography.

Table 2 represents some quantitative variables including Doppler findings of the study sample. The mean spans of liver and spleen were higher in the patients with cirrhosis. The mean values of portal and splenic vein diameter were statistically higher in the patients in comparison with controls. In addition, mean velocity (SD) of portal vein was 15.03 (7.3) in patients and 16.47 (6.4) in control group ($P = 0.51$, independent *t*-test). Doppler parameters of hepatic artery (such as PSV, EDV, RI, and PI) as well as liver vascular index were not found to be statistically different between patients and controls.

Furthermore, Table 3 represents the same Doppler parameters only in cirrhotic patients with respect to the presence of esophageal varices. Patients with varices were found to have lower portal mean velocity in comparison with patients without varices ($P = 0.015$, independent *t*-test). Doppler parameters of hepatic artery were not statistically different in above-mentioned groups as well.

Table 1: Doppler ultrasound and clinical findings of the two study groups

Variables	Cirrhotic children (*n*=33)	Healthy children (*n*=19)	*P*
Direction of portal vein flow			
Hepatofugal	1 (3)	0 (0)	>0.99*
Hepatopetal	32 (97)	18 (100)	
Parenchymal echo patterns			
Homogeneous	4 (12.1)	18 (0)	**<0.001**
Coarse	29 (87.9)	0 (0)	
Surface nodularity			
Normal	5 (15.2)	18 (0)	**<0.001**
Nodular	28 (84.8)	0 (0)	
Ascites			
No	27 (84.4)	18 (100)	0.145
Yes	5 (15.6)	0 (0)	
Esophageal varices			
No	20 (64.5)	18 (100)	**0.004***
Yes	11 (35.5)	0 (0)	
$EDV_{hepatic\ artery}$/mean $velocity_{portal\ vein}$			
<1	22 (71)	17 (94.4)	0.07*
>1	9 (29)	1 (5.6)	

**P* value here is resulted from Fisher's exact test. Other *P* values in the table are resulted from Chi-square tests. Significant *P* values are bolded for emphasis. Data are presented as *n* (%). Hepatofugal=Retrograde; Hepatopetal=Anterograde. EDV=End diastolic velocity

Table 2: Mean values of Doppler ultrasound parameters among the two study groups

Variables	Cirrhotic children (*n*=33)	Healthy children (*n*=19)	*P*
Liver span (mm)	102 (17.8)	91 (18)	**0.049**
Left liver lobe diameter (mm)	64.9 (30.31)	58.6 (13.9)	0.33
Caudate lobe diameter (mm)	20.16 (8.98)	14.1 (3.7)	**0.003**
Spleen span (mm)	132 (40.4)	83.1 (15.1)	**<0.001**
$PSV_{hepatic\ artery}$ (cm/s)	42.5 (17.2)	40.8 (18.8)	0.74
$EDV_{hepatic\ artery}$ (cm/s)	11.2 (5.5)	12.2 (5.9)	0.56
$PI_{hepatic\ artery}$	1.3 (0.34)	1.2 (0.46)	0.46
$RI_{hepatic\ artery}$	5.52 (14.64)	1.04 (1.49)	0.096
Portal vein diameter (mm)	8.3 (2.5)	5.9 (1.8)	**0.001**
Portal vein mean velocity (cm/s)	15.03 (7.3)	16.47 (6.4)	0.51
Vascular index*	13.9 (8.6)	15.4 (6.9)	0.53
$PSV_{hepatic\ vein}$ (cm/s)	34.7 (20.9)	25.9 (19.54)	0.24
Splenic vein diameter (mm)	5.8 (2.1)	3.7 (0.8)	**<0.001**

*Vascular index=Portal vein mean velocity/hepatic artery pulsatility index. *P* values are resulted from independent *t*-tests. Significant *P* values are bolded for emphasis. Data are presented as mean±SD. PSV=Peak systolic velocity; EDV=End diastolic velocity; PI=Pulsatility index; RI=Resistive index; SD=Standard deviation

DISCUSSION

In this study, we investigated the hemodynamic changes of hepatic artery and portal vein in children with cirrhosis as well as in healthy controls. The normal liver vascular flow patterns including direction and velocity of flow can be identified via spectral and color Doppler US due to special characteristics and parameters of each vessel.[10,11] Doppler US is performed for cirrhotic patients as an important part of the diagnosis, since it may provide beneficial information about severity of liver fibro nodular alterations, the presence of portal hypertension and development of portacaval shunts in the form of various intra-abdominal varices and collaterals.[12,13] Therefore, a main part of scientific efforts, have been focused on the sensitivity and specificity of the radiologic findings, parameters and indices in Doppler US, which may help in the identification of cut of points for diagnosing the patients at earlier stages. Here, some of the above-mentioned parameters have been discussed.

