Correlation between hepatitis C viral load and hepatitis C Core antigenaemia among Egyptians

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الارتبــاط بــين حمــل فــيروس الالتهــاب الكبــدي C ووجــود المســتضدات اللبيــة لفــيروس التهــاب الكبــد الوبائــي C في صفــوف المصريــين

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الخلاصـة: تنتشـر الإصابـة بعـدوى فـيروس الالتهـاب الكبـدي C عـلى نطـاق واسـع في مـصر. وعَمَدَت هـذه الدراسـة إلى مقارنـة الحمـض النـووي الريبـي لفـيروس الالتهـاب الكبـدي C مـع المسـتضدات اللبّيـة للفـيروس مـن أجـل الكشـف عـن وجـود الفـيروس بالـدم وتحديـد كميتهـا في عينـة مـن المواطنـين المصريـين. وأُجري تحليـل متزامـن لعينـات مصليـة أُخـذت مـن 80 فـرداً اشتُبـه في إصابتهـم بفـيروس الالتهـاب الكبـدي C لقيـاس حمـل الحمـض النـووي الريبـي لفـيروس الالتهـاب الكبـدي C باسـتخدام PCR اللحظـي، ومسـتوى المسـتضدَّات اللبّيـة للفـيروس باسـتخدام ELISA. ومـن العينـات الثمانـين، جـاءت 25 ٪ مـن النتائـج سـلبية لتحليـل الحمـض النـووي الريبـي لفـيروس الالتهـاب الكبـدي C. وتـم الكشـف عـن المسـتضدَّات الرئيسـية للفـيروس في جميـع العينـات: حيـث بلـغ المـدى 0.4-2462 نانوجـرام/ مللـيمـتر بمتوسـط 460 نانوجـرام/ مليلمـتر (506 = SD). وبلغـت نسـبة حساسـية ونوعيـة المسـتضدَّات اللبّيـة لفـيروس الالتهـاب الكبـدي C 96.7 ٪ و90.9 ٪ عـلى التـوالي. وتبيّـن وجـود علاقـة ترابُـط واضحـة وذات دلالـة إحصائيـة بـين المسـتويات المصليـة للحمـض النـووي الريبـي لفـيروس الالتهـاب الكبـدي C وبـين مسـتويات المسـتضدات الرئيسـية للفـيروس (0.0001 > P ,0.4 = r). ويظـل تحليـل الحمـض النـووي الريبـي لفـيروس الالتهـاب الكبـدي الوبائـي C هـو القاعـدة الذهبيـة لتشـخيص العـدوى النشـطة للفـيروس، ولكـن تتميّـز المسـتضدات الرئيسـية للفـيروس بارتفـاع حساسـيتها ونوعيتهـا مـع إمكانيـة اسـتخدامها في حالـة عـدم توفـر تقنيـة PCR.

ABSTRACT Hepatitis C virus (HCV) infection is widespread in Egypt. This study compared HCV RNA with HCVcAg for the detection and quantification of viraemia among a sample of Egyptians. Sera from 80 suspected HCV-positive individuals were tested simultaneously for HCV-RNA load using real-time polymerase chain reaction (PCR) and HCVcAg level using ELISA. Of the 80 samples, 25% were HCV-RNA-negative. HCVcAg was detected in all samples: range 0.4–2462 ng/mL, mean 460 (SD 506) ng/mL. The sensitivity and specificity of HCVcAg were 96.7% and 90.9%, respectively. There was a significant correlation between serum HCV-RNA and HCVcAg levels ($r = 0.4$, $P < 0.0001$). HCV-RNA remains the gold standard for diagnosis of active HCV infection but HCVcAg can be used where PCR is not available.

