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Original article

Prevalence and risk factors of asymptomatic hepatitis C virus infection among a sample of school aged Egyptian children

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ABSTRACT

Background: Hepatitis C virus (HCV) is a global health problem .Egypt reports the highest incidence in the world. **Objectives:** The objectives of this work were to detect the prevalence of asymptomatic HCV infection among a sample of non risky school aged Egyptian children in comparison with other two high risk groups, and to identify some underlying factors of seropositivity. **Materials and methods:** This comparative cross sectional study was conducted upon 3 groups of children attending Benha University Hospital; group (1) included 300 non risky children, group (2) included 20 thalassemic patients on repeated blood transfusion and group (3) included further 20 patients with chronic renal failure on regular hemodialysis. All children were subjected to history taking, physical examination and laboratory investigations for HCV antibodies by 4th generation ELISA, for positive cases RT- PCR, complete blood count (CBC), and liver function tests (LFT) were done. **Results:** The results revealed that asymptomatic HCV infection was detected in 3% of group (1), 45% in group (2) and 50% in group (3). The main risk factors for transmission were blood transfusion, frequent intravenous injections, circumcision by non medical personnel, surgical and dental procedures. **Conclusion:** The results revealed that HCV seropositivity is detectable in 4% of apparently healthy school aged children. PCR should be done for all HCV seropositive cases to confirm the presence of viremia.

KEYWORDS: Prevalence, Risk factors, Asymptomatic HCV, Egyptian children

INTRODUCTION

Hepatitis C virus (HCV) infection is a major cause of liver diseases related morbidity and mortality worldwide and represents a major public health problem[1].The most recent estimates of disease burden show an increase in seroprevalence over the last 15 years to 2.8%, equating to >185 million infections worldwide[2].Egypt has the highest HCV prevalence in the world[3],so HCV infection and its complications are among the leading public health challenges in Egypt[4].The prevalence in healthy Egyptian children is reported to be 5.8% [5].

Another Egyptian study reported that asymptomatic HCV seropositivity was detectable in 2.02% of Egyptian children and 33.3% of them were HCV RNA positive[6].Blood transfusion is the commonest mode of virus transmission. The blood screenings to avoid HCV contaminated transfusion has reduced its incidence. Injections, intravenous drug users (IDUs) and shaving by barbers have been reported as major risk factors [8].Multiple transfused patients represent a major risk group for HCV acquirement. Haemophiliac and thalassaemic patients treated with virus contaminated blood or blood derivatives frequently exhibit anti-HCV antibodies and signs of chronic hepatitis **[**9].

Globally, hepatitis C prevalence rates in thalassemic patients vary between 4.4% and 85.4% [10].Over the last decade, seroprevalence of HCV Ab among Beta-thalasemia in different countries including Egypt ranged from 12.5–100**%** [11].The link between HCV infection and kidney disease is well recognized[12].Many studies have clearly shown that HCV-infected end stage renal disease (ESRD) patients on maintenance dialysis are at increased risk of liver-related

mortality[13,14].In addition, HCV infection adversely decreases the health-related quality of life in these patients [15].

The prevalence of anti-HCV in hemodialys (HD)patients in developing countries ranges between 7% and 40% [16,17],while in developed countries it ranges from 3.6 to 20% [18],prevalence of HCV-Ab was 35% in HD patients in Egypt, This high prevalence may be due to repeated blood transfusions, shared dialysis machines, surgery, nosocomial route, and multi-dose drug vials[19]. Furthermore, Alter et al [20] found that the risk of infection is correlated to the duration of dialysis.HCV could accelerate the progression of chronic kidney disease (CKD) towards the final stages of renal disease[21].

Diagnostic tests used for the detection of HCV infection include the HCV antibody enzyme immunoassay, recom-binant immunoblot assay, and quantitative HCV RNA polymerase chain reaction (PCR) [22].

Objectives:

The objectives of this work were to detect the prevalence of asymptomatic HCV infection among a sample of non risky school aged Egyptian children in comparison with other two high risk groups; thalassemia and chronic renal failure patients, and to identify risk factors of seropositivity among the non risky group.

