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RAPID COMMUNICATION

Prevalence and risk factors of asymptomatic hepatitis C virus infection in Egyptian children

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Abstract

AIM: To identify the prevalence, risk factors and manifestations of asymptomatic hepatitis C virus (HCV) infection in Egyptian children.

METHODS: Children at the age of 1-9 years were screened for HCV antibodies and alanine aminotransferase (ALT) levels. Every child with elevated ALT and/or detectable HCV antibodies was tested for HCV RNA by RT-PCR and compared with two negative controls for risk factors and signs and symptoms of liver disease.

RESULTS: We screened 1042 children, six of them had elevated ALT, negative HCV antibody and positive RNA, likely representing acute hepatitis C cases. Fifteen children were HCV seropositive, 5 of them were HCV RNA positive. Asymptomatic HCV infection was present in 2.02% (positive results for either HCV antibodies or HCV-RNA or both). Symptoms such as diarrhea, abdominal pain, history of fatigue and school absence because of illness and risk factors such as dental care were significantly more common among HCV positive cases than among controls. None of the HCV positive children was diagnosed as having signs of advanced liver disease upon clinical or ultrasonographic examination.

CONCLUSION: Asymptomatic HCV infection is detectable in 2.02% Egyptian children.

Key words: Hepatitis C virus; Child; Egypt; Prevalence; Transfusion; Risk factor

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INTRODUCTION

The prevalence of hepatitis C virus (HCV) infection is relatively low in children, with an anti-HCV prevalence rate of 0.2%-0.4% in the Western world[1]. Blood transfusion is the principal route of transmission of HCV in children[2]. Recent evidence suggests that new cases are due to perinatal (vertical) transmission[3].

Egypt has the highest prevalence of adult HCV infection in the world, averaging 15%-25% in rural communities[4-6]. The main (90%) HCV genotype is type 4[7-9]. The magnitude of HCV infection in children is not well understood, apart from subgroups in two-community based cross sectional studies[10,11]. In the first study from upper Egypt[10], 84 (3%) out of 2967 subjects under 19 years of age screened for HCV antibody using ELISA technique, were found to be positive. The overall prevalence in the 6033 screened subjects was 8.7%. In the second study from Lower Egypt[11], 178 (9%) out of the 2010 screened subjects under 19 years of age were found to be positive. The overall seroprevalence in the 3999 screened subjects was 24.3%. Analysis of risk factors was significant for male circumcision by informal health care provider[11]. Although blood transfusion, circumcision, vertical transmission, and living in a house with an infected family member are the established risk factors for HCV transmission, approximately 70% of acquired infections are due to unidentified risk factors[11]. A recent study of intrafamilial transmission showed that the incidence of offsprings to acquire HCV from anti-HCV–positive parents is slightly higher (incidence rate of 8.7/1000 per year) in the positive mother than in the anti-HCV positive father (6.6/1000)[12].

According to a study by El-Raziky *et al*[13] HCV infection is not always benign in the Egyptian children as ALT levels are elevated in half of the subjects and

histological abnormalities are detectable in three quarters of HCV-RNA positive cases. It is not clear whether identification of HCV early in childhood can alter the course of the disease due to the limitations of current antiviral therapies. Therefore long-term morbidity of the disease is a concern. The aim of the present study was to identify the prevalence and possible risk factors of asymptomatic HCV infection in Egyptian children and to detect the underlying signs and symptoms of liver disease associated with asymptomatic HCV in Egyptian children.

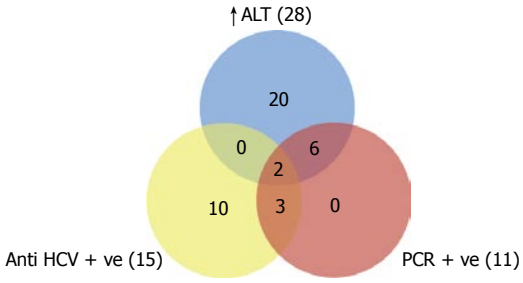

Figure 1 Abnormal laboratory results from 1042 screened children.

MATERIALS AND METHODS

Subjects

A hospital-based study of patients was carried out from January to August 2004 at the General Outpatient Clinics of Cairo University Pediatric Hospital (CUPH) which provides medical care to attending children (without reference or residence area restriction).

