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Role of Liver Ultrasound in Diagnostic Process of Hepatitis C Disease: Comparison with Serum Inflammatory Indices Level and T-Helper 1 Cytokine Responses

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Abstract: To diagnose of Hepatitis generally an ultrasound of the abdominal area should be performed. The most useful laboratory tests, particularly for screening evidence of liver disease, are serum aminotranspherases and alkaline phosphatase levels. Undoubtedly, cell-mediated immune responses of antiviral cytokines contribute to the pathogenesis of liver injury associated with Hepatitis C. This study aimed to evaluate role of liver ultrasonography in detecting HCV-infected patients and comparison it with serum inflammatory indexes level and with serum T-helper 1 cytokines level. Fifty four serologically confirmed HCV-infected patients and 31 healthy controls were enrolled using sequential sampling method. Ultrasonography (US) (using Medison 8000, Korea) was performed by one radiologist for investigation the liver echogenicity after the patients and control groups underwent an overnight fast. Serum levels of IFN-γ, TNF-α and IL-2 cytokines was checked in all participants, using ELISA. Serum levels of ALT, AST and ALP were also determined (using Photometer) in both patients and control group. T-test was used to test the differences between the patients and control groups. Associations between the quantitative data were studied by correlation analysis. Data analysis of US results for liver echogenicity showed significant differences between patient and control groups ($p<0.05$). About 47.1% of patients had elevated serum ALT level and 74.5% of them had also elevated serum ALP levels. Serum levels of cytokines were higher in patient group than control but it was only significant for TNF-α. Serum AST level in increased liver echogenicity group was higher than normal group. There was no other significant relationship between liver US results and serum inflammatory indexes or cytokines level. According to considerable proportion of agreement in liver ultrasonography results and relationship between liver echogenicity and serum AST levels, we concluded that sonography may play an important role in the detection, characterization and management of Hepatitis C.

Key words: Sonography, Hepatitis C, inflammatory indexes, cytokines

INTRODUCTION

An early diagnosis in the course of the disease can increase the chances of successful treatment, increase impact of essential lifestyle changes and limit cross-infection (WHO, 1995). Diagnosis of liver and biliary system disorders may include laboratory tests, imaging tests and liver biopsy. Laboratory tests generally are effective in detecting hepatic dysfunction, assessing the severity of liver injury, refining the diagnosis concerning any identified abnormalities, monitoring the course of liver disease and evaluating the response to treatment. The most useful laboratory tests, particularly for screening evidence of liver disease, are serum aminotransferases, bilirubin and alkaline phosphatase levels (Porter *et al*., 2008a). Alkaline phosphatase is usually only moderately raised; marked elevation suggests extrahepatic cholestasis and prompts imaging tests, example ultrasound (Porter *et al*., 2008b). Mortele *et al*. (2004) suggested recent technologic advances have significantly enhanced the role of imaging in the detection, characterization and management of infectious diseases involving the liver. Infectious liver diseases can be accurately evaluated with ultrasonography. It is the least expensive, safest and most sensitive technique (Porter *et al*., 2008c). Inflammation is a common cause of damage to the delicate liver cell membranes. Liver inflammation is medically termed Hepatitis. To diagnose of Hepatitis generally an ultrasound of the abdominal area should be performed. Many cases of fatty liver can be picked up this way. The ultrasound will detect areas of increased echogenicity meaning that the liver tissue is beginning to become infused with fat (Sandra, 2003). Undoubtedly, cell-mediated immune responses and

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elaboration by t-cells of antiviral cytokines contribute to the containment of infection and pathogenesis of liver injury associated with Hepatitis C. Yet a consensus has emerged supporting a role in the pathogenesis of HCV-associated liver injury of virus-activated t-cell cytokines they elaborate (Kasper *et al*., 2005). However, individual tests, particularly those of liver biochemistry and excretion, often have limited sensitivity and specificity (Porter *et al*., 2008a). In most cases radiologic findings are not sufficiently characteristic to help identify the type of infection. In addition, access to epidemiologic and clinical information remains extremely important for obtaining a more accurate presumptive diagnosis (Mortele *et al*., 2004). Therefore, combined and serial testing is used to better diagnose and assess the cause and severity of disease (Porter *et al*., 2008a). This study aimed to evaluate role of liver ultrasonography in detecting HCV-infected patients and comparison it with serum inflammatory indexes level contain; aminotransferases (ALT and AST) and Alkaline Phosphatase (ALP) and with serum T-helper 1 cytokines level contain; interleukine-2 (IL-2), interferon-gamma (IFN-γ) and tumor necrosis factor-α (TNF-α).