MATERIALS AND METHODS

Subjects:

This comparative cross sectional study was conducted at the Pediatrics Department in Benha university hospital upon three groups in the school age. Group (1) included 300 school aged children attending the outpatient clinic at Benha university hospital for minor ailments as fever, tonsillitis, gastroenteritis and others. Group (2) included 20 thalassemia patients on repeated blood transfusion from the hematology unit and group (3) included another 20 patients with chronic renal failure on regular hemodialysis from nephrology unit, Patients with known or clinically suspected chronic liver or metabolic diseases were excluded. The field work was conducted over a period of 9 months; from the beginning of April, till the end of December, 2015.

Sample:

The minimal sample size was calculated according to the equation: $n=Z^2(p*q)/E^2$, where n=minimal sample size that gives accurate results, p=proportion of the prevalence of HCV infection among healthy children (obtained from previous literature)[5], it was 0.058, q=(1-p), E=Standard error=0.03, so (n) was 234, "n" was increased to 300 children for more accuracy.

Ethical considerations:

A written informed consent (in Arabic language) was obtained from the patients' guardians before participation; it included data about aim of the work, study design, site, time, subject and tool. They were informed that all collected data will be confidential and used for scientific purposes only and they will be informed by the results to be able to receive the proper treatment. Also, an approval from The Research Ethics Committee in Benha faculty of medicine was obtained before the conduction of this work, and lastly an official permission was obtained to interview the patients and their parents from the Dean of the Faculty of Medicine and the Head of the Pediatrics Department.

Tool of data collection

All children were subjected to

1. Full history taking: where an interview questionnaire sheet was used, it included data about age,sex, residence, socioeconomic state, and items about exposure to some risk factors associated with HCV transmission.
2. Thorough clinical examination: including weight, height ,and proper examination of liver size.
3. Laboratory investigations: measurement of HCV antibodies by ELISA using (INNOTEST HCV Ab 4th generation kit, distributed by INNOGE NETTICS GmbH, Hannover, germany)[23].The blood specimen (5ml) was collected, serum was separated by centrifugation and kept frozen (-20˚C) until analysed, positive samples by ELISA were then tested for HCV RNA by PCR using (Thermo Fisher Scientific Real-Time PCR system) as confirmatory test, also complete blood count (CBC) and liver function tests (LFTs) were done for positive cases by ELISA.

   (CBC) was performed by Sysmex XS-800I cell counter. Liver function tests including total and direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and albumin were done for positive cases by Biosystem A 15 autoanalyzer[24].

Statistical Analysis:

The collected data were tabulated and analyzed using SPSS version 16 soft ware (Spss Inc, Chicago, ILL Company). Categorical data were presented as number and percentages while quantitative data were expressed as mean and standard deviation. Chi square test (X^2), Fisher's exact test (FET), student "t" test and Kappa test were used as tests of significance. Odds ratios (OR) and the corresponding 95% CI were calculated when applicable. The accepted level of significance in this work was stated at 0.05 (P <0.05 was considered significant**)** [25].

RESULTS

The results demonstrated that the mean age of the studied children was 10.4±3.3 years, ranging from 6-17 years. 52.1% of them were males while females represents 47.9%. The majority (80%) of them were rural residents, 40.6% and 44.7% belonged to low and middle social classes, while 14.7% of them were from high social classes respectively (Table 1). The Prevalence of HCV seropositivity was 4% among the group 1, 55% among group 2 and 50% among group 3 (Table 2). The results showed that the positive predictive value (PPV) of ELISA was75% when confirmed by PCR in group 1, 81.8% in group 2 and 100% in group 3. Indicating asymptomatic infection of 3% among group 1, 45% among group 2 and 50% among group 3.

Table 1: Socio-demographic characters of the study groups.

