HEPATITIS C AND CIRRHOTIC LIVER DISEASE IN THE NILE DELTA OF EGYPT: A COMMUNITY-BASED STUDY

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Abstract. Residents of Egypt's Nile river delta have among the world's highest seroprevalence of hepatitis C virus (HCV) infection. To assess the impact of HCV on chronic liver disease, we studied the association between HCV, other hepatitis viruses, and cirrhotic liver disease in a cross-sectional, community-based survey of 801 persons aged ≥ 10 years living in a semi-urban, Nile delta village. Residents were systematically sampled using questionnaires, physical examination, abdominal ultrasonography and serologically for antibodies to HCV (confirmed by a third-generation immunoblot assay) and to hepatitis A virus (HAV), hepatitis B virus (HBV), and hepatitis E virus (HEV). The seroprevalence of HCV increased with age from 19% in persons 10–19 years old to about 60% in persons 30 years and older. Although no practices that might facilitate HCV transmission were discovered, the seroprevalence of HCV was significantly associated with remote (> 1 year) histories of schistosomiasis. Sonographic evidence of cirrhosis was present in 3% (95% CI: 1%, 4%) of the population (0.7% of persons under 30 years of age and in 5% of older persons), and was significantly associated with HCV seroreactivity. Our findings are consistent with the hypothesis that past mass parenteral chemotherapy campaigns for schistosomiasis facilitated HCV transmission, and that HCV may be a major cause of the high prevalence of liver cirrhosis in this Nile village.

INTRODUCTION

Since its discovery in 1989, the hepatitis C virus (HCV) has been found to cause significant morbidity and mortality in tropical settings. Studies of the epidemiology of HCV infections have suggested that the Nile delta region of Egypt has among the highest prevalence rates of HCV in the world, with seroprevalence rates of 30–40% in villagers over the age of 30 years.

While these high prevalence rates raise substantial concern, the interpretation of past epidemiologic studies of HCV in Egypt has been limited by the sparse availability of population-based data, particularly from studies that have used modern laboratory techniques capable of diagnosing HCV infection with suitable high levels of diagnostic specificity. It is also unclear what the long-term outcomes of these infections in Egyptians will be, particularly since the predominant HCV genotype in Egypt (type 4) differs from genotypes found in many other parts of the world and since HCV of Egyptians act within a milieu of many other infectious assaults capable of causing chronic liver sequelae, including hepatitis B infection and schistosomiasis.

Because of these uncertainties, we have undertaken a series of studies of HCV and other hepatic infections in Kalama, a Nile delta village near Cairo. As reported elsewhere, we first conducted a pilot survey in this village, using ad hoc sampling of the population, to determine whether the village might be suitable for the study of prevalence and sequelae of HCV. This initial study revealed an astonishingly high seroprevalence of hepatitis C in persons ten years of age and over, peaking at 51% for persons aged 40–67 years. In this paper we report findings from a follow-up survey in which subjects were formally sampled to ensure a representative study population and in which both the seroprevalence of hepatitis C and the prevalence of ultrasonographic evidence of cirrhosis were assessed in the sampled population. Our findings confirm the high burden of HCV in this population, and raise the possibility that a high fraction of cases of cirrhosis may be attributable to HCV.

MATERIALS AND METHODS

Site. We conducted this study in Kalama, a semiurban village in the Nile delta, 19 km north of Cairo. Most of the estimated 17,000 residents of Kalama engage in agricultural occupations. The village is surrounded by irrigated farmland and irrigation canals typical of the Nile delta.

Census, household sampling, and informed consent. In autumn 1994, we constructed a complete map of Kalama, giving each of the 2,431 houses a consecutive number. Next, for purposes of sampling, we divided the village into 12 sectors, and sampled every fifteenth house of each sector.

The heads of the 172 selected households were then approached to obtain written informed consent to participate in the study. One hundred sixty eight (98%) household heads agreed to participate. The protocol was approved by Institutional Review Boards of the Ain Shams University School of Medicine, Cairo, Egypt and the University of Maryland School of Medicine, Baltimore, Maryland.

