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Research Article

Genetic epidemiology of Hepatitis C Virus infection outcome in Upper and lower Egypt: A multicenter Family based study

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Abstract

Background and Aim: Egypt has high prevalence of HCV. The household contacts of HCV seropositive patients had been shown to have a high risk of HCV infection.

The aim was to determine the HCV infection outcome and genotyping among household contacts of patients in Upper and Lower Egypt.

Methods: In this multicentre study a total of 4891 individuals were recruited from Upper and Lower Egypt. The index HCV patients were 1106 cases while their household contacts were 3785 cases. All cases with HCV infection were confirmed by PCR HCV RNA technique as well as sequencing analysis of the 5′ UTR of HCV was performed and genotypes were recorded.

Results: The HCV prevalence among house hold contacts was 17.29 % and 19.17% while the spontaneous viral clearance (SVC) was 2.49% and1.55% in lower and Upper Egypt respectively.

Different genotypes and subtypes of HCV which were detected in Upper and Lower Egypt respectively: (genotype 4a (90.3% & 70.1%), 4m (4.8% & 11.8%) 4n (0.5% & 3.2%) 4o (0.2% & 2.9%) 4i (0.5% & 1.9%) 4v (0.8% & 1.2%) & 1a (2.9% & 8.3%) but 1g and 1b found in Lower Egypt with (0.3%) and didn't detected in Upper Egypt. Genotype 4a was higher in Upper Egypt (90.3%) than in Lower Egypt (70.1%) and genotype 1a was higher in Lower Egypt (8.3%) than in Upper Egypt (2.9%).

Conclusion: Higher HCV prevalence in Household contacts in Upper more than lower Egypt while SVC was higher in Lower than Upper Egypt. Genotype 4 was more in Upper than Lower Egypt while genotype1a was increased in lower than Upper Egypt.

Introduction

Hepatitis C virus has a high distribution globally as about 170 -210 million individuals were infected. The lowest ranges of HCV incidence are between 0.01% - 0.1% which found in Netherlands and the highest prevalence is 14.7% that found in Egypt [1] Chronic hepatitis C is developed after a time of infection exceeded more than six months and such infection leads to very low rate of spontaneous clearance [2]. HCV infection is usually asymptomatic slowly progressive [3,4]. Eventually while about 20% of people can clear the virus the rest developed cirrhosis after 20 - 30 years period of time which may complicated by Hepatocellular carcinoma or progressed to end stage liver disease [5]. Plancoulaine et al, 2008 investigated intrafamilial transmission in Egypt and found strong correlations in HCV seroprevalence between first-degree relatives parent-offspring and sib-sib after adjustment for risk factors [6]. However Jimenez et al 2010 reported that the role of intrafamilial transmission to HCV spread seems to be limited in Egypt [7].

HCV is grouped via RNA sequence analysis into seven genotypes and more than 100 subtypes [8]. Genotypes are differentiated from each other at the nucleotide level in ranges between 25-35%, but subtypes differ in low ranges by 15–25% [9].

The 5` Un Translated Region (5` UTR)is highly conserved and used for diagnosis, because sequences which encode the viral envelope have similarities between each other's and also have

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60% identity between isolates that collected all over the world [10,11]. According to the phylogenetic relations of sequences from the core/E1 and NS5B genomic regions, there are 7 different HCV genotypes and each genotype contains multiple subtypes (e.g., HCV 1a, 1b) [8].

Specific distribution of HCV genotypes geographically were detected as following: As in Europe and USA have prevalence of genotype 1 but G2, G3 are less common in such regions and genotypes 4, 5 and 6 are rare in these regions [13] India, Far East and Australia have predominance of G3 in Africa, the Middle East have G4 the most common in such regions [14]. In southern Africa has G5 that is highly found and genotype 6 is the most prevalence in Vietnam, Australia and Hong Kong [15]. The novel genotype 7 is the newer genotype that is recently was reported and detected in patients from Belgium and Canada who are possibly infected in Central Africa [16]. The aim of this multicentre study was to determine the HCV infection prevalence among families and determine the outcome of HCV infection and their genotyping among household contacts of patients in upper and Lower Egypt.