Variable		Number (N=340)	% (100%)
The studied groups	Group 1	300	88.2
	Group 2	20	5.9
	Group 3	20	5.9
Age (years)	Mean ±SD	10.4±3.3	
	Range	6-17	
Sex	Male	177	52.1
	Female	163	47.9
Residence	Urban	68	20.0
	Rural	272	80.0
Social class*	Low	138	40.6
	Middle	152	44.7
	High	50	14.7

*Social class was calculated according to El-Gilany et al, 2012 [52]

Table 2: Prevalence of HCV seropositivity among the study groups

HCV ab	Group 1 (n=300)		Group 2 (n=20)		Group 3 (n=20)		Total (n=340)		FET (P)
	No.	%	No.	%	No.	%	No	%	
Negative	288	96.0	9	45.0	10	50.0	307	90.3	61.9 (<0.001) (HS)
Positive	12	4.0	11	55.0	10	50.0	33	9.7	
OR	†R		29.3		24.0				
95%CI			10.2-84.1		8.4-68.5				

†R: Reference category

Table 3: Association between socio-demographic characters and HCV seropositivity among group (1)

Variable		HCV ab Negative (N=288)		HCV ab Positive (N=12)		Total (N=300)		Test of sig.	P
		No.	%	No.	%	No.	%		
Age (Years)	**Mean ± SD**	10.1±3.1		10.3±3.4		10.4±3.3		St. "t" =0.28	0.78 (NS)
Sex	**Male**	150	52.1	7	58.3	157	52.3	X^2=0.18	0.67 (NS)
	Female	138	47.9	5	41.7	143	47.7		
Residence	**Urban**	57	19.8	4	8	61	20.3	FET	0.27 (NS)
	Rural	231	80.2	8	66.7	239	79.7		
Social class	**High**	45	15.7	3	25	48	16.1	FET= 0.68	0.93 (NS)
	Middle	135	47	5	41.7	140	46.8		
	Low	107	37.3	4	33.3	111	37.1		

Table 3 showed that there was no statistically significant association between HCV seropositivity and sociodemographic characters as age, sex, residence and social class among group 1, P value > 0.05 for all. The results revealed that there was a statistically significant association between HCV seropositivity and blood transfusion, frequent IV injection, prior surgical or dental procedures and circumcision (P value <0.05 for all), where, seropositive children were about 8 times more likely to had blood transfusion, frequent IV injection and prior surgical or dental procedures than seronegative ones.

They were about 9 times more likely to be medically circumcised and about 13 times more likely non medically circumcised than the seronegative children. On the other hand, there was no significant (P >0.05) association as regard the other factors as ear piercing, family history of HCV, shaving in common barbers, use of common

razors/brushes, tattooing, exposure to blood, mode of delivery or history of schistosmiasis (Table 4). Our results also showed no significant differences in the clinical manifestations, CBC or liver function tests (LFT) between HCV Ab positive and negative children in group 1.

Table 4: Association between risk factors and HCV seropositivity among group (1)

Risk factors		HCV ab Negative (N=288)		HCV ab Positive (N=12)		Total (N=300)		Test of sig.	P
		No.	%	No.	%	No.	%		
Blood transfusion	No	257	89.2	6	50	263	87.7	FET	0.001 (HS) OR=8.3, 95% CI=(2.5-27.3)
	Yes	31	10.8	6	50	37	12.3		
Frequent IV injection	No	175	60.8	2	16.7	177	59	FET	0.004 (S) OR=7.7, 95%CI= (1.7-36.0)
	Yes	113	39.2	10	83.3	123	41		
Prior surgical procedures, dental procedures	No	177	61.5	2	16.7	179	59.7	FET	0.004 (S) OR=8.0, 95% CI= (1.7-37)
	Yes	111	38.5	10	83.3	121	40.3		
Prior hospitalization	No	170	59.2	7	58.3	177	59.2	FET	1.0 (NS)
	Yes	117	40.8	5	41.7	122	40.8		
Circumcision	No	139	48.3	3	25	142	47.3	FET=22.9	0.002 (S) ‡OR_1=9.1 (2.2-37) §OR_2=12.9(2.8-58.5)
	Medical	131	45.5	4	33.3	135	45		
	Non medical	18	6.2	5	41.7	23	7.7		
Ear piercing	No	154	53.5	5	41.7	159	53	X^2= 0.65	0.42 (NS)
	Yes	134	46.5	7	58.3	141	47		
Family history of HCV	No	236	81.9	8	66.7	244	81.3	FET	0.25 (NS)
	Yes	52	18.1	4	33.3	56	18.7		
Shaving in common barbers	No	160	55.6	7	58.3	167	55.7	X^2= 0.04	0.85 (NS)
	Yes	128	44.4	5	41.7	133	44.3		
Common razors/brushes	No	287	99.7	12	100	299	99.7	FET	1.0 (NS)
	Yes	1	3	0	0	1	3		
Tattooing	No	288	100	12	100	300	100	----	------
Exposed to blood	No	265	93.6	10	83.3	275	93.2	FET	0.19 (NS)
	Yes	18	6.4	2	16.7	20	6.8		
Delivery	Doctor	200	69.4	6	50	206	68.7	FET	0.2 (NS)
	B. attendant	88	30.6	6	50	94	31.3		
History of schistos	No	288	100	12	100	300	100	------	------