Baseline questionnaire and bleeding. In December 1994, we conducted a census of the 168 participating houses, in which we collected demographic and socioeconomic data about all household residents. We next solicited permission from each resident aged 10 years and older, or their parents, to be interviewed, to receive a brief physical examination, and to contribute up to 7 ml of blood via venipuncture. Persons under the age of 10 years were excluded because our earlier study had found no serological evidence of HCV in

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* Deceased.
this age group. A total of 801 (88%) of the age-eligible residents agreed to participate in the study, after providing written informed consent. The baseline questionnaire solicited sociodemographic information and information about medical and behavioral risk factors for liver disease. Household socioeconomic status was classified as high, medium, or low according to a locally developed scale that took into account the occupation of the household head, as well as ownership of several selected items (Gadallah M, unpublished data). Acquisition of baseline data was completed between January and June of 1995.

**Abdominal ultrasonography.** Beginning in June 1995, and continuing for the next 6 months, all participants were invited to receive an abdominal ultrasound at the Kalama district hospital. Ultrasonography was performed with use of an Aloka SSD 500 Ultrasonography Unit with a 3.5 MHz convex probe. The sonographer for these examinations (MSE-S) had had several years of experience in sonographic evaluations of liver disease in Egypt. As detailed elsewhere, the procedure for the examination was standardized, and data were recorded on a structured and pre-coded report form. Of the 801 participants in the study, 689 (86%) agreed to ultrasonographic examinations.

The diagnosis of cirrhosis was made for patients in whom a normal- or small-sized fatty liver was observed in association with one of the following: 1) coarse, bright hepatic parenchyma; or 2) a caudate-to-right lobe ratio of 0.6.9–12 Portal hypertension was deemed present if the main portal vein measured >13 mm. Liver disease due to schistosomiasis was presumptively diagnosed on the basis of periportal fibrosis (PPF),13 defined as portal venule wall thickness ≥4 mm.14 Periportal fibrosis was classified in three grades: Grade 1 (least severe) was defined as PPF that was central in location only. Grade 2 was defined as PPF that reached to the hepatic surface. Grade 3 (most severe) was PPF that had the characteristics of Grade 2 but also was associated with surface irregularity. Photographs taken during ultrasonographic procedures were reviewed by a second sonographer (KG) who was blinded to the interpretations of the first sonographer. Any disagreements between the two sonographers were discussed and resolved. All interpretations were performed blinded to the results of the baseline questionnaire, findings on physical examination, and the results of serological tests.

**Serological analyses.** Sera were stored in aliquots at −20°C until testing. Antibodies to hepatitis A virus (HAV), hepatitis B virus (HBV), HCV, and hepatitis E virus (HEV) were detected with commercial enzyme immunoassay (EIA) kits: HAVAB-EIA (Abbott Laboratories, Abbott Park, IL) for anti-HAV antibodies; Enzygnost anti-HBc monoclonal (Behringwerke, AC, Marburg, Germany) for anti-hepatitis B core antibodies; the second-generation Abbott HCV-EIA (Abbott Laboratories) for anti-HCV antibodies; and the Abbott HEV EIA (Abbott Laboratories) for anti-HEV antibodies. The presence of circulating HBV surface antigen (HBsAg) was detected with the Enzygost HBsAg monoclonal assay (Behringwerke, AC). Because our earlier research had demonstrated that antibodies to HAV were evident in nearly 100% of residents of the Nile delta by early childhood,3 we tested only a random sample of 194 sera for these antibodies.

Because of the reported non-specificity of the second-generation Abbott EIA for anti-HCV antibodies, we employed this assay as a screening test and used a Chiron recombinant immunoblot assay (RIBA-2, Chiron Corporation, Emeryville, CA) to evaluate all EIA-reactive sera. Manufacturer’s criteria were employed to classify sera as positive, indeterminate, or negative. Moreover, because a more sensitive, third-generation immunoblot assay (RIBA-3, Chiron Corporation), containing two recombinant antigens and three synthetic peptides, became available shortly after we had completed this testing sequence, we used the RIBA-3 to evaluate all available sera that were EIA-reactive but were negative or indeterminate by the RIBA-2 test.14 One-hundred and one of 106 such sera were available for testing, so that a total of 796 sera were considered fully evaluable for determining reactivity to HCV. Again manufacturer’s criteria were used to classify sera as positive, indeterminate, or negative by the RIBA-3. Of 352 sera positive by second-generation EIA, 321 (91%) were confirmed positive by either RIBA-2 or RIBA-3.