Subjects and Methods

Study populations

In this Multicentre hospital case control based study a total of 4891 Egyptian individuals were recruited to the hospitals from different Egyptian population in Upper& lower Egypt governorates). The index HCV patients were 1106 cases whereas the families or close household contacts of these index cases were 3785 subjects. The basis for family selection was presence of at least one index patient positive for HCV and all household contacts with age more than 3 years.

Inclusion criteria of index cases were: adults of both sexes aged above 18 years, PCR detection of HCV RNA positivity for >6 months and presence of HCV-related liver disease regardless of stage. Where exclusion criteria for index cases were HCV patients co-infected with hepatitis B or HIV, as well as patients with anti-HCV positivity in absence of detectable serum HCV RNA. Similarly excluded were patients with Hepatocellular Carcinoma (HCC), autoimmune hepatitis, and any metabolic liver disease. Inclusion criteria for healthy household contacts used as control were subjects of both sexes aged above 3 years, first-and second-degree consanguinity to the index case, living and sharing usual family activity with the index case, having no serological evidence of HCV, HBV or HCC and with no history of liver disease.

Cases with Spontaneous Virus Clearance (SVC) was diagnosis based on presence of evident HCV antibody positivity in absence of detectable HCV-RNA when measured successively in two samples taken at least 6 months apart, without history of prior receiving anti-viral treatment for HCV infection.

Every member participating in this study was subjected to conventional clinical examination and routine laboratory investigations by a staff clinician. Confirmation of HCV infection was done by molecular diagnosis and HCV RNA analysis in the Molecular Genetic Unit in Endemic Hepatogastroenterology and Infectous Diseases (MGUHID) in Mansoura Faculty of Medicine. Each test subject was required to sign a written informed consent. The protocol of this study is in agreement with the ethical guidelines founded by the 1975 Declaration of Helsinki as reproduced in the prior approval by Mansoura Faculty of Medicine Institution Research Board.

Sampling techniques

Samples were collected in vacutainer blood collection tubes from each patient and 3 ml blood sample were withdrawn from Patients by vein puncture then was allowed to clot for 15 minutes and centrifugation for 10 minutes at 7000 rpm for serum separation, then the sera were stored in 2 ml micro tubes and frozen at -80°C.

HCV antibodies and RNA detection

The serostatus of HCV for each participant was detected via testing of HCV antibodies (anti HCV Ab) using Enzyme-Linked Immunosorbent Assay (ELISA) test using (Murex anti-HCV version 4.0) Kit (Murex Biotech S.A. Kyalami, South Africa) and then determine: Quantitative estimation of viral load: HCV RNA in serum was detected by RT-PCR-based assay for quantification of HCV RNA using ABI 7500 real time PCR (Applied Biosystems, Foster City,CA, USA). Sero- negative HCV Ab samples were pooled and for sero-positive HCV Ab samples were used to do HCV-RNA extraction, then one Step RT-PCR.

RNA preparation and PCR amplification

Viral RNA was extracted and purified from serum using Qiagen RNA extraction kit (Qiamp® RNA Minikit, Qiagen, Germany) According to the protocol 250 µl of serum was allowed to be out the freezer for 15 minutes, then spint gently at 8000 rpm for 30 seconds. Then 500 µl of AVE buffer containing carrier RNA were added to serum sample, mixed gently, incubated at room temperature for 10 minutes. 560 µl of cold absolute ethanol were added to the mixture then centrifugation for 1 minute at 8000 rpm and introduced carefully to the spin column with collection tube. Centrifugation for 1 minute at 8000 rpm then add 500 µl of AW1 buffer and centrifuged at 8000 rpm for 1 minute, then add 500 µl of AW2 buffer and centrifugation for 1 minute at 13000 rpm, then add 250 µl of AW2 buffer then centrifuged for 1 minute at 13000 rpm. After that every column was applied into a clean collection tube and centrifugation for 10 minutes at 13000 rpm to be dry. Then 60 µl of AVL buffer were added on the membrane and left at room temperature for 5 minutes then centrifugation for 1 minute at 8000 rpm. Columns were thrown out and the expenders with extracted RNA samples were stored at -20°C. The extracted viral RNA was then converted to cDNA and amplified using Quant One Step RT-PCR Kit (TIANGEN Biotech (Beijing,China) according to manufacturer's instructions. then analyze the PCR products using 2% agarose gel electrophoresis.

