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Incidence and risk factors for community-acquired hepatitis C infection from birth to 5 years of age in rural Egyptian children

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Abstract

A prospective study in three Egyptian villages (A, B and C) having a high prevalence of hepatitis C virus (HCV) infection examined incidence of community-acquired HCV infection in children; 2852 uninfected infants were prospectively followed from birth for up to 5.5 years. Fifteen seroconverted for either HCV antibodies and/or HCV-RNA (incidence of 0.53%). Ten had both anti-HCV and HCV-RNA; four had only anti-HCV; and one had HCV-RNA in the absence of antibody. The incidence rate at all ages was 2.7/1000 person-years (PY). It was 3.8/1000 PY during infancy and 2.0/1000 PY for the 1–5-years age group. Hospitalization and low birth weight increased the risk of infection; while living in village B, the family having a higher socioeconomic status, and advanced maternal education were protective. Six of eight HCV-infected infants reported iatrogenic exposures (e.g. hospitalization, therapeutic injections, ear piercing) prior to infection whereas only 2/7 children older than 1 year reported these exposures. Having an HCV-positive mother was the only other reported risk in two of these older children. The virus cleared in six (40%) children by the end of follow-up. Health education targeting iatrogenic exposures and focusing on risk factors could reduce HCV infection in children in high-risk populations.

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Ethical approval: The study protocol was approved by the institutional review boards of the University of Maryland, Baltimore, MD, USA; the Egyptian Ministry of Health and Population; and the National Liver Institute, Menoufia University, Shibin El Kom, Egypt. All subjects or their mothers provided informed consent.

Keywords

Hepatitis C; Children; Incidence; Risk factors; Rural community; Egypt

1. Introduction

Egypt has the highest prevalence of hepatitis C virus (HCV) infection of any country in the world. It is estimated to be 8% in urban and 25% in rural areas, with 8 million to 10 million inhabitants having HCV antibodies (anti-HCV) and 5 million to 7 million having active infections (i.e. HCV-RNA positive).^{1,2}

This high HCV prevalence has been linked to the intravenous tartar emetic injections given with reusable glass syringes during mass treatment campaigns to control schistosomiasis from the 1960s until 1982.³ The resulting high reservoir of infection in the older adult population has led to a greater likelihood of exposure leading to increased incidence of HCV infection in Egyptian children.

We and others reported that prevalence of HCV infection in children younger than 10 years in rural villages ranged from 2 to 7%,^{4,5} while incidence was 5.9/1000 person-years (PY).⁶ Children living with HCV-infected mothers and other family members were at highest risk of infection.^{6,7} We also recently reported prevalence⁸ and incidence⁹ of HCV infection in a large cohort of women living in three villages in the Nile Delta, as well as perinatal HCV infection rates of infants born to these women.¹⁰ Herein, we report the incidence of, and risk factors for, community-acquired HCV antibodies and RNA in children born to this cohort of women.

2. Materials and methods

2.1. Study sites and subjects

A prospective cohort study was conducted in three rural villages in Menoufia Governorate in the Nile Delta from 2000 until 2006. Two of the villages each had approximately 30 000 inhabitants, and the third had a population of around 9000.

The subjects were 2852 children followed prospectively from birth up to 5.5 years of age. Slightly more than half (1444) of the children were male and 42 were twins. These children had 2469 mothers who entered the study during their second or third trimester of pregnancy while visiting the antenatal clinics in their Community Health Units (CHU). Questionnaires that included demographic and health information and previous potential exposures to HCV infection were administered. Each expectant mother received antenatal consultation from the project's obstetrician, and a blood sample was collected. Subsequent follow-up of the woman and her child was scheduled for 2 months after birth, and then yearly for 5 years. An extra visit at the age of 6 months was conducted at one of the three villages.

During the follow-up visits, information was obtained about the mode of delivery, breastfeeding practices, infants' and mothers' health, and risk factors for HCV infection in both mothers and their children during the interim period between visits. Infants were examined by paediatricians, and blood samples were obtained from both the mother and child. We herein report only community-acquired incident HCV infections in these children.

2.2. Laboratory procedures

Sera were tested for anti-HCV with a third-generation enzyme immunoassay (EIA; Abbott, Wiesbaden, Delknheim, Germany). Testing for HCV-RNA was performed on sera using

reverse transcriptase PCR (RT-PCR) without RNA extraction as previously described.¹¹ Sera that were anti-HCV positive and HCV-RNA negative were retested following RNA extraction using QIAamp Viral RNA kit (Qiagen, Santa Clarita, CA, USA).