Inclusion criteria were attendants to the CUPH Outpatient Clinics, children at the age of 1-9 years*, children not known to have liver disease, parent's informed consent to participate in the study. Exclusion criteria were attendants to the Hepatology Clinic and the Haematology Clinic, and critically ill patients. Parents of the participants or legal guardians signed an informed consent approved by the IRB, if they fulfilled the criteria of screening. Oral consent, in the presence of a witness, was provided for illiterate participants. *We excluded participants below the age of one year due to the expected presence of passively acquired maternal anti-HCV in children of this age group. Those older than 9 years were also not included because inclusion of older children would include adolescents who might have different risk factors and enough time to follow them up when they were still in the paediatric age group.

Laboratory, physical and social assessment

Alanine aminotransferase (ALT), antibodies to hepatitis C virus (anti-HCV) (Axsym system HCV version 3.0 Abbott Diagnostics Division: Germany) were detected in all children. Any case with elevated ALT and/or positive HCV antibody was subjected to HCV RNA by an in-house reverse transcription-polymerase chain reaction (RT-PCR) on whole sera amplification of DNA by PCR[14] and asked to fill in a questionnaire about risk factors for transmission and a questionnaire about symptoms, while the mothers were blinded to results.

A full general and local abdominal clinical examination was performed on patients with positive results and 2 randomly selected matched negative controls. Abdominal ultrasonography was done with ultrasound Toshiba 250, 3.5/5.0 MHz convex probes. The socioeconomic status was calculated according to Egyptian score including education of father and mother, crowding index and sanitation of the house[15].

Sample size and analysis

The sample size was calculated and estimated to be approximately one thousand children according to the reported HCV seroprevalence ranging from 0.5%-3% in Egyptian children[10].

Univariate statistical results (mean ± SD) were used to estimate the prevalence of risk factors and liver function morbidity in the HCV positive cases and HCV negative controls. Chi-square test or Fischer's exact test (when appropriate) was used to assess the statistical significance of associations between individual risk factors and liver function morbidity with HCV infection, and Odds ratios were used to measure the strength of associations (OR > 3). $P < 0.05$ was considered statistically significant. SPSS program 12.0 was used for analysis.

RESULTS

A total of 1042 children were enrolled in this study. The results obtained from these cases were analyzed. The mean age of screened children was 3.88 ± 2.13 years. Male to female ratio was 1.1:1. Forty-one out of the 1042 children had elevated ALT and/or positive HCV antibody. Of these 41 children, 26 had elevated ALT, 13 positive HCV antibody alone and 2 both. HCV-RNA was amplified by RT-PCR revealing positive results in 11 out of the 41 children. The abnormal laboratory results of the 1042 screened children are shown in Figure 1. Among the 41 children, 6 had elevated ALT, negative HCV antibody and positive RNA, likely representing acute hepatitis C cases (0.58%). Their mean age was 2.8 years, ranging 2-4 years. The mean ALT was 231.5 IU + 262.61 IU ranging 43-633 IU. These laboratory results were tested once. Four out of six children had less than 5-fold elevation of ALT and the remaining two had more than 10 -fold elevation of ALT.

Fifteen children were HCV seropositive. Of them, 5 were HCV RNA positive, 2 had elevated ALT. Among the 28 children (2.7%) with elevated ALT, 20 were negative for both markers of HCV, 9 out of these 20 children were diagnosed as acute hepatitis A in 7 and hepatitis B in 1, and 1 developed HCV antibodies 4 mo later suggesting occult acute hepatitis C. Evidence of HCV infection was present in 21 cases (2.02%) positive for HCV antibodies and/or HCV-RNA.

Clinical data and possible risk factors for HCV acquisition were compared between the 18 children with evidence of HCV infection except for 3 who were lost in follow-up and 112 age, sex, residence and socioeconomically matched negative controls. Relevant and statistically significant clinical data are shown in Table 1. Symptoms such as diarrhea and abdominal pain,