cDNA purification from gel

cDNA was purified from gel using (MEGA quick-spin™ Total fragment DNA purification kit, Intron (iNtRON Biotechnology, Korea) According to the protocol supplied by manufacturer's instructions. Extracted PCR product was stored at -20°C for sequencing.

5` UTR sequencing of HCV cDNA

Each isolate of HCV was sequenced using the Big Dye Terminator Cycle Sequencing Ready Reaction kit (Applied Biosystems) then data collection was done on an automated ABI PRISM 310 genetic analyser (Applied Biosystems), then nucleotide sequences of each isolate were used for phylogenetic analysis.

Table 1: Catchment areas of Index Cases and Household Contacts by Governorates of Egypt.

Governorate	Index	Contacts
Dakahlya	473	1630
Gharbya	96	350
Cairo	80	309
Giza	91	281
Helwan	31	123
El-fayoum	11	46
Elmenia	4	21
Benisuif	27	103
Hurghada	21	46
Menoufia	16	53
Kafr El-sheikh	17	66
Damietta	25	61
Sianai	13	66
Souhag	25	63
Kena	5	15
Aswan	45	163
Assiut	55	166
Sharkya	24	79
The new vally	5	15
Kaliobya	16	54
El-wahat	16	46
Suez	10	29
	1106 (22.6%)	3785 (77.4%)

Sequencing data analysis

Computational blast data analysis for nucleotide sequences of each isolate were assigned online by alignment using (http://www.blast.ncbi.nlm.nih.gov) and detecting different genotypes.

Statistical analysis

Data were analyzed with SPSS version 21. The normality of data was first tested with one-sample Kolmogorov-Smirnov test. Qualitative data were described using number and percent. Association between categorical variables was tested using Chi-square test and Fischer exact test. Continuous variables were presented as mean ± SD (standard deviation) for parametric data and Median for non-parametric data. The two groups were compared with Student t test (parametric data) and Mann-Whitney test (nonparametric data).

Table 2: Distributions of index & Household contact cases between upper & lower Egypt.

	Index cases	Household contacts +ve	Household contacts -ve	Total
Lower Egypt	771	466 (**17.29%**)	2229	3466 (70.68%)
Upper Egypt	335	209 (**19.17%**)	881	1425 (29.14%)
	1106 (22.6%)	3785 (77.4%)		4891 (100%)

Table 3: Percentage of positive household contact cases and Spontaneous Virus Clearance (SVC) among studied families.

	Index cases	Household contacts	%	
Anti HCV +ve	1106	783	20.69 %	
PCR HCV +ve	1106	675	17.83 %	P value<0.05
SVC	-	108	2.85%	
Male for SVC		40	37%	*P* value<0.05%
Female for S VC		68	63%	
Lower Egypt SVC	771	86	2.49%	*P* value<0.05%
Upper Egypt SVC	335	22	1.55%	
Total	1106(22.6%)	3785	77.4%	4891(100%)

SVC: Spontaneous virus clearance.

P value is considered significant when ≤ 0.05.

Results

Catchment areas of Index Cases and Household Contacts by Governorates of Egypt

In this Multicentre hospital case control based study a total of 4891 Egyptian individuals were recruited to the hospitals from different Egyptian population in Upper and lower Egypt (mainly from Dakahlya, Cairo and Assuit governorates).The index HCV patients were 1106 cases whereas the close household contacts of these index cases were 3785 cases as shown in table1.