2.3. Criteria of incident cases

Community-acquired incident HCV-infected children were defined as individuals who seroconverted from negative to positive for anti-HCV and/or HCV-RNA for at least two subsequent samples.

2.4. Statistical analysis

Incidence rates (IR) were calculated by dividing the total number of HCV infections by the PY of follow-up. The follow-up time used for IR calculations was the sum of the time from birth until either each child's last HCV-negative blood sample, or in the case of incident infection, it was the time from birth until the estimated time of infection. The estimated time of infection for these children was calculated as the mid-point between their last negative and first HCV-RNA and/or anti-HCV positive blood sample. The post-infection follow-up of the incident cases was the time between their first HCV positive sample and their last blood sample.

Confidence intervals for IR were calculated using an exact approach based on the Poisson distribution. Confidence intervals for incidence rate ratios (IRR) were calculated by inverting an exact hypothesis test procedure.¹²

Socioeconomic (SE) assessment was based upon responses to questions about household possession of various items, monthly financial expenditures and highest level of education. The SE index established used values ranging from 4 to 12, divided into three groups (4 to 6: low; 7 to 9: middle; 10 to 11: high) was used to compare SE factors with risk of infection.⁸

3. Results

The study ended before some of the subjects were old enough to be followed for the full 5 years. A total of 2832 (99.3%) attended for the 2-month visit; 1795 (64.8%) of 2768 eligible children returned for the 1-year visit; 1252 (55.5%) of 2257 eligible children returned for the 2-year visit; 829 (49.4%) of 1678 eligible children returned for the 3-year visit; 552 (51.3%) of 1076 eligible children attended at 4 years; and 374 (58.8%) of 636 eligible children were seen at the CHU at 5 years. The follow-up rate for the 6-month visit scheduled in one of the study villages was 873 of 1269 eligible children (68.8%). This provided a total of 5573 PY of follow up; 353 children dropped out of the study: 7 died; 39 families moved away; and 307 mothers removed their children from the study. The reasons for removal were: 99 did not wish to have blood drawn; 46 husbands ordered the mother to stop participating; 40 mothers said they were too busy; 35 said their child was in poor health and did not wish to continue participating; 15 mothers did not wish to come to the CHU; 13 mothers were in poor health themselves; and 59 mothers gave no reason for dropping out.

3.1. Incidence of HCV infection

Fifteen incident HCV cases (15/2852, 0.53%) were observed during the follow-up (Table 1). Ten (66.7%) were both anti-HCV and HCV-RNA positive (cases no. 2, 4, 5, 7–13); four (26.7%) were anti-HCV positive and HCV-RNA negative (cases no. 1, 6, 14, 15); and one had detectable HCV-RNA in the absence of anti-HCV (case no. 3). Two of the 10 children who had both HCV antibodies and RNA had only HCV-RNA detected in their first positive

blood sample (cases no. 4, 5). The anti-HCV EIA became positive in subsequent blood samples.

The anti-HCV and/or HCV-RNA IR was 2.69/1000 PY (95% CI 1.49–4.49). The detectable viraemia (HCV-RNA positive) IR was 1.97/1000 PY (95% CI 0.97–3.57). Eight of the incident cases were detected during the child's first year of life; two were first detected during their second year, and two and three were detected during the third and fourth years of life, respectively. Thus, the incidence rate during the first year of life was 3.81/1000 PY vs. 2.02/1000 PY for the 1–5-years age group (IRR = 1.89).

3.2. Risk factors for HCV infection

Eight incident cases had one or more parenteral exposures known to transmit blood-borne infections; three of the seven children without a history of parenteral exposures had HCV-RNA positive mothers (Table 1). The four infants who weighed less than 2.5 kg at birth all had parenteral exposures.

Individual risks for HCV infection included hospitalization (IRR = 4.65), low birth weight (IRR = 4.42) and the mother receiving Rh immunoglobulin during delivery (IRR = 7.64; Table 2). However, a higher SE status (IRR = 0.24) and advanced maternal education (IRR = 0.22) appeared to protect the child from infection ($P < 0.05$). Although the differences were statistically insignificant because the exposures were uncommon in the entire cohort, blood transfusion (IRR = 17.15), surgery (IRR = 3.26), ear piercing (IRR = 2.85) and a household contact with someone having hepatitis (IRR = 1.50) were all associated with an increased incidence of HCV. The three children with HCV-RNA positive mothers had a 1.7 times higher risk of acquiring HCV infection than those with HCV-RNA negative mothers: 0.44% vs. 0.26% acquired HCV infection annually.