**Data analysis.** We used the chi square test, or the Fisher exact test when mandated by sparse data, to compare groups for categorical outcomes. For comparisons of dimensional outcomes, we used the Student’s t-test, or the Mann-Whitney U test when parametric assumptions were not fulfilled.

To assess correlates of HCV infection, we conducted case-control analyses. Cases were defined as persons whose sera were reactive by either the RIBA-2 or the RIBA-3 tests. Controls were those whose sera were not reactive by either test. We excluded from these analyses the five subjects whose sera were reactive with the screening EIA test and were either negative or indeterminant with the RIBA-2 test, but for whom no sera remained for RIBA-3 testing. To evaluate correlates of cirrhosis, we compared cases (persons with ultrasonographic evidence of cirrhosis) with controls (persons whose sonograms gave no evidence of cirrhosis). We excluded from these comparisons the 112 persons who did not have abdominal ultrasonography performed.

Associations between exposure variables and case-control status were expressed as odds ratios. In simple analyses, confidence intervals for these odds ratios were computed with test-based techniques.16 To assess the simultaneous association between several exposure variables and case-control status, we employed multiple logistic regression models, taking case-control status as the dependent variable and fitting exposure variables as independent variables. Potential confounders selected as independent variables in these models were chosen as those significantly related to case-control status in crude analyses and those judged to make sense based on biological plausibility. In these models the coefficients for the independent variables were exponentiated to estimate adjusted odds ratios, and standard errors for the coefficients were used to construct confidence intervals for the adjusted odds ratios. The “etiologic fraction”, corresponding to the percentage of cases that could be attributed to a particular exposure variable, was computed with standard techniques appropriate for stratified data.16 All statistical tests were interpreted in a two-tailed fashion to estimate P values and confidence intervals.
Age-specific pattern of seroprevalence of different hepatitis viruses. The age-specific patterns of the seroprevalence of HAV, HBV (defined as having antibodies to HBV core antigen or having circulating HBsAg), HCV (RIBA-2 or RIBA-3 positive), and HEV revealed important differences (Figure 1). For the two orally transmitted viruses, HAV and HEV, the trend of seroprevalence with age was flat—at nearly 100% for HAV and at about 60% for HEV—reflecting infection early in life. For the two parenterally transmitted viruses, HBV and HCV, seroprevalence increased steadily with age, reaching levels of about 75% at ages ≥40 years for HBV and of about 60% at ages ≥30 years for HCV. In contrast, the prevalence of HBsAg seropositivity remained at about 10% throughout the age range under study.

Correlates of HCV infection. Of the 796 subjects who were fully evaluable for HCV infection, 321 (40%) were seroreactive to HCV. Table 1 shows that HCV-positive cases were significantly older than HCV-negative controls. Otherwise, cases and controls had virtually identical distributions of sociodemographic characteristics, including primary source of drinking water and primary type of defecation site. None of several candidate practices or procedures by which HCV might be transmitted parenterally—illicit drug use, surgery, blood transfusions, injections, tattoos, circumcision, acupuncture, being shaved by the village barber, and ear-piercing—exhibited significant associations with HCV seroprevalence after controlling for age. Seroreactivity to HEV revealed a marginally significant association with HCV seroreactivity, but serological evidence of HAV, HBV and HBsAg were not significantly associated with HCV seroreactivity (Table 2).

Subjects who recalled having had a remote (more than one year ago) diagnosis of schistosomiasis were more likely to be HCV-positive (adjusted odds ratio 1.75, \( P < 0.05; 95\% \text{ CI}: 1.14, 2.67 \)) (Table 2). A nearly identical association was observed between having ultrasonographic evidence of portal fibrosis (PPF), a lesion that is characteristic of chronic hepatic schistosomiasis, and HCV seroreactivity (adjusted odds ratio 1.76, \( P < 0.05; 95\% \text{ CI}: 1.01,3.05 \)). In contrast, having only a recent (within the past year) diagnosis of schistosomiasis, and recalling having received injections for schistosomiasis (adjusted odds ratio 1.51; 95%CI: 0.78,2.91) were not associated with HCV seroreactivity (Table 2).