Distributions of index and household contact cases between Upper and lower Egypt

Table 2 showed that index patients that were recruited from Lower and Upper Egypt were 771 cases and 335cases respectively while their HCV positive household contacts were 466 cases (17.29%) and 209 cases (19.17%) respectively. On the other hand, other negative household contacts were 2229 subjects and 881subjects respectively. The total population in the Lower Egypt were 3466 (70.68%) while in the Upper Egypt were 1425(29.14%).

Percentage of positive HCV household contact and Spontanous Virus Clearance (SVC) cases among studied families

Table 3 revealed that the anti HCV positive household contacts were 783 cases representing 20.69% of the total household contacts but only 675 were only positive with PCR HCV RNA representing 17.83% of the total household contacts. While subjects who spontaneously clear HCV infection were 108 cases representing 2.85% of the total household contacts. The SVC cases were higher in females 68 cases (63%) than male's 40 cases (37%) with P value < 0.05%. While those who had spontaneous virus clearance were 86 cases (2.49%) and 22 cases (1.55%) in the Lower and Upper Egypt respectively (P value < 0.05 %.).

Distribution of Genotypes and subtypes of HCV patients among studied families in Upper and Lower Egypt

Table 4 showed the different genotypes and subtypes of HCV which were detected in Upper and Lower Egypt respectively: (genotype 4a (90.3% & 70.1%), 4m (4.8 % & 11.8%) 4n (0.5% & 3.2%)

Table 4: Genotyping and subtyping among the studied families in Upper and Lower Egypt.

HCV genotype	Upper Egypt (%)	Lower Egypt (%)	Fisher exact test
4a	90.3	70.1	P = 0.0053*
4m	4.8	11.8	P = 0.0376**
4n	0.5	3.2	P = 0.4462
4o	0.2	2.9	P = 0.4681
4i	0.5	1.9	P = 0.634
4v	0.8	1.2	P = 0.5934
1a	2.9	8.3	P = 0.0438**
1g	0.0	0.3	NA
1b	0.0	0.3	NA

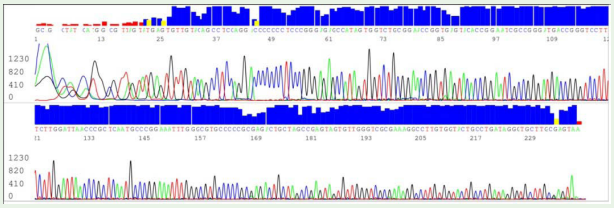

Figure 1: Sequence-Based Typing (SBT) technique using specific primers based on 5`UTR and detecting different genotypes via (http://www.blast.ncbi.nlm.nih.gov) that detect this sequence as genotype 4a.

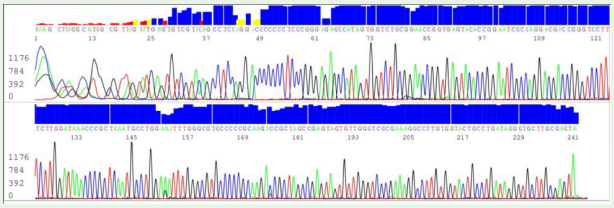

Figure 2: Sequence-Based Typing (SBT) technique using specific primers based on 5`UTR and detecting different genotypes via (http://www.blast.ncbi.nlm.nih.gov) that detect this sequence as genotype 1a.

4o (0.2% & 2.9%) 4i (0.5% & 1.9%) 4v (0.8% & 1.2%) & 1a (2.9% & 8.3%) but 1g and 1b found in Lower Egypt with (0.3%) and didn't detected in Upper Egypt. Genotype 4a was higher in Upper Egypt (90.3%) than in Lower Egypt (70.1%) and genotype 1a was higher in Lower Egypt (8.3%) than in Upper Egypt (2.9%) as shown in figure 1 and figure 2.

