

RAPID COMMUNICATION

Correlation between ultrasonographic and pathologic diagnosis of liver fibrosis due to chronic virus hepatitis

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Abstract

AIM: To evaluate the validity of ultrasonographic and pathologic diagnosis of liver fibrosis in patients with chronic viral hepatitis.

METHODS: The liver fibrosis status in 324 patients was evaluated by both needle biopsy and ultrasonography. Liver fibrosis was divided into S0 -S4 stages. S4 stage was designated as definite cirrhosis. The ultrasonographic examination included qualitative variables, description of liver surface and parenchyma, and quantitative parameters, such as diameter of vessels, blood flow velocity and spleen size.

RESULTS: Ultrasonographic qualitative description of liver surface and parenchyma was related with the severity of fibrosis. Among the quantitative ultrasonographic parameters, cut-off value of spleen length (12.1 cm) had a sensitivity of 0.600 and a specificity of 0.753 for diagnosis of liver cirrhosis. The diameters of spleen (8 mm) and portal vein (12 mm) had a diagnostic sensitivity of 0.600 and 0.767, and a diagnostic specificity of 0.781 and 0.446, respectively. The diagnostic accuracy for liver cirrhosis was moderately satisfactory, and the negative predictive values of these parameters reached near 0.95.

CONCLUSION: Ultrasonography can predict the degree of liver fibrosis or cirrhosis. A single ultrasonographic parameter is limited in sensitivity and specificity for the diagnosis of early cirrhosis. The presence or absence of liver cirrhosis in patients with chronic virus hepatitis can be detected using 2 or 3 quantitative and qualitative parameters, especially the length of spleen, the diameter of spleen vein and echo pattern of liver surface.

INTRODUCTION

Chronic hepatitis virus B or C infection results in damage to hepatocytes and may eventually lead to liver fibrosis, cirrhosis and/or hepatocellular carcinoma^[1-3]. The diagnosis of liver fibrosis and cirrhosis in patients with chronic virus hepatitis is of therapeutic and prognostic importance.

Although histologic examination of percutaneous biopsy specimens is the gold criterion for the severity of fibrosis and cirrhosis, biopsy is invasive and cannot be used repeatedly in follow-up. Moreover, liver biopsy can yield false negative results in nearly 20-30% of cases^[4-7]. Therefore, it is important to use noninvasive methods in differentiation between liver fibrosis and cirrhosis.

Ultrasonography (US) is a noninvasive and inexpensive procedure for diagnosis of focal and diffuse parenchymal disease of liver. Although US cannot detect minute changes, it can show liver cirrhosis in patients with decompensated liver function^[8-11]. However, correlation between US and histologic diagnosis has not been fully investigated in large series of patients. We conducted a prospective study to evaluate the validity of US for diagnosis of liver fibrosis in patients with chronic liver hepatitis without clinical or biochemical evidence of cirrhosis.

MATERIALS AND METHODS

Patients

From July 1999 to August 2002, 324 patients with chronic viral hepatitis undergoing US and histologic examination, were enrolled. Inclusion criteria included positive HBsAg and HBV-DNA or anti-HCV and HCV-RNA determined by PCR methods for at least 6 mo, and abnormal serum alanine transaminase level in recent 6 mo. Patients who had clinical or biochemical evidence of decompensated liver

Table 1 Relation between US quantitative parameters and fibrosis stages

Parameters	Stage of fibrosis	Mean±SD	F	P
Length of spleen (cm)	S0	10.81±1.32	5.1947	0.0005
	S1	10.82±1.45		
	S2	11.35±2.02		
	S3	13.31±2.68		
	S4	12.66±2.06		
Diameter of portal vein (cm)	S0	1.17±0.11	1.0369	0.3882
	S1	1.18±0.17		
	S2	1.19±0.13		
	S3	1.20±0.12		
	S4	1.27±0.13		
Diameter of spleen vein (cm)	S0	0.62±0.16	6.7896	0.0000
	S1	0.67±0.15		
	S2	0.72±0.18		
	S3	0.69±0.15		
	S4	0.81±0.20		

function or portal hypertension, positive HIV antibody, serum titer of antinuclear antibody >1:160, serum creatinine level over 1.5 upper limit of normal value, or known liver diseases of other etiologies, were excluded.