MATERIALS AND METHODS

Subjects of this study were the people referred to Iran red crescent society clinic in Baku, Azerbaijan Republic. Blood samples were collected from each subject and tested twice for anti-HCV antibody by ELISA (Monobind, USA). Anti-HCV antibody less than one unit considered as negative, 1-1.2 unit borderline and higher than 1.2 considered as positive. Accordingly, thus 54 serologically confirmed HCV-infected patients and 31 healthy controls were enrolled using sequential sampling method. Mean age of patients and healthy controls were 42.40±12.75 and 43.55±12.97, respectively. Ultrasonography (US) (using Medison 8000, Korea) was performed by one radiologist for investigation the liver echogenicity after the patients and control groups underwent an overnight fast. Serum levels of IFN-γ, TNF-α and IL-2 cytokines was checked in all participants, using ELISA (Euro clone, Italy). Serum levels of ALT, AST and ALP were also determined using STATFAX (1902, USA) for the patient group. Serum ALT <38 unit, AST <42 unit and ALP <180 unit L^{-1} were considered as normal. Collected data were analyzed by SPSS software. ANOVA was used to compare means of >2 independent groups. T-test was used to test the differences between the patients and control groups. Associations between the quantitative data were studied by correlation analysis. The level of significance in all cases was set at a 2-tailed $p<0.05$.

Table 1: Demographic and variables finding of patient and control groups (Mean±SD)

Variable	Control	Patient	p-value
Age	43.55±12.97	42.40±12.75	>0.05
Sex (female/male)	16.15	19.35	>0.05
ALT (normal/increased)	29.2	27.24	<0.05
AST (normal/increased)	29.2	40.10	>0.05
ALP (normal/increased)	19.12	13.38	<0.05
Liver echogenicity (normal/increased)	23.7	20.32	<0.05
IFN-γ	0.49±1.114	3.045±13.383	>0.05
TNF-α	0.393±2.117	2.892±8.245	<0.05
IL-2	0	0.517±2.184	>0.05

RESULTS

Data analysis of US results showed significant differences between patient and control groups for liver echogenicity. According to results, 61.5% of patients and 30.4% of control group had increased liver echogenicity (Table 1, $p<0.05$). Age and sex were similar in control and patient groups. The results of inflammatory parameters showed significant difference between 2 groups for ALT and ALP. 47.1% of patients had elevated serum ALT level and 74.5% of them had also elevated serum ALP levels ($p<0.05$). 20% of patients had elevated serum AST but it was not significant (Table 1, $p>0.05$). Serum levels of cytokines (IFN-γ, TNF- α, IL-2) were higher in patient group than control but it was only significant for TNF-α (2.892± 8.245 for patients, 0.393± 2.117 for controls). Serum AST level in increased liver echogenicity group (41.47±8.11) was higher than normal group (36.82±4.49) ($p<0.05$). There was no other significant relationship between liver US results and serum inflammatory indexes or cytokines level.

DISCUSSION

Approximately, 80-90% of patients acutely infected with Hepatitis C virus develop persistent infection, about one half of them have elevated transaminase indicative of ongoing liver inflammation (Abbas *et al*., 2005). Our study results showed elevated serum level of ALT in 47.1% and serum level of ALP in 74.5% of patients infected with Hepatitis C virus.

In the context of an inflammatory response against the virus, variable cytokine response of the host may be responsible for the variable liver damage (Kasper *et al*., 2005). In our study, serum cytokine TNF-α level in patients infected with HCV was higher than healthy controls. Abbas *et al*. (2005) and Barry and Rafi (2001) have showed increased circulating immunoregulatory cytokines in patients with HCV liver disease. TNF-α is the principal mediator of the acute inflammatory response to

infectious microbes and is responsible for many of the systemic complication of sever infections (Krams *et al*., 1996).

Imaging plays a pivotal role in the work-up of patients with suspected liver infections (Mortele *et al*., 2004). We also assessed the role of tested and validated US findings (liver echogenicity) for prediction of the presence of hepatitis. As shown in our study, a considerable proportion of agreement was observed between liver ultrasonography results in patients with hepatitis C virus infection. All cross-sectional techniques allow highly accurate detection of hepatic infections (Mortele *et al*., 2004). Characteristic changes in US echogenicity can contribute to the diagnosis of specific infectious diseases, including viral hepatitis (Mortele *et al*., 2004). Mortele and Ros (2001) suggested at US, in acute hepatitis, the liver is often enlarged and may demonstrate a diffuse decrease in parenchymal echogenicity, which causes a relative increase in the echogenicity of the portal vein walls. Although, chronic hepatitis displays normal US findings in many cases, it can manifest with a coarsened hepatic echotexture and increased parenchymal echogenicity, causing portal vein radicals to be less conspicuous. The appearance of the liver is essentially identical to that seen with diffuse fatty change (Igel and Nelson, 1998). According to results of a study by Mathiesen *et al*. (2002) increased liver echogenicity at ultrasound examination reflects degree of steatosis. Results of Stransky *et al*. (2002) showed steatosis (fatty degeneration) in chronic HCV infection is a very frequent finding particularly in patients with serious fibrosis (42%). Our study also showed relationship between liver echogenicity and serum AST levels. According to results of study by Stransky *et al*. (2002) AST more than ALT levels predict the progression of liver fibrosis in chronic HCV infection. The imaging features of acute hepatitis are nonspecific and the diagnosis is usually based on serologic, virologic and clinical findings (Mortele *et al*., 2004).

CONCLUSION

We concluded that sonography may play an important role in the detection, characterization and management of infectious liver diseases. In certain entities, the imaging findings are characteristic and lead to a specific diagnosis. Characteristic changes in US echogenicity can contribute to the diagnosis of specific liver infections. In most instances, however, the radiologic features are less specific, but the imaging findings together with appropriate clinical information may provide the most likely diagnosis.

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