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Frequency of HCV Infection in Children of HCV Infected Mothers

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Egypt has the largest epidemic of Hepatitis C Virus (HCV) in the world and the overall prevalence of positive cases for antibody to HCV was 14.7% from all population. To assess the frequency of hepatitis C infection in children of HCV infected mothers. The present study included 200 normal healthy children of HCV infected mothers aged 1.5-3 years of both sexes with different residence and socioeconomic level. All included children were submitted to full history taking and clinical examination, proper vaccination history that documented by registration, measurement of hemoglobin levels, ELISA test for detection of HCV antibody and PCR test for HCV RNA for HCV positive cases only. The HCV positive antibodies were reported in 5 children (2.5%); low viremia (by PCR) was reported in 3 out of 5 cases (60.0%) and moderate viremia was reported in 2 cases (40.0%). Comparison between HCV Ab-positive and negative cases revealed that there was no statistically significant difference between both groups; as regard any of studied variables. The results of the present study proved that the overall risk of HCV transmission among children of HCV infected mother was low and the rate of transmission represent only 2.5% of all studied cases.

Key words: Vertical transmission, hepatitis C virus, antibody

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INTRODUCTION

Hepatitis C Virus (HCV) is a small, enveloped, positive sense, single-stranded RNA virus of the Flaviviridae family (Zaltron *et al*., 2012). The HCV was first cloned in 1989 after more than 6 years of work to extract the virus from infected patients by a group of scientists from California in the United States (Choo *et al*., 1989). The HCV infection is recognized nowadays as a disease of global importance (Lavanchy, 2009). Children represent a small but important portion of those infected with the HCV and understanding the disease is limited in the pediatric population. Hepatitis C virus differs in children with regards to mode of transmission, rates of clearance, natural history and treatment (Khaderi *et al*., 2014).

Viral hepatitis is the most common cause of liver disease in the world. Acute infections with their sequelae are responsible for 1-2 million deaths/year. Of them 54000 deaths are due to acute HCV infection (Hanafiah *et al*., 2013). Unfortunately spontaneous clearance of HCV occurs only in a minority of cases as 54-86% of adult patients establish a chronic infection (Wiegand *et al*., 2008). Many chronically infected patients do not know that they have been infected with HCV because infection is largely asymptomatic (Vietri *et al*., 2013). In the approximately 86% of infected patients who develop a chronic infection, HCV progresses insidiously with 10-20% progressing to cirrhosis and approximately 7% of cirrhotic patients developing HCC (Blachier *et al*., 2013).

Prior to the 1990s, the principal routes of HCV infection were via blood transfusion, unsafe injection procedures and intravenous drug abuse. These modes of acquisition are estimated to account for approximately 70% of cases in industrialized countries (Zaltron *et al*., 2012). Following the implementation of blood and blood product screening, vertical transmission has gained importance as the primary HCV transmission route among children (Roberts and Yeung, 2002). However, in developing countries, insufficient screening of blood, blood products and parenteral exposure, continue to be the major causes of HCV transmission and are still reported among Egyptian children (Esmat *et al*., 2012). Unsafe use and reuse of injection equipment in hospitals is still a threat in many parts of Africa (Okwen *et al*., 2011). Intra-familial transmission may occur, but specific immune responses may be protective against house-hold infection in some children (Hashem *et al*., 2011).

Egypt has the highest worldwide prevalence with 9% countrywide rate and up to 50% rates in certain rural areas due to specific modes of infection (Kamal and Nasser, 2008). Prevalence in healthy Egyptian children is reported to range from 1.4-5.8% (El-Karaksy *et al*., 2010; Barakat and El-Bashir, 2011).

Assessment of the burden of vertical transmission is essential in countries with high HCV prevalence, such as, Egypt (Mohamoud *et al*., 2013).