Discussion

Hepatitis C is a worldwide health problem with about 300 million patients globally infected [16]. Positive HCV individuals varied in its ranges among all nations from 0.01% in Scandinavia to 3% in North Africa [17].

HCV prevalence in Eastern countries of the Middle East had ranges from 1% - 4% but in Egypt according to Egypt Demographic Health Survey 2008 (EDHS) reported an overall anti-HCV antibody prevalence of 14.7% but only 9.8% of them were chronically infected [1]. However the Demographic National survey in Egypt in 2015 reported that people who aged (1-59 Y) had prevalence of anti-HCV antibody was 6.3% but the positive PCR HCV RNA was 4.4% [18].

In the current study among household contacts genotype 4 was the most prevalent one followed by genotype1. Furthermore different sub genotypes were detected in Upper and Lower Egypt.

Genotype 4 of HCV is the main genotype in Egypt as represent about 93% [12,19] and other HCV genotypes as genotypes 1 and 3 have low distribution as they represent 6% and 1% respectively [19]. A Previous study from Egypt on small sample size where restriction fragment length polymorphism (RFLP) patterns of the PCR products were analyzed and giving the following pattern: 91% were consistent with genotype 4_1 where 1% was subtype 1a and 1% was subtype 1b on the other hand 7% could not be typed by this method and the prevalence of genotype 4 was more or less similar between upper and lower Egypt [11].

Some studies suggested that the genotype 4a epidemicity was more recent and fairly dissimilar from the endemic pattern in sub-Saharan Africa [20,21]. The investigations of molecular diagnosis on the Egyptian isolates of genotype 4a determined that the epidemicity of Egyptian HCV pattern was due to widespread of anti schistosomiasis mass treatment campaigns as reported in many studies. These mass campaigns were documented in the period between 1930s to1980s parallel with intense rapid progression between 1930 to1955 [21].

Previous studies reported that the prevalence of genotype 4 of HCV was widely distributed in the Middle East region (Egypt, Iraq, Jordan, Saudi Arabia, Kuwait, Qatar, Palestine,Yemen) with a prevalence rate of 74.7%, then genotype 1 had a prevalence ratio of 15.1% that found in Lebanon, Bahrain, UAE and Lybia, followed by genotype 3with rate of 4.2% that predominant in Bahrain and UAE then genotype 2 that had low rate at 1.7%. On the other hand rare genotypes such as 5 and 6 and genotypes that could not be typed accounted had a rate of 4.3% of the total infection of HCV in the Middle East. This indicate that HCV genotypes had different distribution in Arabian countries of the Middle East and also it is probably to be related with the introducing of the virus by visitors traveling to these countries for different purposes as business or therapeutic or because of the limited number of existing studies in most of such Arabian countries [22]. In Saudi Arabia about 62% of HCV patients were genotype 4 with predominance of subtypes 4c/4d, followed by subtypes 4h, 4e, and 4a while in Egypt subtype 4a is the most prevalent one suggesting that the origin and transmission of HCV-4 is different from that in Egypt [23].

In the current study the prevalence of HCV among household contacts (based on positive PCR HCV RNA) was 17.29% and 19.7% in lower and Upper Egypt respectively. Although it was reported that prevalence of HCV infection among general population had higher rate in Lower Egypt more than Upper Egypt [17]. Previous reports from Egypt estimated The prevalence of anti-HCV antibodies among household contacts of infected patient to be 13.7% [24]. In contradiction to our results A cohort study conducted by Mohamed et al 2005 in 2 Egyptian rural villages found that over an average of 1.6 years, asymptomatic anti-HCV seroconversion occurred in3.1/1,000 Person-Years [PY]) including (6.8/1,000 PY) in the Nile Delta village , and 0.8/1,000 PY in the Upper Egypt village [25]. But this study

was not multicentre and only in 2 villages. This high prevalence in upper Egypt may be attributed to the nature of closed communities, less developed areas and absence of more effective infection control measures in Upper than Lower Egypt.