Incident HCV infection was not significantly associated with any of the following: child's gender, mode or place of delivery, type of delivery attendants present at birth, place of circumcision (at home or in a health facility), receiving of dental treatment or reported history of playing with sharp objects (e.g. used needles, razors) that could penetrate the skin. However, potential modes of infection appeared to differ by age. Among the eight infants infected by their first birthday, six had histories (usually multiple) of parenteral exposures. One of the two infected infants who did not have a parenteral exposure had a mother who had HCV (Table 1). Only two of the seven children infected after the age of 1 year gave histories of parenteral exposures. Two of the five in this group who had no other known potential exposures had mothers who were HCV-RNA positive.

Children residing in villages A and C had almost a three-times higher risk of acquiring HCV infection than those living in village B (Table 2). This reduced incidence of HCV in children in village B correlated with the lower prevalence and incidence of HCV in pregnant and postnatal women in this village (Figure 1).

3.3. Effect of HCV infection on the child's health

No mother reported that her child was jaundiced or diagnosed as having acute hepatitis, or gave a medical history compatible with hepatitis preceding the first HCV positive sample. However, the mother of case no. 3 later reported her child was hospitalized because of acute hepatitis. The child had clinical findings of acute hepatitis (i.e. fever, jaundice, dark urine, pale stools) after HCV-RNA, in the absence of anti-HCV, was detected in her blood sample.

3.4. Post-infection follow-up of the HCV incident cases

Follow-up blood samples were collected annually. Case no. 3 had two HCV-RNA positive blood samples before it cleared in her third and fourth post-infection samples. She was never positive for anti-HCV. Case no. 5 was anti-HCV and HCV-RNA positive in his first three post-infection blood samples but cleared HCV-RNA in the fourth one. Case no. 11 had three follow-up blood samples that were all anti-HCV and HCV-RNA positive. Cases 2, 4, 7–10, 12 and 13 each had two post-infection samples 1 year apart that remained positive for both anti-HCV and HCV-RNA. Cases 1, 6, 14 and 15 continued to have anti-HCV in absence of HCV-RNA in both their post-infection samples. Thus, HCV-RNA clearance was detected in 40% (6/15) of the infected children.

4. Discussion

This report describes 15 community-acquired HCV infections among children less than 5 years of age. Along with our recent report of 33 transient and persistent perinatal infections in the same cohort,¹⁰ it defines the incidence of, and risks for, HCV infections among young children living in three rural Egyptian communities having large reservoirs of HCV. Although the risk for perinatal infection among infants born of mothers who are HCV-positive was 12.5%, most of these infections cleared with only 2.4% of the children having persistent viraemia at 3 years of age.¹⁰ At the same time that infants were clearing their perinatal infections, others in the communities were acquiring infections. The incidence of community-acquired HCV infection during the first 5 years of these children's lives was 0.27% per year. The risk of infection during the first year was 0.38% which dropped to 0.20% annually from years 1 to 5.

Data on community-acquired incident HCV infection is rare and is almost exclusively for adult populations. For instance, an overall IR of 3.1/1000 PY based upon seroconversions among an HCV-negative cohort was reported in an Egyptian population, 36% of which were less than 10 years old.⁶ We also recently reported the postnatal HCV infection rate in the mothers of the current cohort of children was 2.3/1000 PY, and that the most important risk factors for infection in these women were iatrogenic exposures.⁹

An HCV IR of 11/1000 PY and 3.6/1000 PY were reported in smaller studies in Taiwan and Japan, respectively.^{13,14} The mean age of persons with newly acquired HCV infection was 50 years in the Taiwanese and 60 years in the Japanese, suggesting that iatrogenic risks, including haemodialysis, medical injections, tattooing and blood transfusions, were the most common causes of infections. In a report from Italy, HCV incidence was only 0.1/1000 PY. Only 2 cases/2032 participants were detected, and no associated risk factors were found.¹⁵ Another study detected 5 cases in a cohort of 16 515 subjects. Iatrogenic risk factors were associated with the infected cases.¹⁶