At the time of delivery and during the first year of life, the anti-HCV positivity detected in the newborn can be due to the passive transfer of maternal antibodies. Therefore, the diagnosis of HCV infection based on antibody assays in children of HCV-infected mothers before the age of 12 months is not reliable. A practical and widely acceptable recommendation by most studies is to consider children born to anti-HCV positive mothers infected with HCV when HCV antibody is positive after 18 months of age. Testing of HCV antibody is of limited value before 18 mo of age due to passive transfer of maternal antibodies (Indolfi and Resti, 2009). For those infants born to mother who is positive for anti-HCV and negative for HCV RNA, an anti-HCV test should be performed later than 18 months after birth to confirm that the infant is negative for anti-HCV. If the infant is still anti-HCV positive, the infant is considered to have been infected with HCV (Yeung *et al*., 2014).

For many years, many studies have been conducted to identify the risk factors of vertical transmission of HCV and potential ways to prevent this infection. High maternal serum viral load during the perinatal period and female sex of the baby are considered to be factors that potentially increase the risk of mother to child transmission (Pawlowska *et al*., 2015). The route of delivery remains controversial and breast feeding has not been associated with the transmission. However, this data dates from the early 2000s or even earlier updated studies are lacking (Garcia-Tejedor *et al*., 2015).

To assess the frequency of hepatitis C infection in children of HCV infected mothers.

MATERIALS AND METHODS

In the present study, Damietta governorate was selected as the study site. Damietta fever hospital was chosen to represent the governorate, where most of the HCV infected mothers receive treatment. The present study included 200 children, aged from 1.5-3 years who were chosen by systematic random sample according to inclusion and exclusion criteria. We visited the fever hospital during the period from August, 2011 to March, 2012; 2 times per week (Sunday and Wednesday) and for 4 h per day (9:30 AM to 1:30 PM), in every visit from 5-8 cases were selected.

Inclusion criteria: Children of infected mothers from 18 months to 3 years of both sexes; children in close contact with their mothers who had been already infected at childbearing age.

Exclusion criteria: Age of children before 18 months (1.5 year) and after 3 years; children who are not in close contact with their mothers; children with chronic blood transfusion. Mothers who have been treated from HCV before pregnancy were also excluded.

A standardized data sheet was utilized to record patients' history, clinical examination and investigations that are performed in a questionnaire sheet as follows:

- Children's data included history taking (age, sex and residence), past and neonatal history, vaccination history, dietetic history as type of feeding and weaning and family history. Clinical examination as vital signs (HR, RR, BP and temperature), general examination (chest, heart and abdominal examination)
- Mothers' data: personal data, time of disease onset; beginning of treatment, close contact with the child and past history of treatment before pregnancy
- The following investigations were done for all children (anti-HCV antibodies by ELISA, PCR for HCV RNA in positive cases and hemoglobin level)

The blood samples were collected by venipuncture (5 mL) and divided into two portions, 1 mL was taken in a clean vacutainer EDTA tube for hemoglobin detection and the remaining blood was collected in dry plain vacutainer tube and allowed to clot naturally and completely. The serum was separated from the clot by centrifugation in two tubes for HCV antibodies and PCR if needed. The serum samples were clear not hemolyzed and not contaminated by microorganisms. To determine if hepatitis C antibodies (HCV Ab or anti-HCV), we used Murex anti-HCV (version 4.0) kits and the absorbance was recorded on ELIZA reader (Tecan Austria GmbH). Approved software (Magellan) was used for calculation and interpretation of results. The PCR was performed by the COBAS Ampliprep/COBAS TaqMan (CAP/CTM), a fully automated real- time PCR used to monitor HCV viremia. The detection limit of the assay is 15 IU mL^{-1}. Mild viremia if less than 200,000 IU mL^{-1}. Moderate viremia: 200,000 to 2 million IU mL^{-1} and high viremia: More than 2 million IU mL^{-1}.

Ethical consent: The study was approved by the Hospital Ethics Committee in accordance with local research governance requirements and it was explained to the prospective participants. All participating mothers signed an informed consent form.