Cirrhotic liver disease. Eighteen (3%) of the 689 subjects who received abdominal ultrasonography met the criteria for cirrhosis. The prevalence of cirrhosis was appreciable (0.7%) even in persons under 30 years of age and rose dramatically to about 5% in older age groups. Twelve (67%) cirrhotics had a history of alcohol intake. Fourteen (78%) cirrhotics were seroreactive to HCV, 4 (22%) had circulating HBsAg, and 3 (17%) had PPF (Table 3), although none of these three patients had Grade 3 PPF.

Of the 14 HCV-associated cases of cirrhosis, 9 (64%) had portal hypertension. Portal hypertension was evident in 5
Selected behavioral, medical, and serological features of hepatitis C virus-positive cases and HCV-negative controls in Kalama, Egypt

<table>
<thead>
<tr>
<th>Feature</th>
<th>Cases (n = 321)</th>
<th>Controls (n = 473)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude</td>
<td>Adjusted</td>
<td></td>
</tr>
<tr>
<td>Illicit drug use</td>
<td>0%</td>
<td>0%</td>
<td>—</td>
</tr>
<tr>
<td>Surgery</td>
<td>12%</td>
<td>7%</td>
<td>1.80 (1.07, 3.05)</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>2%</td>
<td>0.4%</td>
<td>3.74 (0.64, 27.43)</td>
</tr>
<tr>
<td>Injections</td>
<td>75%</td>
<td>73%</td>
<td>1.13 (0.81, 1.58)</td>
</tr>
<tr>
<td>Circumcision</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>97%</td>
<td>97%</td>
<td>1.20 (0.34, 4.75)</td>
</tr>
<tr>
<td>Females</td>
<td>95%</td>
<td>96%</td>
<td>0.77 (0.26, 2.36)</td>
</tr>
<tr>
<td>Tattoos</td>
<td>0.3%</td>
<td>1%</td>
<td>0.37 (0.006, 3.49)</td>
</tr>
<tr>
<td>Acupuncture</td>
<td>0.6%</td>
<td>0%</td>
<td>—</td>
</tr>
<tr>
<td>Shaved by village barber (males ≥ 15 years)</td>
<td>61%</td>
<td>44%</td>
<td>2.04 (1.28, 3.26)</td>
</tr>
<tr>
<td>Ears pierced</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>4%</td>
<td>2%</td>
<td>1.91 (0.53, 7.07)</td>
</tr>
<tr>
<td>Females</td>
<td>95%</td>
<td>94%</td>
<td>1.15 (0.44, 27.85)</td>
</tr>
<tr>
<td>Serological evidence of:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAV</td>
<td>97%</td>
<td>99%</td>
<td>0.33 (0.01, 6.54)</td>
</tr>
<tr>
<td>HBV</td>
<td>57%</td>
<td>45%</td>
<td>1.57 (1.17, 2.11)</td>
</tr>
<tr>
<td>HBsAg</td>
<td>10%</td>
<td>8%</td>
<td>1.25 (0.75, 2.08)</td>
</tr>
<tr>
<td>HEV</td>
<td>56%</td>
<td>51%</td>
<td>1.21 (0.90, 1.63)</td>
</tr>
<tr>
<td>Schistosomiasis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>30%</td>
<td>14%</td>
<td>2.72 (1.88, 3.93)</td>
</tr>
<tr>
<td>Time of Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>70%</td>
<td>86%</td>
<td>1.00</td>
</tr>
<tr>
<td>Only in year before baseline</td>
<td>4%</td>
<td>3%</td>
<td>1.38 (0.60, 3.14)</td>
</tr>
<tr>
<td>Periportal fibrosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated by injection</td>
<td>19%</td>
<td>6%</td>
<td>3.61 (2.13, 6.16)</td>
</tr>
</tbody>
</table>

Table 3 compares cirrhotic cases and non-cirrhotic controls for serological markers of hepatitis viruses and for sonographic evidence of PPF. In crude analyses, HCV was significantly associated with cirrhosis (odds ratio 5.36, P < 0.01; 95% CI: 1.66, 22.56), while the relationship between HBsAg and cirrhosis was suggestive but non-significant (odds ratio 3.47; 95% CI: 0.80, 11.58). Antibody to HAV and HEV, and PPF were not associated with cirrhosis. After adjusting for age, sex, and socioeconomic status, HCV alone remained significantly associated with cirrhosis (odds ratio (83%) of 6 HCV-associated cirrhotic cases under the age of 35 years and in 4 (50%) of the 8 older HCV-associated cirrhotic cases.

