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Davut Tüney
M. Erkin Aribal
Deniz Ertem
Esin Kotiloğlu
Ender Pehlivanoğlu

Diagnosis of liver cirrhosis in children based on colour Doppler ultrasonography with histopathological correlation

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D. Tüney · M. E. Aribal
Department of Radiology,
Marmara University Faculty of Medicine,
Istanbul, Turkey

D. Tüney (✉)
Marmara Üniversitesi Tip Fakültesi,
Radyodiagnostik Anabilim Dali,
Tophanelioğlu cad. 13–15,
TR-81190 Altunizade-Istanbul, Turkey

D. Ertem · E. Pehlivanoğlu
Division of Paediatric Gastroenterology,
Marmara University Faculty of Medicine,
Istanbul, Turkey

E. Kotiloğlu
Department of Pathology,
Marmara University Faculty of Medicine,
Istanbul, Turkey

Abstract *Background.* Changes in hepatic architecture in cirrhosis and chronic active hepatitis affect liver vascular haemodynamics.
Objective. To determine the criteria for the diagnosis of liver cirrhosis using Doppler US.
Materials and methods. Twenty-two children with liver disease of unknown histology were prospectively examined and compared with eight normal children. Doppler US of portal vein velocity, arterio-portal velocity ratio, loss of reverse flow component in the hepatic vein and hepatic artery visualisation were examined prior to liver biopsy. Doppler results were compared with histological activity indices. Twelve patients had cirrhosis and ten had chronic active hepatitis.
Results. The most sensitive method (83 %) for the assessment of cirrhosis was portal vein velocity less than 20 cm/sec. Arterio-portal velocity ratio (greater than 3) and hepatic artery visualisation were less sensitive (75 % and 33 % respectively) but specificity was 100 % for all three methods. When these three methods were evaluated together, sensitivity increased to 91 % and accuracy to 96 %. Loss of reverse flow component was less specific (77 %) but was sensitive (75 %).
Conclusions. Portal vein velocity, arterio-portal vein ratio and hepatic artery visualisation together were reliable in diagnosis of cirrhosis in the paediatric age group.

Introduction

Cirrhosis is the final stage of chronic active hepatitis (CAH), a necroinflammatory process of the liver [1, 2]. Although these patients are followed clinically and biochemically, histopathology is the gold standard for diagnosis and outcome prediction [3]. There is a need for a non-invasive examination that is clinically useful and accurately reproducible. Doppler US has been performed widely for the assessment of cirrhosis [4–14] and in the paediatric age group is also useful in the assessment of acute appendicitis, liver transplantation, superior mesenteric artery blood flow, portal hypertension and abdominal masses [15–18]. Although there are many recent reports regarding colour Doppler US in cirrhosis there is, to our knowledge, only one report in the paediatric age group [14].

The US features of cirrhosis include a small right hepatic lobe and medial segment of the left lobe, with compensatory hypertrophy of the lateral segment of the left lobe and caudate lobe, irregularity of the liver surface, coarsened or heterogeneous echogenic parenchyma, decreased beam penetration as a result of fibrosis or fat, displacement and compression of portal and hepatic vessels and a small or non-visualised gallbladder. Secondary sign of cirrhosis such as ascites, splenomegaly, increased lesser omental thickness and varices, are common when portal hypertension develops. US is unable to determine the severity of diffuse parenchymal disease, as there are no objective criteria in the follow-up of chronic disease [19, 20].

This prospective study using colour Doppler US investigates the haemodynamic changes in liver cirrhosis by a non-invasive means, correlates the results with the

histological findings and evaluates Doppler criteria for the diagnosis of cirrhosis.

Material and methods

Twenty-two patients (12 boys, 10 girls, aged 0.5–16 years, mean 7.5), under investigation for liver disease, were examined prospectively. Eight children with a mean age of 8.9 years were examined as the control group without liver disease. All patients were examined clinically, the laboratory investigations were requested and a liver biopsy was obtained using a 14-G Menghini needle for the final diagnosis. Patients with decompensated liver disease or right heart failure were not included in the study. All patients were studied with duplex Doppler US before percutaneous liver biopsy. The specimens were categorised according to the classification of Knodell et al. [3]. This classification, known as "Histology Activity Index", grades the liver histology according to periportal and intralobular necrosis, portal inflammation and fibrosis. Fatty infiltration was also indexed in addition to this classification.