Statistical analysis of data: Data analysis was performed using Statistical Package of Social Science (SPSS) version 16.0 for windows. Numerical variables were reported in terms of mean and standard deviation. Categorical variables were reported in terms of numbers and percentages. Independent samples (t) test was used to compare between two means and Fisher exact test for comparison between categorical variables. The p-value<0.05 was considered statistically significant for interpretation of results.

RESULTS

Results of the present work are demonstrated in Table 1-3.

As regard to general data of studied children, mean age of studied children was 2.4±0.46 years and mean maternal age was 34.99±3.5 years. Most of the studied cases were males (56.5%) and living at rural areas (59.5%). Socioeconomic level was low in 101 cases (50.5%). Most of the studied children were delivered by Cs section (57.5%), feeding was mainly breast feeding (94%). Positive history for hepatitis A was reported in 6 cases (3.0%) and positive family history of hepatitis C was reported in 53 cases (26.5%) (Table 1).

In the present work, mean hemoglobin concentration was 10.63±0.98 g dL^{-1}, PCR values for mothers ranged from

Table 1: General data of studied cases

	Values	
Variables	No.	Percentage
Child age		
Mean±SD	2.4±0.46	-
Minimum-Maximum	1.5-3	-
Mother age		
Mean±SD	34.99±3.5	-
Minimum-Maximum	28-42	-
Sex		
Male	113	56.5
Female	87	43.5
Residence		
Rural	119	59.5
Urban	81	40.5
Socioeconomic level		
Low	101	50.5
Moderate	52	26.0
High	47	23.5
Mode of delivery		
NVD	85	42.5
CS	115	57.5
Feeding		
Breast	188	94.0
Artificial	12	6.0
Family history of hepatitis C	53	26.5

-: Not available

Table 2: Laboratory finding of studied cases

Investigation	Mean±SD	Range
Hemoglobin (g dL^{-1})	10.63±0.986	8.5-12.9
PCR (viremia in mothers)	4651701.8±6311389.97	1250557-1590000
PCR (positive cases in children)	706496.0±560911.20	660000-1200000
	No.	Percentage
HCV Ab positive children	5	2.5
PCR		
Low viremia (<200,000 IU mL^{-1})	3	60.0
Moderate viremia (200,000 to 2 million IU mL^{-1})	2	40.0

Table 3: Comparison between HCV-ab positive and negative children

	HCV Ab-negative (n = 195)		HCV Ab-positive (n = 5)			
Variables	No.	Percentage (%)	No.	Percentage (%)	Test*	p-value
Sex						
Male	111	56.9	2	40.0	0.56	0.7^{NS}
Female	84	43.1	3	60.0		
Residence						
Rural	116	59.5	3	60.0	0.01	1.0^{NS}
Urban	79	40.5	2	40.0		
Socioeconomic level						
Low	96	49.2	5	100.0	5.03	0.08^{NS}
Moderate	52	26.7	0	0.0		
High	47	24.1	0	0.0		
Mode of delivery						
NVD	48	43.1	1	20.0	1.06	0.4^{NS}
CS	111	56.9	4	80.0		
Feeding						
Breast	183	93.8	5	100.0	0.33	0.99^{NS}
Artificial	12	6.2	0	0.0		
Positive family history of HCV	52	26.7	1	20.0	0.11	0.98^{NS}
HCV in pregnancy						
Asymptomatic	188	96.4	4	80.0	3.42	0.2^{NS}
Symptomatic	7	3.6	1	20.0		

*: Independent samples test to compare between two means, NS: Non significant

1250557-1590000 IU mL^{-1}, while PCR for positive children ranged from 660000-1200000 IU mL^{-1}, HCV positive antibodies was reported in 5 children (2.5%), 3 of them had low viremia and 2 of them had moderate viremia.

Table 3 demonstrates that comparison between HCV Ab-positive and negative cases revealed that, there was no statistically significant difference between both groups; as regard any of studied variables.