Corrélation entre la charge virale de l'hépatite C et l'antigénémie du virus de l'hépatite C chez les Égyptiens

RÉSUMÉ L'infection par le virus de l'hépatite C (VHC) est répandue en Égypte. La présente étude compare l'ARN du VHC et l'antigène de la nucléocapside du VHC pour la détection et la quantification de la virémie au sein d'un échantillon d'Égyptiens. Des échantillons sériques prélevés sur 80 personnes suspectes d'être positives au VHC ont été testés simultanément pour la charge d'ARN du VHC au moyen de l'amplification en chaîne par polymérase en temps réel (RT-PCR) et pour les concentrations de l'antigène de la nucléocapside par ELISA. Sur les 80 échantillons, 25 % étaient négatifs pour l'ARN du VHC. L'antigène de la nucléocapside a été détecté dans tous les échantillons : les valeurs étaient comprises entre 0,4 et 2462 ng/mL et la moyenne était de 460 ng/mL (E.T. 506). La sensibilité et la spécificité de l'antigène de la nucléocapside étaient de 96,7 % et 90,9 % respectivement. Il y avait une corrélation significative entre l'ARN du VHC sérique et les concentrations d'antigène de la nucléocapside (r=0,4, $p < 0,0001$). L'ARN du VHC demeure la méthode de référence pour le diagnostic d'infection à VHC active mais l'antigène de la nucléocapside peut être utilisé lorsque la PCR n'est pas disponible.

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Introduction

Hepatitis C virus (HCV) infection is widespread in Egypt and threatens the lives of many Egyptians. Egypt has the highest prevalence of HCV infection in the world among adults (14.7%) (*1*). The disease causes chronic hepatic inflammation leading to liver fibrosis, cirrhosis and hepatocellular carcinoma (*2*). HCV infection is often further complicated by underlying hepatitis B and Shistosoma mansoni co-infection. Co-infection leads to higher morbidity and chronicity (*3,4*).

Virological diagnosis and monitoring of HCV infection are based on the use of a variety of virological markers. In clinical practice, 4 HCV markers can be used, namely total anti-HCV antibodies, HCV-RNA levels, HCV genotype and recently HCV core antigen (HCVcAg) levels (*5*).

Detection of anti-HCV antibodies using an enzyme immunoassay (EIA) is a well-known routine screening test for the diagnosis of HCV infection (*6*). HCV-RNA is the most reliable marker for HCV viral replication and is the gold standard for diagnosis of active HCV infection. HCV-RNA appears within 1–2 weeks of infection, before any alterations in liver enzymes occur or anti-HCV antibodies appear. RNA testing is also called nucleic acid testing (NAT) and is used to detect (qualitative assay) and quantify (quantitative assay) HCV-RNA (*6*). Both real-time polymerase chain reaction (RT-PCR) and NAT are advanced techniques that require special equipment, setting and expertise to perform, thus limiting their use in low/middle-income countries. Total serum HCVcAg can be detected using an ELISA-based test. HCVcAg is considered a surrogate marker of HCV replication and can be detected on average 1–2 days after HCV-RNA during the pre-seroconversion period (*7*). Compared with RT-PCR for the detection of HCV-RNA, the detection of HCVcAg using ELISA is a simple and cost-effective test (*8*) which does not require specialized equipment or expertise to perform.

There are very few studies that have compared HCVcAg with HCV RNA in genotype 4 infected patients (*9–11*). There are no reports from Egypt where HCV genotype 4 prevails (*12*) and findings may differ between countries. This study therefore aimed to compare HCV-RNA quantification with HCVcAg presence and quantification as a marker for HCV replication among HCV-infected Egyptians.

Methods

Study setting and sample

This study was conducted from December 2012 to March 2013 at the Viral Hepatitis Research Laboratory at the National Hepatology and Tropical Medicine Institute, Cairo, Egypt.

A convenience sample of 80 subjects was selected from people suspected of HCV infection who were referred to the Institute for HCV-RNA testing using quantitative RT-PCR.

Data collection

Serum samples were collected from all the participants and their demographic data were recorded, including name, age, sex and residence.