Table 1 Comparison of clinical data obtained from HCV cases and control children

	HCV cases n = 18 (%)	Controls n = 112 (%)	P
Age at screening in years (mean ± SD)	4.00 ± 2.1	3.89 ± 2.0	NS
Male: female ratio	0.6:1	1.4:1	NS
BMI	16.61	16.76	NS
Residence			
Urban	16 (88.9)	104 (92.9)	NS
Rural	2 (11.1)	6 (5.4)	
Semi rural	0 (0)	2 (1.8)	
Socioeconomic score			
High class 20-26	2 (11.1)	8 (7.1)	NS
Middle class 15-20	4 (22.2)	36 (32.1)	
Low class 10-15	9 (50)	41 (36.6)	
Very low class less 10	3 (16.7)	27 (24.1)	
ALT folds (mean ± SD)	2.3 ± 4.1	0.4 ± 0.1	0.045
Present history			
Dark urine	4 (22.2)	14 (12.5)	NS
Diarrhea	5 (27.8)	12 (10.7)	0.046
Yellowish sclera	1 (5.6)	4 (3.6)	NS
Abdominal pain	3 (16.7)	2 (1.8)	0.002
Past history			
Jaundice	3 (16.7)	20 (17.9)	NS
School absence because of illness	3/7 (42.9)	1/48 (2.1)	0.01
Poor general health	6 (33.3)	20 (17.9)	NS

NS: P value is nonsignificant.

Table 2 Comparison of clinical data obtained from acute and chronic cases of HCV infection

	Likely acute HCV n = 4 (%)	Chronic HCV n = 14 (%)	P
Present history			
Dark urine	2 (50)	2 (14.3)	0.20
Diarrhea	2 (50)	3 (21.4)	0.53
Yellowish sclera	1 (25)	0 (0)	0.22
Abdominal pain	0 (0)	3 (21.4)	1.0
Past history			
Jaundice	0 (0)	3 (21.4)	1.0
School absence because of illness	1 (25)	2 (14.3)	0.43
Poor general health	1 (25)	5 (35.7)	1.0

history of easy fatigue and school absence because of illness were significantly more common among HCV positive cases than among controls. These relations were not significant when the clinical data were compaired between those who were considered as acute cases and others with chronic HCV (Table 2).

Risk factors are listed in Table 3. HCV cases were found to have 3.5 times of exposure to dental care than their controls. In addition, surgical interventions such as operations, stitches, catheterization, abscess drainage and cautery were not statistically significant.

Examination of the 18 cases with evidence of HCV infection revealed jaundice in 3 cases. None of the HCV positive children had splenomegaly. Ultrasonographic examination revealed evidence of periportal thickening in only one case (5.6%).

DISCUSSION

HCV can cause asymptomatic infection[16]. Children with chronic HCV infection are usually free of symptoms, frequently with normal or borderline alanine aminotransferase (ALT) values[17]. The worldwide seroprevalence of HCV ranges 0.2%-2%[18]. Egypt has the highest prevalence of adult HCV infection in the world. The natural history of HCV infection in children is ill-defined. In our study evidence of HCV infection was present in 2.02% cases, which is lower than 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)[10,11]. In India, a hospital-based serological survey showed that the prevalence of HCV in children at the age of 0-9 year is 3.6%[16]. Anti-HCV antibodies were detected in 4.09% hospitalised Pakistani children screened for markers of HCV[19]. However, a more recent Pakistani screening showed that the seroprevalence of anti HCV antibodies in asymptomatic children (3-15 years old) is 0.58%[20]. The prevalence of hepatitis C in children of developed countries is lower (0.05%-0.4% in USA)[21]. The seroprevalence in the third national health and nutrition examination survey (NHANES Ⅲ) was 0.2% in children aged between 6 and 11 years[22].

Much higher prevalence rates are reported in adult Egyptians with 12%-24% anti-HCV seropositivity in the general population[4,5,23]. The higher rate in adults is explained by the consistent increase of seropositivity with age.

In the present primary health care-based case-control study, no definite significant risk factor for acquisition of HCV could be detected both in cases and in controls. Lu *et al*[24] reported that no statistically significant difference in risk factors could be found among HCV antibody positive and negative children.

Egyptian studies documented that analysis of risk factors is significant for male circumcision by informal health care provider[11]. Blood transfusion, circumcision, vertical transmission, and living in a house with infected family member are not reported in more than 20% individuals, but about 70% have infection without identified risk factor in subjects under 19 years of age[11]. Hyder *et al*[20] showed that multiple exposures to unsterilized needle pricks, razors or dental procedures are responsible for a higher carrier rate in low socioeconomic groups.