Comparison of the 18 cirrhotic cases with the 671 non-cirrhotic controls revealed that cases were significantly older than controls (median age of 36.5 years for cases versus 25 years for controls, P < 0.01), that cases were significantly more likely than controls to be male (83% versus 49%, P < 0.01), and that cases were from households with significantly lower socioeconomic status (low-medium-high status: 65%, 35%, 0%, respectively, for cases versus 35%, 61%, 4% for controls, P < 0.05).

Table 3 compares cirrhotic cases and non-cirrhotic controls for serological markers of hepatitis viruses and for sonographic evidence of PPF. In crude analyses, HCV was significantly associated with cirrhosis (odds ratio 5.36, P < 0.01; 95% CI: 1.66, 22.56), while the relationship between HBsAg and cirrhosis was suggestive but non-significant (odds ratio 3.47; 95% CI: 0.80, 11.58). Antibody to HAV and HEV, and PPF were not associated with cirrhosis. After adjusting for age, sex, and socioeconomic status, HCV alone remained significantly associated with cirrhosis (odds ratio...
3.65, \( P < 0.05; 95\% \text{ CI}: 1.09, 12.23 \). Finally, we evaluated the simultaneous relationship of HCV, HBsAg, age, sex, and socioeconomic status with cirrhosis. In this model, HCV remained significantly associated with cirrhosis (odds ratio 3.84, \( P < 0.05; 95\% \text{ CI}: 1.16, 12.23 \)), while the association of HBsAg with cirrhosis remained non-significant (odds ratio 2.16; 95\% CI: 0.64, 7.33).

If it is assumed that HCV infections preceded the onset of cirrhosis in all 18 cases, it is possible to calculate the fraction of cirrhosis cases that might be attributable to HCV in Kalama. Because of the small number of cirrhotic cases, it was possible only to control for the confounding effects of age in this calculation. After controlling for age, this fraction was 0.52.

**DISCUSSION**

The representative, community-based sample of persons evaluated in our study had an extraordinarily high seroprevalence of HCV, reaching about 60\% in persons aged 30 years and older. These data are concordant with the findings of other community-based studies in the Nile delta that have indicated that this region of Egypt has among the highest levels of seroprevalence of HCV in the world.\(^{1,4,17,18}\) Indeed, if as seems plausible,\(^{17,18}\) the high seroprevalence of HCV is relatively uniformly distributed throughout the Nile delta, the 40\% seroprevalence of HCV among persons aged ten years and over in Kalama would translate into approximately eight million HCV-infected Nile delta residents in this age group.

Cirrhosis, evident in 3\% of subjects receiving abdominal ultrasonography, imposed a major burden of illness in Kalama. The prevalence of cirrhosis among residents of Kalama was unexpectedly high (0.7\%) during the second and third decades of life, and it rose dramatically to about 5\% in older age groups. Since ultrasonographic criteria have been documented to be relatively insensitive for detecting the presence of cirrhosis, our estimates of prevalence are likely conservative.\(^{3,19}\) Moreover, our study did not identify additional cases of chronic, non-cirrhotic liver disease that did not meet the sonographic criteria for cirrhosis.

Our study represents the only community-based study to estimate the prevalence of cirrhosis in a developing country. To our knowledge, only one other community-based study of the prevalence of cirrhosis has been conducted.\(^{19}\) This study, which evaluated subjects aged 12–65 years in two towns in northern Italy, found the prevalence of cirrhosis to be 1\%. The Italian study accepted either sonographic or clinical evidence to make the diagnosis of cirrhosis, whereas our study accepted only sonographic evidence, and the persons undergoing sonography in our study were younger (64\% under 35 years) than the population evaluated in the Italian study (39\% under 35 years). As the result of these differences, the prevalence of cirrhosis found in Kalama (3\%) is under-estimated compared to Northern Italy, and could be substantially more than 3-fold.