All patients and controls were examined with a colour Doppler scanner and a 5-MHz or 7-MHz convex probe according to the size of the child or the depth of the examined structure. All patients were examined in the supine position after fasting. Children up to 2 years old were fasted for 4 hours, children from 3 to 8 years for 6 hours and those over 8 years for 12 hours. Five of the patients were recalled for a second examination, two because of poor cooperation and three because of overlying abdominal gas. One of the uncooperative patients was examined for a third time because of superposing abdominal gas. None of the patients required sedation. Infants were examined during normal sleep, and in three of these, helped by use of a sugar nipple.

All Doppler measurements were obtained three times and the mean value was used for the final report. Duplex Doppler examinations were performed by the same radiologists (D. T. and M. E. A) who were experienced in gastrointestinal and paediatric radiology respectively. Both radiologists performed the studies without knowledge of the clinical status of the patients.

Doppler colour flow parameters were as follow. The wall filter was kept equal to or lower than 50 MHz. Pulse repetition frequency (PRF) was set to the lowest value possible that would not create aliasing artefact. Doppler insonation angle was below 60° and sampling volume was set narrower than the vessel lumen, although during hepatic artery examination, sampling volume was wider than the vessel and the portal vein was sampled simultaneously.

Spectral Doppler was performed as described below:

Hepatic veins: samples were taken at least 2 cm from the inferior vena cava (IVC) in order to eliminate misregistration due to diaphragmatic and cardiac movements. Middle or right hepatic vein was examined. Flow in the hepatic veins was categorised as (1) normal triphasic waveform, or (2) loss of reverse flow component (LRFC).

Portal vein: the main portal vein was examined at the midpoint between the spleno-portal junction and the intrahepatic bifurcation. Portal vein flow pattern, cross sectional area and velocity (PW) were measured.

Hepatic artery: visualisation of the left or right hepatic artery (HA) branches on grey-scale was sought. When an artery adjacent to a portal vein branch was seen on grey-scale and showed arterial flow on colour Doppler study, that finding was deemed positive. The intrahepatic main hepatic artery was evaluated simultaneously with the portal vein and the velocity ratio of hepatic artery to portal vein was calculated (APVR).

Criteria for the diagnosis of cirrhosis were (1) loss of reverse flow component in the hepatic veins [14], (2) portal vein velocity less than 20 cm/sec, (3) arterio-portal velocity ratio more than 3 [14] and (4) hepatic artery branch visualisation (HAV).

Statistical analyses of age differences between the groups were made with one-way analysis of variance (ANOVA) and the groups were compared with the Tukey-Kramer multiple comparison test. Sex differences between groups were analysed with the chi-square test. The differences between groups for Doppler results were analysed with the chi-square test and the groups were compared with Fisher's exact test. P values less than 0.05 were regarded as significant.

Table 1 Portal vein velocities (cm/sec) in the three groups

	Cirrhosis	Chronic active hepatitis	Normal
Mean velocity	18	24	33
Maximum velocity	34	40	62
Minimum velocity	12	17	23

Results

There was no significant age or sex difference between the groups ($P > 0.05$). Histopathological study of the liver biopsies showed that 12 of the patients had cirrhosis and 10 had CAH.

Portal vein velocity

The mean portal vein velocity was 18 cm/sec in the group with cirrhosis, 24 cm/sec in the CAH group and 33 cm/sec in the group of normal children. Table 1 shows the mean, maximum and minimum velocities for each group. There was significant difference between the groups ($P < 0.05$). When groups were compared, the cirrhosis group was significantly different from the CAH and normal groups ($P < 0.05$, $P < 0.05$ respectively). There was no difference between CAH and controls ($P > 0.05$). When portal vein velocity lower than 20 cm/sec was taken as a criterion for cirrhosis, the sensitivity of the method was 83 %, specificity was 100 % and overall accuracy 93 %.