All sera were tested for HCVcAg level according to the manufacturer's instructions (Cell Biolabs Inc., USA). The sera were also tested for HCV antibodies (Murex anti-HCV, version 4.0 EIA, Diasorin Diagnostics Inc., Italy), hepatitis B surface antigen (HBsAg) (AiDTM HBsAg EIA, Diagnostic Automation, USA), S. mansoni antibodies (Cellognost-Schistosomiasis H, Siemens Healthcare Diagnostics Inc., Germany), alanine aminotransferase (ALT) level, and HCV-RNA quantification by RT-PCR (Qiagen extraction kit and Abbott real-time HCV kit, USA) according to the manufacturers' instructions. S. mansoni and HBV tests were performed to further characterize the participants because both infections are common in Egypt and both are known to complicate HCV disease progression and can lead to increased HCV morbidity, viral persistence and accelerated progression of hepatic complications (*13,14*).

Ethical considerations

The institutional review board of the National Hepatology and Tropical Medicine Institute approved the study protocol before collection of samples and each participant signed a written consent form prior to participating in the study.

Statistical analysis

All data were entered into a Microsoft Excel worksheet and statistical analysis was performed using SPSS for Windows, version 19.0. The chi-squared test was used to compare qualitative variables while the Student t-test was used to compare quantitative variables (between HCV-RNA positive and negative groups and between the 4 HCV viraemia groups) with one-way ANOVA test. The Pearson correlation coefficient was determined to estimate the correlation between HCV-RNA and HCVcAg levels. A P value < 0.05 was considered statistically significant.

Results

The demographic and laboratory characteristics of the study participants are shown in Table 1. The ages of the participants ranged from 23 to 57 years with a mean of 41.7 [standard deviation (SD) 8.7] years; 50 were men (62%) and 36 (45%) were urban residents.

Out of the 80 participants, 20 (25%) were positive for HCV-antibody but negative for HCV-RNA, while 60 (75%) were positive for both HCV antibody and HCV-RNA. The ALT levels were elevated in 35 (44%) participants. ALT levels ranged from 13 to 141 U/L

Table 1 Demographic and laboratory characteristics of the study participants

Characteristic/laboratory marker	Total (n = 80; 100%)	HCV-RNA-negative (n = 20; 25%)	HCV-RNA-positive (n = 60; 75%)	P-value
Age (years) [Mean (SD)]	41.7 (8.7)	42.1 (9.7)	41.5 (8.4)	0.8
Sex [No. (%)]				0.4
Male	50 (62)	11 (55)	39 (65)	
Female	30 (38)	9 (45)	21 (35)	
Residence [No. (%)]				1
Urban	36 (45)	9 (45)	27 (45)	
Rural	44 (55)	11 (55)	33 (55)	
ALT level (U/L) [Mean (SD)]	41.9 (26.6)	22.6 (8.9)	48.4 (27.4)	< 0.001
HCV Ab-positive [No. (%)]	80 (100)	20 (100)	60 (100)	1
HBsAg-positive [No. (%)]	4 (5)	0 (0)	4 (6.7)	0.2
Positive for Schistosoma mansoni antibodies [No. (%)]	43 (54)	14 (70)	29 (48)	0.09

P < 0.05 considered statistically significant.
HCV = hepatitis C virus.
SD = standard deviation; ALT = alanine aminotransferase; HCV Ab = hepatitis C virus antibody; HBsAg = hepatitis B surface antigen.

(0.4–2.8 fold in males and 0.4-4.5 fold in females), with a mean of 41.9 (SD 26.6) U/L [1.05 (SD 0.6) fold among males and 1.3 (SD 0.9) fold among females]. All the participants were anti-HCV positive, 5% were HBsAg positive and 6.7% were co-infected with HCV and HBV. S. mansoni antibodies were present in 54% of the participants and

HCV co-infection was present in 48% (Table 1).

