High prevalence of hepatitis C in Egyptian patients with chronic liver disease

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Abstract
The highest prevalence rates of hepatitis C virus infection in the world have been recently reported among Egyptian blood donors and frequent recipients of transfusions and other blood products. This is the first report, however, demonstrating hepatitis C as the most frequent association with chronic liver disease in Egypt. Of 1023 patients referred to the Liver Institute in Menoufia governorate for evaluation of chronic liver disease, 752 (73·5%) had antibodies to hepatitis C compared with 168 (16·4%) with hepatitis B surface antigen. Hepatitis C antibody was more common in patients with active schistosomiasis and patients without hepatitis B surface antigenaemia. Of 100 patients having liver biopsies, histological findings consistent with chronic viral hepatitis or its complications were found in 89 and antibody to hepatitis C was present in 75 (84·3%) of these patients with chronic hepatitis, active cirrhosis or hepatocellular carcinoma. These data pointing to the importance of hepatitis C as a cause of chronic liver disease in Egypt emphasise the necessity of studies delineating its routes of transmission in this country.
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Hepatitis C virus (HCV), the main cause of parenterally acquired non-A, non-B hepatitis worldwide, becomes a chronic infection in about 70% of persons infected.[1–3] In most chronic cases, HCV infection progresses to chronic active hepatitis, which in turn may cause cirrhosis and hepatocellular carcinoma.[2 3] In Egypt, where hepatitis is an important public health problem, hepatitis B virus (HBV) and schistosomiasis are the most widely recognised causes of liver disease.[4] Many cases of acute and chronic liver disease in Egypt, however, cannot be related to schistosomiasis or HBV, and antibodies to HCV (anti-HCV) were detected in two thirds of patients with acute non-A, non-B hepatitis.[5] In addition, the prevalence of HCV (11–22%) in Egyptian blood donors has recently been reported to be among the world's highest.[6–9] Despite the high prevalence of HCV in Egypt and its propensity to cause chronic liver disease, the importance of HCV as a cause of chronic liver disease in Egypt is unknown.

To determine the relative significance of HCV as a cause of chronic liver disease in Egypt, the prevalence of anti-HCV was determined in a cohort of adult patients with chronic liver disease and compared with the prevalence of hepatitis B surface antigen (HBsAg) and schistosomiasis.

Methods
From July to December 1992, 1023 adult patients referred to the outpatient clinic of the Liver Institute at Menoufia University were assessed as follows: (1) anti-HCV was detected using a second generation enzyme immunoassay (Ortho Diagnostic Systems, Beerse, Belgium), and a randomly selected subset of 27 samples positive on enzyme immunoassay were also tested using a second generation recombinant immunoblot assay (Ortho Diagnostic Systems); (2) HBsAg was assayed by enzyme immunoassay (Sorin Biomedica, Seluggia, Italy); (3) alkaline and alanine aminotransferase activities were determined by Synchron AS (Beckman Instruments, USA); and (4) abdominal ultrasound was performed by trained clinicians. In addition, rectal snip biopsy specimens were examined microscopically for schistosoma ova in 592 patients who had a history of exposure to schistosome infested water or had clinical findings suggestive of schistosomiasis. Liver biopsy specimens were taken from 100 patients for clinical indications of a suspicious liver mass or persistently increased alanine aminotransferase activity and rated according to the accepted international classification by a pathologist blinded to the serological results.

All laboratory tests and procedures performed upon the patients were believed clinically indicated by the physicians responsible for the patient's care and were not performed for the purpose of this study. Informed consent was obtained before rectal snip and liver biopsies. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Liver Institute's human research review committee.

Statistical comparisons were made of the proportion of persons with anti-HCV by sex, HBsAg status, and the presence of *S mansoni* eggs using the Mantel-Haenszel χ^2 test (EPI INFO 5·0).

Results
All of the 1023 patients enrolled in this study had clinical, biochemical, or ultrasonographic

TABLE I *Associations of HBsAg and schistosomal eggs in rectal snip biopsy specimens with anti-HCV in 1023 Egyptian patients with chronic liver disease**

Characteristic		No	% HCV	OR (95% CI)	p Value
Sex					
	Female	378	64·0	1·0	
	Male	645	79·1	2·1 (1·6, 2·8)	<0·001
HBsAg status					
	Positive	168	23·8	1·0	
	Negative	855	83·3	16·7 (11·1, 28)	<0·001
†S mansoni eggs					
	None	136	68·4	1·0	
	Positive – dead	128	62·5	0·8 (0·5, 1·3)	0·38
	Positive – living	328	82·0	2·1 (1·3, 3·4)	0·002

*No=number of patients in each category. OR=odds ratio. CI=confidence intervals.
†x^2 test for trend (Mantel extension) was also calculated assuming uniform degrees of exposure for none, positive – dead, and positive – living: p<0·001.

evidence of chronic liver disease. The mean age of patients (range) was 42 (16–75) years, and 645 (63·0%) were male. While 767 (75·0%) of patients presented to the clinic with symptoms compatible with chronic liver disease, 256 (25·0%) were referred because of increased serum aminotransferase activities or asymptomatic liver enlargement.