‡OR_1 →compares medical circumcision≠ non, §OR_2→→compares non medical circumcision≠ non

DISCUSSION

Egypt has one of the highest prevalence rates of HCV infection worldwide, averaging 12–24% in the general population [26,27]. In our study the prevalence of HCV seropositivity among the non risky group was 4% with positive predictive value of ELISA was 75% when confirmed by PCR, indicating HCV viraemia in 3% of these children, this is similar to that reported in other Egyptian studies in rural communities (3% and 9%) of subjects under 19 years of age were found to be positive in two-community based studies respectively [28,29].This is in agreement with Barakat and Elbashir [5] who found that HCV seroprevalence was 5.8% in the studied children, with HCV viraemia in 4.4% of them. However, Hyder et al [30] found that the seroprevalence of anti HCV antibodies in asymptomatic children (3-15 years old) in Pakistan was 0.58%.

Our results observed increased percentage of HCV seropositivity among males (58.3%), rural areas (66.7%) and middle class (41.7%). This is in agreement with a study which reported that higher HCV prevalence rates are observed in males compared to females [31], also in agreement with Mostafa et al [32] study which demonstrated that higher prevalence was observed in rural dwellers compared to individuals living in urban areas. These differences may also be in part due to the parenteral anti schistosomasis treatment campaigns (PAT) campaigns, as rural areas were more affected by the schistosomiasis disease, consequently, were more involved by these campaigns.

As regard risk factors for HCV seropositivity among non risky group we found that children who were exposed to risk factors like blood transfusion, surgical and dental procedures, frequent intravenous (IV) injections and circumcision by non medical personnel were significantly more likely to be a case of HCV than those who were not exposed.

Regarding blood transfusion, Soza et al [33] demonstrated that the most common risk factor for HCV infection was blood transfusion in 54% versus just 5% with intravenous drug users(IVDU)in a study of 147 Chilean patients with chronic hepatitis C. Regarding frequent IV injection Aceijas and Rhodes [34]stated that intravenous drug using is the main drive of HCV incidence and prevalence in many countries.

Regarding surgical and dental procedures Kalil et al [7]stated that experiencing various facility-based medical procedures however minor they are, contributes to susceptibility to HCV. Surgical procedures, and dental treatment have been incriminated in HCV transmission**.** Regarding circumcision by non medical personnel, Habib et al [29] documented that analysis of risk factors is significant for male circumcision by informal healthcare provider.

As regard clinical manifestations among non risky group such as diarrhea, abdominal pain, dark urine, easy fatigue, and poor general health, there were no significant differences between HCV seropositive and seronegative group, no abnormalities were detected in CBC or LFTs in seropositive cases which were in agreement with another study that stated that HCV can cause asymptomatic infection [35].

Tovo and Newell [36]concluded that Children with chronic HCV infection are usually free of symptoms, frequently with normal or borderline alanine aminotransferase (ALT) values. Also this was similar to the study of Jonas et al [38]who reported that most chronically infected children with HCV have mild elevations in ALT levels [37]. In contrast, persistently elevated ALT levels were recorded in several Egyptian pediatric and adult studies and consequently, HCV infection is not always benign in Egyptian children.