The normal direction of portal venous blood is toward the liver and the heart which is called anterograde or hepatopetal flow. The opposite flow direction is called retrograde or hepatofugal flow and associates with the advanced cirrhosis or the development of portal hypertension. In our study, we have one cirrhotic patient with hepatofugal flow which was characterized by a retrograde, nonphasic, monophasic, and aninflectional waveform in Doppler US.[10,14] Therefore, flow reversal was not consistent with the diagnosis of cirrhosis in children in our sample. It has been shown that

Table 3: Mean values of Doppler ultrasound parameters among children with liver cirrhosis considering esophageal varices

Variables	Patients with varices (*n*=11)	Patients without varices (*n*=20)	*P*
$PSV_{hepatic\ artery}$ (cm/s)	40.2 (11.4)	41.6 (16.8)	0.81
$EDV_{hepatic\ artery}$ (cm/s)	10.5 (4.6)	11.3 (6.2)	0.70
$PI_{hepatic\ artery}$	1.4 (0.4)	1.3 (0.3)	0.42
$RI_{hepatic\ artery}$	7.41 (17.68)	4.58 (13.81)	0.63
Portal vein mean velocity (cm/s)	11.6 (4.7)	17.9 (7.3)	**0.015**

Data are presented as mean±SD. *P* values are resulted from independent *t*-tests. Significant *P* values are bolded for emphasis. PSV=Peak systolic velocity; EDV=End diastolic velocity; PI=Pulsatility index; RI=Resistive index; SD=Standard deviation

the flow velocity of portal vein decreases in liver cirrhosis due to higher intrahepatic resistance caused by fibrosis and regeneration processes.[15] With regard to main portal vein flow, the normal peak velocity should vary between 16 or 20–40 cm/s and the values <16 cm/s suggests portal hypertension, especially when it is found along with the increased values of portal venous diameter.[10,16] In our patients, the portal vein mean diameter was statistically different comparing two groups (8.3 ± 2.5 mm in cirrhotics vs. 5.9 ± 1.8 mm in controls). The portal vein mean velocity was significantly lower in cirrhotic children with esophageal varices than those without varices, although this value was not found to be statistically different comparing cirrhotic and healthy children. Furthermore, we found that the means of the liver and the spleen spans, as well as caudate lobe diameter, are statistically different between our two study groups. It has been shown that splenomegaly, right lobe atrophy and surface nodularity are markers for detection of liver cirrhosis in ultrasonography.[17] It should be noted that pulsatility in portal vein waveforms may be measured with PI in which the values <0.5 are correlated to pulsatile or abnormal waveforms.[10] The sensitivity and specificity of this pulsatile waveform for portal hypertension in end-stage liver disease are 94% and 90%, respectively.[18] We did not calculate this index.

Moreover, the indices and measurements related to hepatic artery are also influenced by cirrhosis. The liver is a hemodynamically active organ, and hepatic artery is a relatively low resistance vessel. The RI normally ranges between 0.55 and 0.7.[19] Although there is research indicating greater values of RI and PI in cirrhotic patients compared with controls,[8] higher or lower RI from the above-mentioned range is not specific for liver cirrhosis.[19] It has been demonstrated that hepatic artery RI has a remarkable variability even among normal adults or children[18] and is not correlated with the severity of liver cirrhosis.[12,20] Similarly, in our study, neither the PI and RI indices nor the PSV and EDV showed significant differences in healthy and patient groups as well as in patient group with respect to the presence of esophageal varices. It is noteworthy that a recently published study indicated that elevated hepatic arterial velocity is positively correlated with increasing a model for end-stage liver disease and can be used as a useful biomarker for evaluating cirrhotic patients.[21] In addition, in cirrhotic children due to biliary atresia, RI is correlated with the degree of liver cirrhosis.[22] The known etiologies of cirrhosis in children include biliary atresia, choledochal cyst, primary sclerosing cholangitis, autoimmune hepatitis, alpha1-antitrypsin deficiency, galactosemia, Wilson's disease, cystic fibrosis, Alagille syndrome, and hepatitis.[3] Finally, we found that liver mean vascular index was not statistically different in our patients and controls, while it has been reported to have decreased values in cirrhotics versus healthy controls.[8]

There are some limitations in our study as well. We did not focus on Doppler evaluation of the hemodynamic alterations related to hepatic vein in our sample. Furthermore, we did not investigate the severity of disease and its correlation with Doppler measurements. Further researches with larger sample sizes are warranted in this field to the best of our knowledge in children with liver cirrhosis.

CONCLUSIONS

In brief, Doppler US examination may provide beneficial information on evaluating children with liver cirrhosis. We found that the diameter of portal vein elevates in these patients. In addition, the velocity of portal vein flow is lower in patients with varices compared with patients without varices. The Liver and spleen spans, caudate lobe diameter and splenic vein diameter have greater values in cirrhotic children. PSV, EDV, PI, and RI for hepatic artery are less reliable in differentiating patients and are not significantly altered with the presence of esophageal varices. In addition, Liver vascular index may not be helpful in evaluating these children.

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Conflicts of interest

There are no conflicts of interest.

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