This study addressed that people who had spontaneous clearance were 2.49% and 1.55% in lower and Upper Egypt respectively. The spontaneous viral clearance was more common in female than males.

Hepatitis C virus infection either leads to viral elimination in about 20% of infected patients as a result of effective immune control of HCV replication or developed chronic HCV infection. This condition may progress to cirrhosis within 15 years or developed hepatocellular carcinoma both eventually complicated by end stage liver disease [26].

On the other hand viral clearance was showed to be in low rates among blacks for unknown causes suggesting that host genetics may be important in determining the outcome of HCV infection [27]. The infection rates in adult is approximately 50 cases/100 000 Inhabitants/ year in rural of north Italy where about 17% of infected patients were eventually clear the virus [28].

2 cohort studies conducted on Irish and German women who were infected with HCV (contaminated anti- D immune globulin) showed that (45% and 43 %) of them eliminated their infection respectively. These data suggest that the interactions between the virus and the host immune response are important in determining the natural history of an HCV infection [29].

In a study of Kong et al., showed that the rs12979860 CC genotype , HBV co infection, a history of icteric hepatitis and female gender are linked with spontaneous virus clearance in Chinese patients and this demonstrate the importance of host and viral determinants in the natural history of HCV infections [30].

Some studies illustrated that rates of HCV clearance is higher in younger patients [31] as shown in the study conducted by Zhang et al. who described enhanced HCV clearance among hemophiliac patients under 2 years when compared to patients who are 16 years or older [32].

Another study showed that the viral clearance was found more in a younger age patients, females, with lower HCV viremia and with co-infection with other viruses especially hepatitis B virus, but patients that injected with drugs have low spontaneous clearance of chronic infection [33].

CD4+ and CD8+ T cell immune response play an essential part in orchestrating the antiviral immune responses during HCV infection as clearance of HCV is associated with strong CD4+ response that elicits Th1 cytokines which is important for elimination of the virus [34]. On the other hand patients who have a weak CD4+ response or strong CD8+ response may eventually lead to persistence of HCV infection.

HLA class II molecules that represent CD4 epitopes and linked with HCV outcome. Two meta-analyses demonstrated that DRB1*11 and DQB1*0301 are linked with HCV recovery [35]. The allele HLA-DRB1 *01 was protective in the Irish cohort as well as in the Caucasians in the study by Thio et al.; thus, it may not be protective in non-Caucasian ethnic groups [35]. While In Egypian children infected with HCV showed that the most frequent alleles demonstrated among patients were DRB1 *03, DRB1 *04 and DRB1 *13 while DRB1*15 was significantly reduced among patients when compared with the control group [36]. HLA class II DQB showed that sponteneous virus clearance of HCV infection is linked with DQB1*03:01:01:01 allele and chronic HCV infection is associated with the risk allele: DQB1*02:01:01[37]. It was demonstrated that HLA DQB1*0301 allele is matched with elimination of the virus among different ethnic groups, showing a weak association in combined ethnic populations (white and black) but a stronger association in African Americans than in Caucasian Americans, while the allele DQB1*02:01 is associated with chronic infection when it is associated with DRB1*0301 as haplotype [38].

The Interleukin-10 (IL-10) is a cytokine and reported to have a vital role in the immune response of HCV. A promoter polymorphism at -1082 that is associated with higher IL-10 levels has also been associated with HCV persistence in women [39]. Some studies as Olekysk et al found associations with HCV outcome in African-Americans through testing polymorphisms in the IL-10 gene region [40].

In conclusion this study addressed that higher HCV prevalence in Household contacts in Upper more than lower Egypt while SVC was higher in Lower than Upper Egypt. Genotype 4 was more in Upper than Lower Egypt while genotype1a was increased in lower than Upper Egypt. Understanding of the difference of HCV infections patterns in Upper and Lower Egypt can lead to improving therapeutic strategies, economic models and health-care policy decisions.

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