We found that the prevalence of hepatitis C antibodies among thalassaemic children was 55%,the positive predictive value of ELISA was 81.8% when confirmed by PCR , this was similar to a study in Iran in 2007, the prevalence of hepatitis C infection in patients with thalassemia in Iran was reported 15.7% to 63.8% [39].

Majeed [40] found that the prevalence of HCV in thalassemic children in Iraq (in Najaf city) was 15%. Many studies reported that HCV infection is spread primarily by direct contact with human infected blood and high risks for HCV infection include intravenous and percutaneous drug use and transfusion of blood products [41]. In our study all patients of thalasemia group share common risk factors such as blood transfusion, frequent intravenous injections and prior hospitalization and all risk factors for HCV transmission in thalasemia group were statistically non significant. in our study no abnormalities were detected in ALT levels. Jensen et al [42] found elevated serum activities of ALT and AST in thalassemic patients with iron overload.

In the present study we found that the prevalence of HCV infection in renal failure patients on regular hemodialysis was 50%, with positive predictive value of ELISA was 100% when confirmed by PCR ,this was nearly similar to the Egyptian Renal Registry [43] which reported that the prevalence of HCV infection was variable ranging from 49% to 64% in Egypt. Our results were relatively high in comparison to the study of Frank et al [44] which reported (10.17%) of HCV infection in dialysis patients.

In our study the prevalence of HCV infection in patients on hemodialysis showing significant increase with increasing age which is similar to Soin et al [45] study which reported that HCV infection increased with increasing the age. In our study all patients of renal failure group received blood transfusion even the seronegative patients so blood transfusion did not have statistical significance between risk factors that lead to acquisition of HCV infection, this was in agreement with other studies that reported that the mode of transmission of HCV among patients on dialysis has not yet been fully elucidated, Correlation with duration of hemodialysis but not with blood transfusions has been described [46].

In our study there were no significant increase in serum ALT level in HCV-positive patients of renal failure under hemodialysis, similar to Hanuka et al [47] study that has verified that liver enzymes and HCV antibody may be negative in the presence of viremia.In contrast to Sabry et al [48]study which detected higher serum ALT and AST levels in group of HCV-positive than in HCV-negative patients of renal failure under hemodialysis.

Prevalence of viremia(positive PCR) was 75% among patients with positive HCV abs in the non risky group,81.8% and100% in thalasemia and renal failure group respectively, other studies have reported rates of HCV-RNA positivity by PCR among children with anti-HCV positivity by ELISA as 40% [49].

The difference in the frequency of PCR positivity among ELISA-positive cases may be attributed to the following. Clearance of HCV-RNA while the subject remains anti-HCV positive &HCV being present in very small amounts in the blood, requiring very sophisticated techniques to pick it up**.** The presence of HCV-RNA in serum is a reliable indicator of infectivity and ongoing viral reproduction, and close follow-up of the infected cases is mandatory[50]**.**

RT-PCR is the gold standard method for the diagnosis of HCV infection, however, obstacles such as technical difficulties, unavailability and expenses may prevent it from being used as a screening test on a large scale of patients on a regular basis[51]**.**

CONCLUSION

Our results revealed that asymptomatic HCV seropositivity is detectable in 4% among 300 screened non risky school aged children, and a significantly high prevalence of asymptomatic HCV seropositivity in children with thalasemia and children with renal failure were reported. Blood transfusion, surgical procedures including dental procedures, frequent IV injection and circumcision by non medical personnel were the most important risk factors for HCV transmission in the non risky group.

Asymptomatic HCV infection was detected in 3% of the school aged children, in 45% of thalasemia patients and in

50% of renal failure patients. So PCR should be done for all HCV seropositive cases to confirm the presence of viremia.

Recommendations:

HCV prevention in Egypt must be a national priority**.** Better screening for donors and blood screening should take place to reduce the number of transfusion related transmissions. Extra attention should be given to high risk groups such as multi transfused thalasemic patients and patients of chronic renal failure who were ever on long-term dialysis. Once a patient is found to have hepatitis C, that patient needs to be counseled to reduce the risk of HCV transmission to others. Future researches in this field should be continued.

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