DISCUSSION

Hepatitis C Virus (HCV) infection is an important global health issue, with as much as 2-3% of the world's population affected (Alter, 2007; Hanafiah *et al*., 2013). It has been estimated that ~170-210 million people worldwide are infected with HCV. Additional 3-4 millions are newly-infected annually. Prevalence of pediatric infection varies from 0.05-0.36% in the United States and Europe, up to 1.8-5.8% in some developing countries. The highest prevalence occurs in Egypt, sub-Saharan Africa, Amazon basin and Mongolia (El-Shabrawi and Kamal, 2013). Egypt has the largest epidemic of Hepatitis C Virus (HCV) in the world as the overall prevalence in Egyptian population for HCV infection was 14.7% (El-Zanaty and Way, 2009). The identification of HCV transmission risk factors is essential for the application of appropriate interventions to prevent it (Garcia-Tejedor *et al*., 2015).

The present study was designed to evaluate the frequency of transmission of hepatitis C infection in children of HCV infected mother to assess the rate of infection transmission to her close contact children. The study included 200 children aged from 1.5-3 years, the mean age was 2.4 years. The study also included the HCV infected mothers of those children in childbearing age with aged from 28-42 years with mean age of 35 years.

In the present work, the rate of maternal to child transmission of HCV was 2.5% (5 cases out of 200).

Several previous studies have investigated the risk of mother to child HCV transmission (e.g., vertical transmission), with variable results. In fact, the rates of transmission varied from 0-30%. This large variability is probably due to differences in study size (e.g., the number of HCV-infected mothers enrolled), the study methodology (prospective or retrospective study, detection of maternal infection based on anti-HCV antibody positivity or on HCV RNA positivity) and the diagnostic criteria of neonatal HCV infection (e.g., number of polymerase chain reactions performed and duration and

timing of follow up in the neonates) (Yeung *et al*., 2001; Arshad *et al*., 2011; Aziz *et al*., 2011).

In Egypt, the results of a community-based study of perinatal HCV transmission in three rural egyptian villages are reported where the overall HCV prevalence is 24.3% (Habib *et al*., 2001). The most recent study was conducted by Shebl *et al*. (2009) and found that 6.5% of children born of mothers who were HCV-RNA positive were infected at 1 or 2 years of age.

Internationally, there is a recent systematic review and meta-analysis designed to estimate HCV vertical transmission, which involved 25 data points extracted from 20 studies. The estimates of HCV vertical transmission from women ranged from 1.1-10.7%. Meta-analysis of the risk of vertical HCV infection to children of HCV antibody-positive and RNA positive women was 5.8%, Confidence Interval (CI) 95%, 4.2-7.8% (Benova *et al*., 2014).

Recent studies also reported variable results. In Brazilian study included 58 pregnant women with HCV infection of whom, 23 (39.6%) fulfilled the inclusion criteria. The VT rate was 13% (3/23) (Gardenal *et al*., 2011). In a large retrospective cohort study with 711 infants born to 710 HCV-infected mothers, which was conducted at the Hospital La Fe, in Valencia, Spain, from 1986-2011 and overall perinatal HCV transmission rate was 2.4% (Garcia-Tejedor *et al*., 2015).

Our study demonstrated that breast feeding and mode of delivery were not risk factors for HCV transmission. Supporting our results, most data agree that breast-feeding does not increase the vertical transmission rate (Shiraki *et al*., 2008). Avoidance of breast feeding is not an effective way for preventing HCV vertical transmission (Bhola and McGuire, 2007). Also, a recent meta-analysis suggested that mode of delivery does not affect perinatal transmission from HCV mothers to infants (Chehreh *et al*., 2011). However, Shebl *et al*. (2009) reported that normal vaginal delivery was borderline protective ($p = 0.05$) and physician assisted deliveries in health care facilities trended towards risk for infection ($p = 0.09$). In addition, they found that the probability of not being infected was higher ($OR = 2.28$, $p = 0.03$) in exclusively breast-fed infants (92.3%) than in infants who received other sources of nourishment (84.0%).