HCVcAg values ranged from 0.4 to 2461.8 ng/mL with a mean of 460 (SD 506) ng/mL. The mean viral load on PCR was 1.38 (SD 1.46) × 10⁶ IU/mL. HCV RNA values were categorized as: low viraemia (HCV-RNA level < 2 × 10⁵ IU/mL), intermediate viraemia

(HCV-RNA level > 2 × 10⁵ to 2.0 × 10⁶ IU/mL) and high viraemia (HCV-RNA level > 2 × 10⁶ IU/mL). The HCVcAg values in the 3 viraemic categories and in the aviraemic individuals are shown in Figure 1. The mean HCVcAg values among negative, low, intermediate and high viraemia groups were 59.8 (SD 135.8), 354.1 (SD 322.6), 656.9 (SD
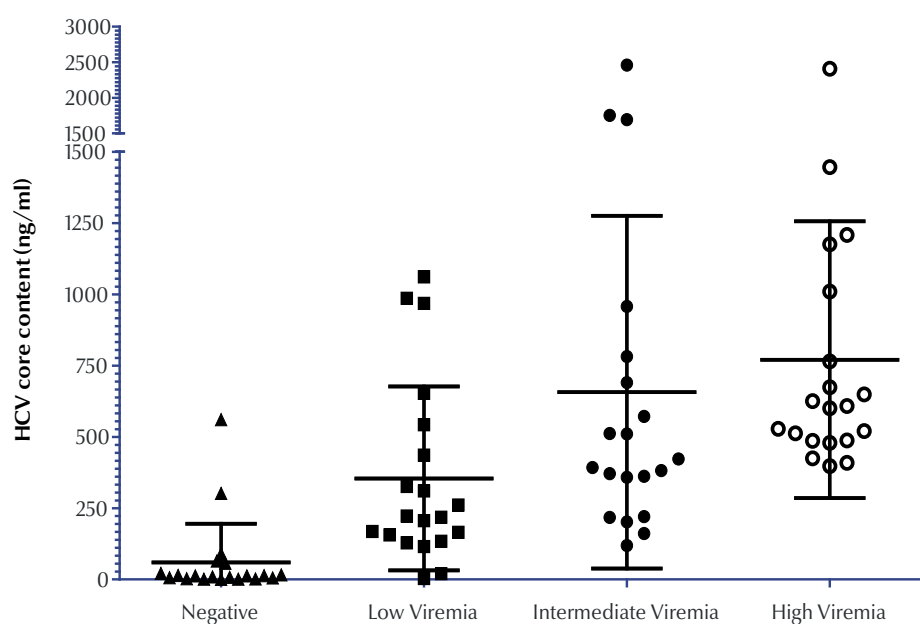

Figure 1 Scattergram of HCV core antigen values with the mean and standard deviation among the 4 viraemia groups (based on HCV RNA levels as described in the text). The difference between the groups was statistically significant (P < 0.001)

618.8) and 770.7 (SD 485.3) ng/mL respectively (P < 0.001).

Figure 2 shows a receiver operating characteristic (ROC) curve of the true positive rate (sensitivity) against the false positive rate (100% specificity) for the different possible cut-off points for the HCVcAg test. The sensitivity and specificity of HCVcAg were 96.7% and 90.9% respectively with positive and negative predictive values of 96.7% and 90.9%, respectively and accuracy of 95.2%.

The correlation between viral load and HCVcAg values among the samples of all the study participants is shown in Figure 3. There was a fair correlation (r = 0.4) between serum HCV-RNA levels and HCVcAg values, which was statistically significant (P < 0.0001).

Discussion

This study showed a fair correlation between HCV-RNA levels and HCVcAg in patients who were HCV-positive. HCVcAg is a simple and sensitive enzyme immunoassay for the detection and quantification of viraemia and can be used as a surrogate marker for HCV replication in Egyptians infected with HCV genotype 4. In our study, 20 (25%) participants were HCV-RNA-negative and 60 (75%) were HCV-RNA-positive whose viral loads were greater than 5.9×10^5 IU/mL. Although HCVcAg had a high sensitivity and specificity, its values were low in HVC-RNA-negative cases. Thus, HCV-RNA remains the gold standard for diagnosis of active HCV infection.