Arterio-portal velocity ratio

Mean APVR was 3.77 in cirrhotic patients, 2.04 in CAH patients and 1.44 in the controls (Table 2). When APVR greater than 3 was taken as a criterion of cirrhosis, the sensitivity of the method was 75 % with a specificity of 100 % and overall accuracy of 90 %. There was significant difference between the three study groups

Table 2 Hepatic artery/portal vein velocity ratios

	Cirrhosis	Chronic active hepatitis	Normal
Mean	3.77	2.04	1.44
Maximum	11.2	4.41	2.43
Minimum	1.75	0.96	0.87

Table 3 Numbers of patients showing the pattern of blood flow pattern in the hepatic veins

	Cirrhosis	Chronic active hepatitis	Normal
Normal flow	5	6	8
Loss of reverse flow component	7	4	0

Table 4 Efficacy of portal vein velocity *(PVV),* arterio-portal vein velocity ratio *(APVR),* loss of reverse flow component *(LRFC),* hepatic artery visualisation *(HAV)* and their combination in the diagnosis of cirrhosis

	Sensitivity (%)	Specificity (%)	Overall accuracy (%)
PVV	83	100	93
APVR	75	100	90
LRFC	58	77	70
HAV	33	100	73
PVV + APVR	91	100	96
PVV + HAV	91	100	96
APVR + HAV	72	100	89
PVV + APVR + HAV	91	100	96
PVV + APVR + HAV + LRFC	100	88	93

($P < 0.01$). The cirrhotic group was significantly different from the CAH group and the controls ($P < 0.05$, $P < 0.05$ respectively). There was no difference between the CAH group and the controls ($P > 0.05$).

Loss of reverse flow component

There were significant differences between the groups ($P < 0.05$). When the groups were compared, the cirrhosis group was different from the CAH group ($P < 0.05$) and the controls ($P < 0.01$), but there was no difference between the CAH group and controls ($P > 0.05$) (Table 3). Sensitivity, specificity and overall accuracy were 58 %, 77 % and 70 % respectively.

Hepatic artery visualisation

Hepatic artery visualisation was not a reliable indicator of cirrhosis. Although its sensitivity was 33 %, it was 100 % specific. The overall accuracy was 73 %. There were significant differences between groups ($P < 0.05$). The cirrhosis group was different from both the CAH group and controls ($P < 0.05$, $P < 0.05$ respectively), but there was no significant difference between the CAH group and the controls ($P > 0.05$).

The most sensitive method was the PVV and all methods, except LRFC, had a specificity of 100 %. When two or three criteria were considered together, the sensitivity reached 91 % with an overall accuracy of 96 %. When four criteria were considered, sensitivity was 100 % but specificity decreased to 88 % (Table 4).

The histopathological findings showed that 8 of 12 patients with cirrhosis had grade 4, and 4 patients had grade 3 fibrosis. Inflammation score for portal inflammation was significantly higher in CAH patients than those with cirrhosis. Periportal necrosis rate (with or without bridging necrosis) was also higher in CAH patients (Table 5).

Discussion

Chronic active hepatitis manifests with varying degrees of hepatocellular necrosis and inflammation and characteristic histopathological findings. The final stage of CAH is cirrhosis, which is characterised by the presence of parenchymal nodules surrounded by fibrous septa. This irreversible stage leads to loss of normal hepatic architecture and to portal hypertension which is caused by functional alterations of blood flow [1–3]. Disturbance of hepatic circulation can cause porto-hepatic and arterio-portal anastomoses which lead to acceleration of hepatic artery flow [16]. Progressive diffuse fibrosis originating from the portal triad and regeneration nodules lead to an increase in peripheral resistance in the arterial microvascular bed, distortion of adjacent vessels and non-compliance of the hepatic parenchyma [6, 11, 13]. This increase in fibrosis is believed to result in increased arterial relative to portal venous flow [4].