Cirrhosis is a well-documented complication of chronic HCV infection.\(^{20–22}\) However, despite recognition of the extremely high seroprevalence of HCV in the Nile delta and the Nile river valley south of Cairo, \(^{17}\) little is known about the relationship between HCV and cirrhosis in this setting. Our study provides the first controlled, community-based estimate of the association between cirrhosis and the seroprevalence of HCV. Persons with cirrhosis were substantially more likely to have been infected with HCV than those without cirrhosis. We cannot be sure that the HCV infections detected in this population preceded the onset of cirrhosis. However, if it is assumed that the HCV infections did precede the detected cases of cirrhosis, our data suggest that there was about a four-fold increase in the risk of cirrhosis in HCV-infected versus non-infected persons in Kalama and that up to 52\% of the cirrhotic cases could be attributed (etiologic fraction) to HCV. If our estimates from Kalama are applied to the population of persons ten years of age and over in the Nile delta (approximately 21 million persons), there may be over 300,000 cases of cirrhosis attributable to HCV in this hyperendemic population.

Our data suggest an association between remote histories of schistosomiasis and HCV seroprevalence. Such an association probably results from past mass campaigns of treatment of schistosomiasis with tartar emetic, in which HCV transmission could have been augmented by use of inadequately sterilized needles and syringes.\(^{1,8,21}\) Although HCV is known to be transmitted parenterally,\(^{24}\) it was striking that none of the examined practices that might facilitate parenteral transmission was associated with the seroprevalence of HCV. There are several possible explanations for these negative findings. First, if it is true that many of the HCV infections detected in Kalama resulted from past anti-schistosomiasis therapeutic campaigns, these campaign-related infections could have diluted our ability to identify contemporary practices associated with transmission. Egyptians may be given injections for many things over a lifetime, the purposes of which are often unclear to the patient. Second, because it was not possible to date the acquisition of HCV infections detected in our cross-sectional seroprevalence survey, our analyses did not discriminate between practices preceding and practices following the occurrence of infections. Inclusion of the latter practices in our analyses could also have diluted the associations. Finally, our study may not have had adequate statistical power to detect significant associations for exposures that were relatively uncommon in the study population.

The lack of an association between seroreactivity to HCV and to HAV was expected, in view of the parenteral mode of transmission of the former and the enteric mode of transmission of the latter. The modest but significant association noted between seroreactivity to HCV and HEV, also an enterically transmitted pathogen, was surprising, but may have been a chance association uncovered in the context of multiple analytic comparisons.\(^{25}\) More puzzling, however, was the lack of an association between seroreactivity to HCV and HBV, both parenterally transmitted pathogens. One possible reason for this dissociation is the relatively greater importance of sexual and perinatal modes of transmission for HBV than for HCV.\(^{1}\)

Our findings raise as many questions as they answer. We do not know the magnitude of transmission of HCV currently taking place in the hyperendemic populations residing in the Nile delta, nor do we understand what practices account for ongoing transmission. This information, which can only be ascertained with longitudinal studies capable of de-
tecting and studying incident HCV infections, will be crucial for designing public health interventions.

Moreover, although our study population demonstrated an extremely high prevalence of cirrhosis and a notably high fraction of cirrhotic cases potentially attributable to HCV, we cannot project how the burden of HCV-related cirrhosis will evolve in the Nile delta during the coming decades. Indeed, chronic liver disease due to HCV is thought to develop at a rather slow pace, ordinarily taking decades, and we have no way of dating the onsets of the infections detected in our study population. Adding to our uncertainties is the fact that little is known about the tendency of genotype 4 HCV, which predominates in Egypt, to produce chronic liver disease. We tested serum samples from 10 HCV-EIA positive Kalama residents by polymerase chain reaction (PCR) for HCV RNA; 8 sera were PCR positive; four of these sera were typed as genotype 4 while the other 4 were genotyped as type 4 or type 1 (Shemer-Avni Y, unpublished data). Portal hypertension evident in 83% of HCV-associated cirrhotics under the age of 35 years in Kalama suggests that the HCV infections affecting the Nile delta population may be highly pathogenic. The pathogenic nature of HCV genotype 4 is supported further by the fact that patients infected with genotype 4 show a meager response to alpha-interferon therapy similar to the more pathogenic HCV genotype 1b, and a poor response compared to patients infected with the less pathogenic HCV genotypes 2 and 3.18,29 The sum of these findings raise concern that the extraordinarily high seroprevalence of HCV now observed in the Nile delta may forebode an explosive epidemic of cirrhosis and other manifestations of chronic liver disease in this region.

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