Our results showed that symptoms such as diarrhea, abdominal pain, history of fatigue and school absence because of illness were significantly more common among HCV positive cases than among controls. Jaundice was present in 3 cases (16.7%) and soft rounded 3 cm liver enlargement below the costal margin was found in two of them. Jara *et al*[25] reported that symptoms such as anorexia, asthenia or abdominal pain, were present in only 14% of their patients, while none of them had jaundice or extrahepatic manifestations. Bortolotti *et al*[26], who conducted a clinical study on 77 Italian and Spanish children, showed that hepatitis C in children is usually asymptomatic.

None of our HCV positive children had splenomegaly.

Table 3 Comparison of risk factors for HCV positive and negative children

Risk factor	HCV cases *n* = 18 (%)	Controls *n* = 112 (%)	*P*	Odds ratio	95% CI	
					Lower	Upper
Circumcision by non medical personnel for males and females	3/9 (33.3)	39/94 (41.5)	0.63 (NS)	0.71	0.17	2.99
Injections by non medical personnel	9/17 (52.9)	57/111 (51.4)	0.90 (NS)	1.1	0.38	2.96
History of HCV in family members	3 (16.7)	21 (19.4)	0.78 (NS)	1.2	0.32	4.55
Ear piercing for females	11/14 (78.6)	43/53 (81.1)	0.83 (NS)	1.2	0.28	5.00
Attendance to medical care	11 (61.1)	99 (88.4)	0.01 (S)	4.9	1.60	14.71
Dental care	5 (27.8)	13 (11.6)	0.07 (NS)	3.5	1.13	10.82
Blood transfusion	3 (16.7)	7 (6.3)	0.12 (NS)	3.0	0.70	12.87
Delivery at home	7 (38.9)	24 (22.0)	0.13 (NS)	2.5	0.85	7.21
Post natal care	3 (16.7)	5 (4.6)	0.09 (NS)	0.24	0.05	1.1
Non medically assisted delivery	5 (27.8)	15 (13.4)	0.16 (NS)	0.42	0.13	1.3
Traditional hair cutting	9 (50)	81 (72.3)	0.14 (NS)	ND	ND	ND
Exposed to used syringes	2 (11.1)	13 (11.6)	0.95 (NS)	0.95	0.20	4.62
Exposed to used razors	4 (22.2)	12 (10.7)	0.17 (NS)	2.381	0.67	8.41
Exposed to blood	1 (5.6)	4 (3.6)	0.43 (NS)	ND	ND	ND
Associated medical diseases	3 (16.7)	17 (15.2)	0.66 (NS)	ND	ND	ND

No urinary catheter or tattoo in cases or controls. ND: not detectable.

Ultrasonography revealed evidence of periportal thickening in only one case (5.6%). Lu *et al*[24] reported that none of their HCV children had sonographic parenchymal changes in the liver when studying an endemic area in Taiwan.

Comparing the clinical data of those considered as acute cases and others with chronic HCV (Table 2) as well as their past history; symptoms were present in acute cases but not statistically significant. Similarly according to the AAP[27], acute infections are usually clinically silent and symptoms if present, are indistinguishable from symptoms found in patients with hepatitis A or B. Infected children may complain of anorexia, malaise, fatigue, and abdominal pain during the acute phase[28]. The acute stage of hepatitis C remains clinically silent in most infected people, and only 15%-20% of individuals develop symptoms[29]. Symptoms such as low-grade fever, fatigue, appetite loss, abdominal pain, nausea, and vomiting usually occur during the sixth or seventh week after infection and resolve within a few weeks[29,30].

In our study, fifteen children were HCV seropositive, 5 of them (33.3%) were HCV RNA positive. Vogt and colleagues[31] found that seventeen years after 67 children were infected with hepatitis C virus from blood transfusions during cardiac surgery, only 37 (55%) had detectable HCV RNA. Sehgal *et al*[28] showed that most children infected with HCV have no long-term complications. Persistent infection occurs in 50%-60% of infected children even in the absence of biochemical evidence of liver disease[27]. Of these, less than 10% develop chronic hepatitis, and less than 5% develop cirrhosis[28]. Hoshiyama *et al*[32] reported that 60%-80% of children with HCV infection develop chronic hepatitis C. The spontaneous clearance of HCV RNA in those vertically infected with HCV is estimated to be around 20%[8,18,33].

The relatively low prevalence of HCV-related morbidity in Egyptian paediatric cases is consistent with the reported result in Egyptian adults[34].

In conclusion, asymptomatic HCV is detectable in 2.02% of Egyptian children. HCV RNA should be tested in children with elevated ALT even in absence of detectable HCV antibodies.

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