The intrahepatic branches of the hepatic artery cannot be visualised with grey-scale US but can be detected with colour Doppler US in normal subjects [20]. We considered that increased hepatic artery flow would make the intrahepatic branches visible on grey-scale US, as the increased flow should widen the lumen of these branches. Hepatic artery visualisation was not reliable but had 100 % specificity. This criterion when used with PVV increased the sensitivity of PVV to 96 % (Table 4). Although it should not be used alone, it can increase the accuracy and specificity when used with other criteria.

Table 5 Doppler criteria and histological activity index scores in patients with chronic active hepatitis *(CAH)* and cirrhosis *(C)*. (*LRFC* loss of reverse flow component, *HAV* hepatic artery visualisation, *PVV* portal vein visualisation, *VR* arterio-portal vein velocity ratio, *FS* fibrosis, *PI* portal inflammation, *N* periportal necrosis (with or without bridging necrosis), *FI* fatty infiltration, *D* diagnosis, *M* male, *F* female)

Patient				Doppler US indicators for liver cirrhosis				Histology activity index				
No	Age (yrs)	Sex	Primary disease	LRFC	HAV	PVV	VR	FS	PI	N	FI	D
1	14.5	M	Chronic hepatitis B	–	–	+	–	4	1	–	–	C
2	2.5	M	Chronic hepatitis B	+	–	+	–	4	1	–	–	C
3	0.7	F	Galactosaemia	+	–	–	–	4	1	–	–	C
4	8.5	F	Wilson's disease	+	+	–	+	3	1	1	–	C
5	10	F	Progressive familial intrahepatic cholestasis	–	–	+	+	4	2	1	+	C
6	14	M	Wilson's disease	–	–	+	+	3	0	–	–	C
7	8	M	Unknown	–	+	+	+	4	2	1	–	C
8	1.5	M	Glycogen storage disease	+	+	+	+	4	1	1	–	C
9	5	F	Congenital hepatic fibrosis	+	+	+	+	4	1	–	–	C
10	12.5	F	Selective IgA deficiency with autoimmune hepatitis	+	–	+	+	4	1	–	–	C
11	8.5	F	Chronic hepatitis B	–	–	+	+	3	1	1	–	C
12	11.5	F	Wilsons's disease	+	–	+	+	3	1	1	–	C
13	16	M	Unknown	–	–	–	–	1	1	2	–	CAH
14	13	M	Wilson's disease	–	–	–	–	1	1	2	–	CAH
15	3	F	Chronic hepatitis B	+	–	–	–	1	3	1	–	CAH
16	6	M	Chronic hepatitis B	–	–	–	–	1	1	4	–	CAH
17	4.5	M	Chronic hepatitis B	+	–	–	–	2	1	4	–	CAH
18	3.5	F	Chronic hepatitis B	–	–	–	–	1	2	3	+	CAH
19	5	M	Chronic hepatitis B	–	–	–	–	1	3	2	+	CAH
20	5	M	Chronic hepatitis B	+	–	–	–	2	3	2	+	CAH
21	7	M	Chronic hepatitis B	–	–	–	–	2	3	2	+	CAH
22	2.5	F	Unknown	+	–	–	–	1	2	2	–	CAH

The effect of fibrosis on the hepatic veins causes damping of the spectral wave. Doppler spectral waveform obtained from normal hepatic veins is multiphasic with two antegrade diastolic and systolic waves and a small retrograde wave corresponding to atrial systole [11, 13, 17, 21, 22]. This normal triphasic waveform changes, with loss of its reversal flow component, especially in cirrhosis [11, 13]. Colli et al. [13] reported significant correlation of LRFC with fibrosis and steatosis but no correlation with portal inflammation, intralobular degeneration or focal necrosis. In our CAH group, we did not find correlation between fatty infiltration and LRFC. Gorka et al. [14] found LRFC the most reliable indicator of liver cirrhosis with 70 % sensitivity for early and 100 % sensitivity for established cirrhosis. In contrast, our findings showed low sensitivity for the diagnosis of cirrhosis (Table 4). Our results, for the diagnosis of cirrhosis using LRFC, were similar to those of Colli et al. (sensitivity 75 %, accuracy 77 %). We agree with them that LRFC is unreliable for monitoring CAH or the diagnosis of cirrhosis.