The 20 participants who were HCV-RNA-negative but were positive for HCV antibody were probably those who had either cleared the virus naturally or following previous treatment. The mean viral load of HCV-RNA-positive cases was 1.38×10^6 (SD 1.46×10^6) IU/mL, which supports our observation that HCV-RNA levels among Egyptians is usually lower than those in other countries such as Saudi Arabia (15). The ALT level often describes the degree of liver damage; this was supported by the significant differences between HCV-RNA-negative and HCV-RNA-positive groups with ALT being more elevated in those with higher viral loads. On the other hand, there was no linear correlation between ALT and HCV-RNA levels as we had a case with a low viral load who had a three-fold elevation in ALT level and another case with a high viral load and a normal ALT level.

All HBsAg-positive participants were also positive for HCV-RNA; 3 had intermediate and 1 had high viraemia. Egypt has an intermediate HBV prevalence (2–7%) (16), which is in line with our findings. The seroprevalence of HBV infection was 5% among all the HCV participants and 6.7% among those who were HCV-RNA-positive (HCV/HBV co-infection). An HBV prevalence of 16% was reported among chronic hepatitis patients in India (17),
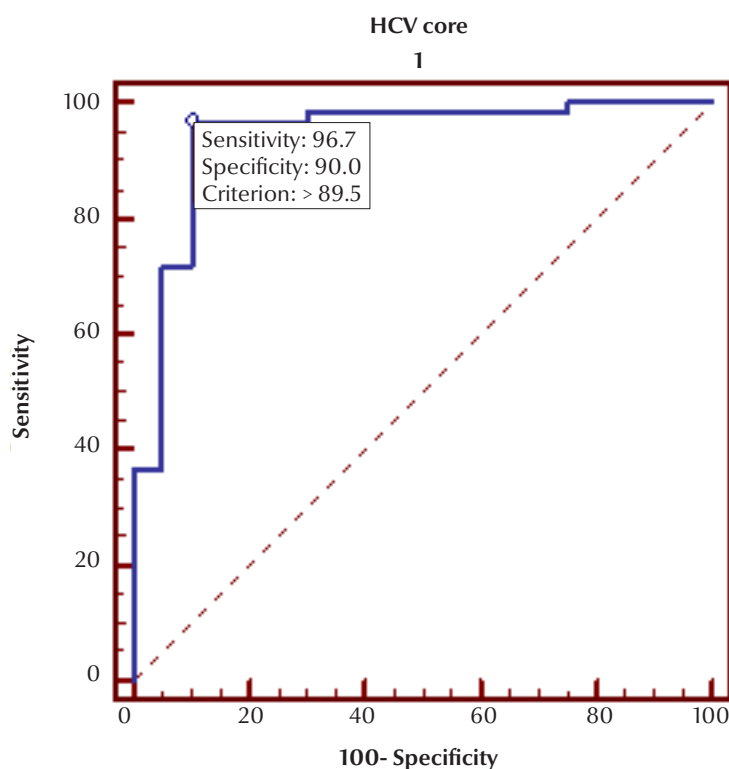

HCV core
1

Sensitivity: 96.7
Specificity: 90.0
Criterion: > 89.5

Figure 2 Receiver operating characteristic (ROC) curve for HCV core antigen test (area under the curve = 0.94; 95% CI: 0.87–1.00)
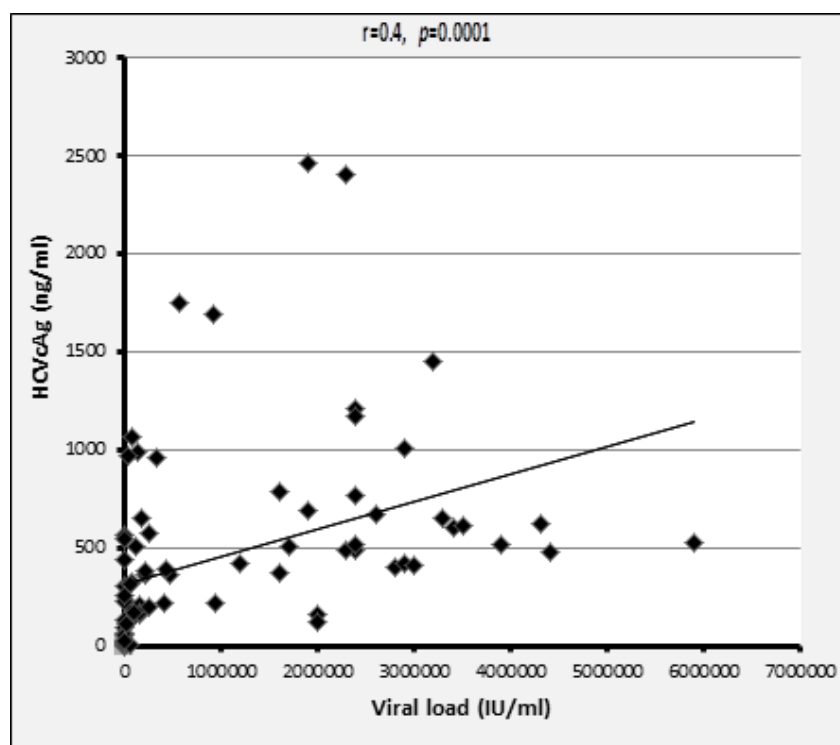
Figure 3 Correlation between viral load (HCV RNA level) and HCV core antigen level among the 80 study samples (*r* = 0.4, *P* = 0.0001)