Histologic examination

Percutaneous liver biopsy specimens were obtained from the anterior segment of the right lobe in each patient under the guidance of US using the quick-cut or Menghini biopsy needle. The satisfactory size of specimens was longer than 1 cm. The liver tissue samples were stained with hematoxylin-eosin, Gordon-Sweet and van-Gieson methods. Three pathologists performed the histological examination. To evaluate the inter-observer variation, Kappa analysis was conducted to control the quality of pathological diagnosis. The average Kappa value was 0.8144, indicating the excellent consistency for the staging of liver fibrosis.

According to the Guidelines of Prevention and Treatment of Viral Hepatitis of Chinese Medical Association (2000), liver fibrosis was divided into S0-S4 stages: S0 stage-no fibrosis, S1 stage-enlarged portal tracts with fiber proliferation, S2 stage-fibrosis of portal tract with formation of fiber septa and intact architecture of liver lobule, S3 stage-fibrosis with distortion of lobule architecture but without cirrhosis, S4 stage-definite cirrhosis. Liver inflammation was divided into grades from G1 (mild) to G4 (severe)^[12].

US examination

US examination was performed within 2 wk before or after liver biopsy. Acuson Aspen system with a 3.5-5.0 MHz curved probe was utilized. The two US operators were unaware of the clinical details and the results of biopsy. The results were recorded on video-tapes and the final report was given based on the consensus of both operators. The standard protocol of US examination included variables describing the liver size, surface and parenchyma, the ves-

sel structure, the blood flow velocity and spleen size.

Statistical analysis

Statistical analysis was performed using the SPSS 9.0 software. The significance of differences between subgroups was tested by the *F* test. $P < 0.05$ was considered statistically significant. A receive-operating characteristic (ROC) curve was used to determine the best cut-off values of US parameters for diagnosis of liver cirrhosis.

RESULTS

A total of 324 patients were collected, 272 men (83.9%) and 52 women (16.1%). Their age ranged from 18 to 60 years with a mean ± SD of 35.56 ± 9.9 years. Based on virus markers, 306 patients had hepatitis B and 18 patients had hepatitis C. The mean duration of hepatitis, namely the duration from the date of clinical diagnosis to the date of liver biopsy, was 4.14 years. The histopathology showed S0 stage in 32 patients (9.9%), S1 stage in 116 patients (35.8%), S2 stage in 111 patients (34.3%), S3 stage in 35 patients (10.8%), S4 stage in 30 patients (9.3%), and inflammation G1 in 117 patients (36.1%), G2 in 110 patients (33.9%), G3 in 70 patients (21.6%) and G4 in 27 patients (8.3%).

The results of qualitative US were different in patients with various stages of liver fibrosis. The appearance of nodularities or irregular lines on liver surface and heterogenous distribution of nodularities in liver parenchyma, were related with advanced stages of liver fibrosis. But these descriptions could not definitely reflect the histopathologic diagnosis, because 97% patients in S0 subgroup and 66% patients in S4 subgroup showed smooth surface echo pattern. Only 13.7% patients in S4 stage subgroup showed moderate saw-teeth like liver surface echo pattern. No severe nodular surface was noted. The echo pattern of liver parenchyma and heterogenous distribution were significantly different in patients with various stages of liver fibrosis and were related to the severity of fibrosis. But coarse nodularity was frequently encountered: 25% in S0 subgroup patients, and 41% in S4 subgroup patients.

Table 1 summarizes the relation between liver fibrosis stages and quantitative US parameters, which showed the differences in subgroups with various stages of liver fibrosis. Among the quantitative US parameters, the spleen length and diameter of spleen vein were correlated with fibrosis stages ($P < 0.05$). The spleen lengths were significantly different in S1/S3, S2/S3, and S1/S4, but not significant in S3/S4 ($P = 0.43$). The diameter of spleen vein was significantly different in S2/S4 and S3/S4 ($P = 0.0068$ and $P = 0.0036$). However, the diameter of portal vein only increased significantly in patients with S4 stage of liver fibrosis. These data suggested that the length of spleen began to increase at S3 of liver fibrosis, so that the difference in S3/S4 was insignificant. The diameter of portal vein began to increase later than the length of spleen and diameter of spleen vein.

Based on receiver-operating characteristic (ROC) curve, the maximal sum of diagnostic sensitivity and specificity was considered as the best cut-off value of US parameters for prediction of the severity of liver fibrosis. The diag-

Table 2 Diagnostic values of three US parameters for early liver cirrhosis

Parameters and cut-off value	Sensitivity	Specificity	Accuracy	Positive predicative value	Negative predicative value
Length of spleen (12.1 cm)	0.600	0.753	0.737	0.198	0.948
Diameter of spleen vein (8 mm)	0.600	0.781	0.765	0.220	0.950
Diameter of portal vein (12 mm)	0.767	0.446	0.475	0.124	0.949

nostic values of three quantitative US parameters are listed in Table 2.