According to the histopathological classification, in four CAH patients where LRFC was evident, we did not find any correlation between LRFC and fibrosis, portal inflammation or necrosis. There was high portal inflammation score in LRFC-positive CAH patients despite low fibrosis grade. We consider that this intense portal inflammation could have caused LRFC. Although our results were contrary to those of Colli et al. and some other reports, we believe that instead of taking fibrosis or portal inflammation alone, all factors affecting the liver parenchyma and its compliance should be evaluated together [13, 14].

Another effect of diffuse progressive fibrosis on vessels is the decrease of PVV due to increased microvascular resistance and loss of compliance [7, 8, 10]. A study by Ohnishi et al. [5] in adults, showed that PVV was significantly reduced in CAH and cirrhotic patients

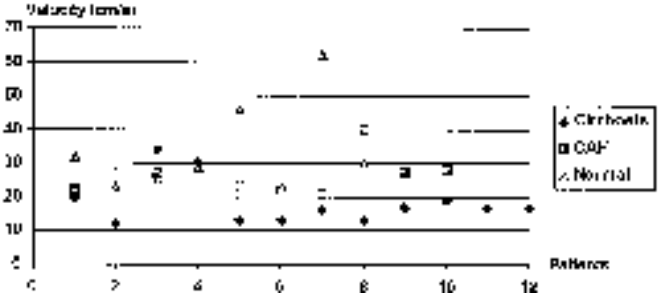

Fig. 1 Portal vein velocities in chirrhosis, CAH and normal groups

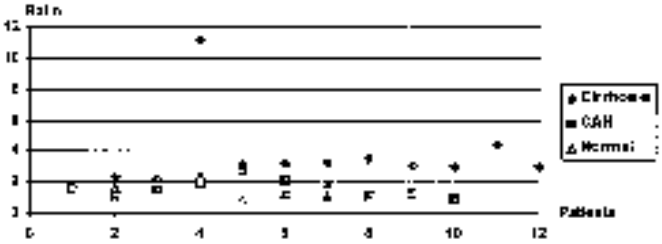

Fig. 2 Relationship of APVR values in cirrhosis, CAH and normal groups

compared with normal subjects. Unlike their study, we did not find a difference between CAH and controls in children (Fig. 1). According to Cioni et al. [23], PVV was usually greater than 20 cm/sec in normal subjects. Gorka et al. [14] found mean PVV 31 ± 1.4 cm/sec in healthy children and 17.1 ± 2.9 cm/sec in cirrhotic patients. Their sensitivity and specificity using 20 cm/sec as a discriminator for cirrhosis were 67 % and 100 % in early cirrhosis and 50 % and 100 % in established cirrhosis respectively. They did not correlate CAH with cirrhotic patients. Our results do not correlate with theirs, as sensitivity of PVV was 83 % in our study. We believe this is because of the high degree of fibrosis in our patients (Table 5). Gorka et al. [14] did not correlate the grade of fibrosis with PVV values. We consider that the grade of fibrosis affects PVV values because we found PVV to be the most sensitive method in differentiating CAH patients and normal children from those with cirrhosis. When PVV was evaluated with HAV and APVR together, the specificity increased to 96 % and sensitivity to 100 %. We believe that these parameters together are reliable for differentiation of cirrhosis from CAH. Highest sensitivity (100 %) was reached with addition of LRFC but the specificity decreased to 88 % (Table 4).

Decrease in PVV and acceleration in arterial flow naturally increase the arterio-portal velocity ratio. Mean APVR was 1.44 in normal subjects and 2.04 in CAH patients (Fig. 2). Although this is not statistically significant, the mean values showed a difference that suggested that APVR had increased slightly in the CAH group. The mean value for cirrhotic patients was 3.77, above the criterion of 3. These results are compatible with those of Gorka et al. [14] Their control group had an APVR of 2.0 while in established and early cirrhosis the APVR was 4.5.

To our knowledge this is the second report concerning the evaluation of cirrhosis with colour Doppler US in children. Our findings showed that three parameters – PVV, APVR and HAV, are reliable in monitoring cirrhosis in this age group.

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