Of the 1023 patients with chronic liver disease, 752 (73·5%) had anti-HCV and 25 (92·6%; 95% confidence intervals=75·7 to 99·1%) of a randomly selected subset of 27 of these were confirmed by supplemental testing. This degree of association between the two tests is in agreement with our experience with other blood samples and with other reports from Egypt.[7][9] Anti-HCV was more frequent in men, in patients without HBsAg, and in patients with living S mansoni eggs in rectal snip biopsy specimens in comparison with those without eggs or those with dead eggs (Table 1). HBsAg was detected in 168 (16·4%) of 1023 patients.

A histological classification was pursued in 100 patients with clinical indications (Table II). Biopsy specimens from 89 of 100 patients showed pathological changes consistent with chronic viral liver disease: chronic persistent hepatitis, chronic active hepatitis, cirrhosis, or hepatocellular carcinoma. Of these 89 patients, 55 (61·8%) had anti-HCV, 11 (12·3%) had HBsAg, and 20 (22·5%) had both anti-HCV and HBsAg (Table II).

Discussion

Anti-HCV was present in almost three quarters of outpatients referred for assessment of chronic liver disease and was present in 84%, and the only viral marker in 62%, of those with liver histology consistent with

chronic viral hepatitis or its complications. These data show that HCV as an important, if not the primary, cause of chronic liver disease in this region of Egypt. This finding is not unexpected as high rates of anti-HCV were reported in Egyptian blood donors,[6–9] and in patients with high risk for blood-transmitted infections,[8] and HCV is known to cause chronic liver disease histologically identical to that found in our patients. In addition, these data are consistent with reports of the association of anti-HCV with hepatocellular carcinoma.[3][10]

Although these data clearly show the high prevalence of HCV in Egyptian patients with chronic liver disease, they may underestimate the relative prevalence of HBV when assessed by HBsAg. Fong et al reported that coinfection of HBV infected patients with HCV suppresses HBV replication.[11] This suppression may cause a decreased expression of HBsAg and an underestimation of HBV prevalence as reflected by HBsAg and may explain why our patients with HBsAg were less likely to have anti-HCV than those without HBsAg.[12] The interrelation between HBV and HCV is complex; however, another study in Egypt has reported a positive association between the two hepatitis viruses in some blood donors.[9]

In this investigation the prevalence of anti-HCV was greater in patients with active schistosomiasis, as shown by living S mansoni eggs detected by rectal snip biopsy. The increased prevalence of HCV infection in patients with concomitant schistosomiasis mansoni could be caused by the additive effects of the two hepatic infections leading to an increased likelihood of those with both infections seeking medical care at the Liver Institute. Also, the increased prevalence of HCV could result from the reuse of needles to give parenteral treatment for schistosomiasis, a common practice before the wide availability of the oral medication, praziquantel, in the past eight or 10 years.[13] In murine models infection with S mansoni causes increased Th2 cytokine production; a down regulation of interleukin 2, interferon gamma, and virus specific CD8+ cytotoxic T cells; and a decrease in clearance of a concomitant viral infection.[14][15] In humans similar immunological suppression from chronic schistosomiasis may lead to less control of viral replication and higher circulating titres of HBV or HCV, as previously suggested by Ghaffar et al.[4] These changes may increase the likelihood of chronic infection and the efficiency of HCV transmission. Immune suppression from human immunodeficiency virus has been shown to increase both perinatal and sexual transmission of HCV.[16][17] Schistosomiasis related immune suppression may similarly enhance transmission and contribute to the very high prevalence of HCV in Egypt.

Given the apparent magnitude of HCV induced chronic liver disease in Egypt and the morbidity associated with this condition, future studies of the routes of HCV transmission and the risk factors that enhance HCV acquisition are urgently needed.

TABLE II *Pathological findings in 100 patients with chronic liver disease according to the presence of anti-HCV or HBsAg in serum samples*

	Anti-HCV	Anti-HCV and HBsAg	HBsAg	Neither anti-HCV or HBsAg	Total
Chronic persistent hepatitis	5 (71·4)	1 (14·3)	0	1 (14·3)	7
Chronic active hepatitis	12 (60·0)	4(20·0)	4 (20·0)	0	20
Active cirrhosis	23 (59·0)	9 (23·1)	5 (12·8)	2 (5·1)	39
Hepatocellular carcinoma	15 (65·2)	6 (26·1)	2 (8·7)	0	23
Schistosomal hepatic fibrosis	1 (33·3)	0	0	2 (66·6)	3
Other	2 (25·0)	0	2 (25·0)	4 (50·0)	8
Totals	58	20	13	9	100

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