which is much higher than our findings. A co-infection prevalence of 4.8% has been reported from Tajikistan (*18*) and 5.9% from another study in India (*19*). Both reports are close to our findings. It should be taken in consideration that co-infection with HBV could affect the course of HCV infection (*14*), but not the correlation between HCVcAg EIA and RT-PCR test.

Forty-three (53.8%) participants were positive for *S. mansoni* antibodies with no significant difference between the HCV-RNA-negative and HCV-RNA-positive groups. A prevalence of S. mansoni of 36.4% in a number of Egyptian governorates has been reported (*20*), which is less than what we report here. Another study on health care workers at the National Liver Institute, Menoufia University (Egypt) reported an S. mansoni seroprevalence of 35.1% (*21*), which is also lower than our finding. The difference in the prevalence between our study and others could be due to Schistosoma infection

being assessed in a high-risk group, who had been referred because of suspected HCV infection, and differences in demographic and clinical characteristics. As with HBV, co-infection with S. mansoni could affect the course of HCV infection (*13*) but not the correlation between HCVcAg EIA and RT-PCR test.

HCVcAg values in the study participants ranged from 0.4 to 2462 ng/mL with a mean of 460 (SD 506 ng/mL). There was a significant difference between HCV-RNA-negative and HCV-RNA-positive groups and between the 4 viraemia groups. Our data show that HCVcAg values can reflect the degree of viraemia despite the absence of strong linear correlation between antigenaemia and viraemia. HCVcAg test sensitivity and specificity were 96.7% and 90.9%, respectively, which were close to those reported in many studies (*22–29*). The test revealed 2 false positive results among HCV-RNA-negative participants, which may be due to the

specificity of the test. Also, the test revealed 2 false negative results among HCV-RNA-positive participants who were in the low viraemia group, which raises a question about the ability of the test to detect antigenaemia in those with low viral load.

We do not know how HCV replicates in vivo and if viraemia always means antigenaemia and if the reverse is true. According to our study, there was a fair correlation between serum levels of HCV-RNA and HCVcAg values. Several other studies using HCVcAg testing reported a significant correlation between serum levels of HCV-RNA and HCVcAg with different linear regression coefficients ranging from 0.6 to 0.8 (*22,24,36,30–33*), which is higher than seen in our study. In addition, the weak correlation reported in our study is lower than that reported elsewhere among those infected with HCV genotype 4 or other genotypes (*9–11,34,35*). This could be attributed to viral genetic differences and/or patient characteristics.

A limitation of this study was the use of a convenience sample of HCV-infected patients, who may not represent the wider population of HCV-infected Egyptians.

In conclusion, HCV-RNA remains the most reliable marker and gold standard for the diagnosis of active HCV infection in Egypt but the HCVcAg ELISA also had a high sensitivity and specificity and could be used for diagnosing viraemia in HCV-infected patients, especially in places where PCR facilities are not available.

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