It has been suggested that the lower odds of viremia in exclusively breast-fed children, may be explained by the presence of HCV-specific immunoglobulins in colostrum and breast milk which might protect against HCV transmission during infancy (Van de Perre, 2003). It is true that HCV RNA has been detected in breast milk and colostrums, however breast-feeding do not shown to be a route of maternal to infant transmission. The HCV infected mothers are encouraged to breast-feed if there are no other contraindications, such as HIV co-infection (Yeung *et al*., 2014). The Centers for Disease Control (CDC) and prevention suggests that mothers should interrupt breast-feeding temporarily if there are bleeding or traumatized nipples, which could increase infants' HCV exposure (Workowski and Berman, 2010).

As for the family history of HCV infection, the majority of cases in this study had negative family history, 73.5% and only 26.5% had positive family history (fathers, grandfather and grandmother). However, Polywka *et al*. (1999) found that there is a close relationship between HCV transmission and the family history as members of a family that has one or more members suffering from infection are more likely to catch up the infection. Also household contact with another household member that has hepatitis C has been strongly implicated and believed to be responsible for approximately 13% of all infections. Also, another egyptian study concluded that children living with an HCV positive parent are at high risk of infection, particularly if their mother is infected (Mohamed *et al*., 2005).

As for the sex of the studied children in relation to HCV Antibody, the negative cases were 195, 111 males and 85 females and the positive cases were 5; 3 females and 2 males while the difference was statistically insignificant. These results are in agreement with Bortolotti *et al*. (1998) who found that there is no relation between the sex and transmission of HCV infection. Also, no significant difference is found in another study (Hayashida *et al*., 2007).

In contrast, two multicentric prospective studies showed that girls were twice as likely to be infected as boys, probably because a different hormonal or genetic response to infection (EPHCVN., 2005; Indolfi and Resti, 2009). Similarly, Garcia-Tejedor *et al*. (2015) observed a transmission rate of 3.5% in females compared with 1.4% in males. There is no accurate explanation for these results but it may be related to difference in sample size.

Regarding the residence of the studied children in relation to HCV Ab assay in this study, the negative cases were 195, from which there were 116 rural and 79 urban while the positive cases were 5; 3 rural and 2 urban that were statistically insignificant. In addition, the socioeconomic level of the studied children in relation to HCV Ab assay revealed that, the negative cases were 195, 96 low, 52 moderate and 47 high level and the positive cases were 5 all of them were low level that were statistically insignificant. The previous two items are not in agreement with Gibb *et al*. (2000) as they reported in their study (Mother-to-infant transmission of hepatitis C virus) in India that the residence and socioeconomic level are very important factors in the transmission of infection especially HCV and they found that people in rural areas with low socioeconomic levels and low educational levels were high risk groups for HCV transmission.

Also, a recent study reported that there were disproportionately higher proportions of vertical infections estimated in Lower Rural and Upper Rural areas. This

geographical clustering was a result of higher-area-level HCV prevalence among women and higher fertility rates (Benova *et al*., 2015).

In our study, the majority of the cases had no history of HCV in pregnancy and only 1 case of 5 positive cases had history of HCV in pregnancy that was statistically insignificant, the results which agree with Lam *et al*. (2010) who reported that the risk of transmitting hepatitis C to the baby during pregnancy probably depends on the level of virus in their bloodstream (virus load). Similarly, a recent study observed significant association ($p<0.05$) between vertical transmission and high maternal serum viremia ($>2.5\times10^6$) (Gardenal *et al*., 2011).

CONCLUSION

In short, the present study highlights the rate of HCV vertical transmission in egyptian neonates; the rate was low in the light of higher rates reported in the literature. So, we recommend that the infected mother must handle with her child normally and give him all care and do not withheld from him fearing from transmission of infection.

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