DISCUSSION

Liver cirrhosis can be detected by US in patients with portal hypertension. Schalm^[13] reviewed the diagnostic methodology of liver cirrhosis and found that percutaneous liver biopsy has a sensitivity of below 85% in detection of liver cirrhosis. Liver biopsy could yield false negative results in nearly one third of cases, but it is currently considered the criterion for establishing a precise diagnosis and assessing the extent of fibrosis. The diagnostic sensitivity and specificity of US examination for liver cirrhosis vary widely with a diagnostic sensitivity of 0.125- 0.95 and a diagnostic specificity of 0.285- 1.0^[14-16]. The diagnostic accuracy of US for early liver cirrhosis in patients with chronic virus hepatitis and compensated liver function has not been fully investigated.

At US scanning, liver surface nodularity reflects the presence of regenerative nodules and fibrous septa. Nodularity on liver surface and in parenchyma is independently associated with the diagnosis of cirrhosis and US is reliable for diagnosis of liver fibrosis. It was reported that the high frequency US transducer (7.5-12 MHz) can obtain satisfactory results for diagnosis of liver cirrhosis^[17] while the low frequency US is not a reliable test for liver cirrhosis^[18].

Gaiani *et al*^[19] showed that 80.4% of cirrhosis can be detected in patients with compensated liver diseases of various etiologies using a US scoring system based on two US parameters. Colli *et al*^[20] reported that US can detect severe fibrosis or cirrhosis with a specificity of 0.95 and a sensitivity of only 0.54. Moreover, surface nodularity could also be influenced by different factors, mainly local fatty infiltration. Hung *et al*^[21] evaluated the validity of US in diagnosis of cirrhosis with a diagnostic sensitivity of liver cirrhosis of 0.775 and a specificity of 0.92 in patients with HBV infection. Zheng *et al*^[22] studied the value of US in evaluation of liver fibrosis and compensated cirrhosis in comparison with serology and histology and found that hepatic parenchymal echo pattern, liver surface and thickness of gallbladder wall are three independent predictors of liver fibrosis. The diagnostic accuracy of US for compensated cirrhosis is 80.7%.

The accuracy of Doppler US measurement for diagnosis of early liver cirrhosis is still controversial. It was reported that decreased flow velocity in portal vein is sufficiently accurate in diagnosis of liver cirrhosis^[23-25]. While other studies^[26-28] showed that substantial variability exists in measurement of portal venous blood flow velocity and volume. Doppler US measurement does not represent the hepatic venous pressure gradient^[29]. This controversy could

be explained by the lack of standard technique of Doppler measurement. Furthermore, changes of hemodynamics in hepatic blood flow are influenced by multiple factors, such as extent of fibrosis, chronic inflammation, presence and size of esophageal varices, as well as porto-systemic shunts.

The results of this study showed that the maximal velocity of blood flow in portal vein was weakly related with liver cirrhosis, but the standard deviation of data was wide, suggesting that this Doppler US parameter is not important in evaluation of liver fibrosis.

Schalm^[13] suggested that if histology shows no cirrhosis (nodules surrounded by fibrosis) but fibrosis and architectural distortion, diagnosis of cirrhosis should still be made when there is a US diagnosis of cirrhosis. Afdhal and Nunes^[30] argued that a proper US examination can identify patients with cirrhosis when the biopsy findings are equivocal, or at variance with the clinical impression.

The results of this study showed that different stages of hepatic fibrosis could not be determined satisfactorily by US parameters. A single US parameter was limited in sensitivity and specificity for diagnosis of early cirrhosis. Early liver cirrhosis could be excluded using two or three quantitative and qualitative US parameters, especially the spleen length, diameter of spleen vein and echo pattern of liver surface, because the negative predictive values of these three quantitative US parameters were high. US can also be used in follow-up of patients with chronic virus hepatitis.

The limitations of our study are the relatively small number of patients with S0- S4 stages of liver fibrosis and no application of the high-frequency US probe in examination of liver surface.

In conclusion, US cannot be used as a specific diagnostic tool for chronic viral hepatitis, but US should be stressed in screening and follow-up of patients with chronic virus hepatitis. However, the results of this study do not decrease the value of liver biopsy because it has other indications in clinical practice of hepatology.

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