Slightly more than half of the 15 infected infants reported typical parenteral risk factors for infection. A third of the infected children were hospitalized subjecting them to nosocomial exposures, including surgery and therapeutic intramuscular and intravenous injections. Four of the infants were hospitalized prior to the 1 year follow-up for fever according to their mothers' report and the fifth was hospitalized and had surgery between his first and second year. Healthcare-related risk factors were also associated with incident and prevalent HCV infection in the women in these villages.^{8,9} Therapeutic injections were involved in the spread of HCV infection in high-risk endemic areas.^{4,17} Low birth weight infants had a tendency to be at greater risk for infection. However, all four of these small infants had multiple parenteral exposures and two were hospitalized (Table 1). Children born of mothers who received Rh immunoglobulin were at increased risk of infection. However, none of the mothers seroconverted for HCV after receiving the immunoglobulin shortly following

delivery, and we cannot explain the reason why this would increase the child's risk of HCV-infection. There could be a confounding factor that we have not detected or the relationship could have occurred by chance alone.

Three children had HCV-infected mothers, a risk we previously documented. One mother seroconverted from HCV-negative to HCV-positive in her first blood sample taken after delivery of case no. 6. A prospective cohort study in other Egyptian villages found the HCV IR in children with RNA positive mothers was as high as 8.7/1000 PY compared to 2/1000 PY for children with RNA negative mothers.⁶ A seroprevalence survey in Egyptian rural communities also found that 14% of children with RNA-positive mothers were anti-HCV positive vs. only 2.6% of children whose mothers were seronegative.⁷ Sequencing viruses from children and their mothers has confirmed that having an infected mother is a major risk factor for childhood HCV infection in Egypt.¹ Intrafamilial transmission could be attributed to certain household activities and behaviours that expose the young children to their mothers' infectious blood or saliva. Thus, special care with close monitoring of offspring of HCV positive women should be considered.

Four children, including three who were age 2 years or older, had no known risks for HCV infection. The assumption that these were community-acquired infections is supported by high prevalence of anti-HCV (13–17.3%) among the pregnant women in the three communities,⁸ and correlation of incidence in the children with the HCV prevalence and incidence in the mothers in the same communities (Figure 1).^{8,9} The large reservoir of infectious blood in these villages would increase the risk of infection from unapparent parenteral exposures.

Additional risk factors that were significantly associated with HCV infection were lower levels of the mothers' education and family SE status. These data support the belief that children with less educated and poorer mothers may have more exposures and be more likely to be infected with the virus.¹⁸

All of the infections were asymptomatic except for one child who had acute hepatitis occurring several months after she was noted to have seroconverted for HCV-RNA during her 1 year follow-up. The initial infection in children is generally asymptomatic and not recognized.^{19,20} Asymptomatic HCV seroconversions were also noted in the mothers of our infant cohort.^{8,9} It was previously reported that HCV hepatitis detected in Egyptian communities was predominately flare-ups of chronic infections rather than acute infections.²¹

Ten of the 15 infected children had both HCV antibodies and RNA. Two of these met the strictest criteria for acute infections having only HCV-RNA in the first blood sample prior to seroconverting for anti-HCV on the next sample.²² One child had detectable HCV-RNA on two successive blood samples in the absence of anti-HCV. The absence of detectable antibodies during HCV infection has several possible explanations. Rarely individuals have viraemia with intermittently undetectable levels of HCV antibodies.^{23,24} Others reported 0.2–0.9% of anti-HCV-negative organ donors were HCV-RNA-positive in France and the USA,^{25,26} and 7 of the 232 mothers in the parent cohort who were HCV-RNA-positive did not have detectable anti-HCV.¹⁰

The child who was viraemic without anti-HCV seroconversion and another child who had both HCV antibody and RNA cleared their infections in follow-up blood samples. The four children having only anti-HCV were considered to have had transient viraemia that occurred prior to their visit to the clinic. Thus, 40% of the HCV-infected children achieved HCV-RNA clearance. Spontaneous HCV-RNA clearance among children has been well documented.^{19,20,27} In the USA, Luban et al. found that 4 of 43 (9%) post-transfusion HCV-

infected children cleared viraemia as assessed by two negative RT-PCR tests 6 months apart, giving an estimated rate of clearance of 1.7% per year.²⁰ Forty-five percent of German children with a mean age of 2.8 years infected by HCV-contaminated blood products resolved their infections after a follow-up averaging 20 years.²⁷ It is possible a higher proportion of our infected children will clear the virus over time. Our data support the suggestion that acquiring HCV infection at younger ages is associated with a greater level of clearance of the virus than in adults.^{10,28}

5. Conclusion

The annual rate of HCV infection was 0.38% for infants and 0.2% for 1–5-year old children in three rural Egyptian communities. Iatrogenic exposures were frequent in the HCV-infected infants while environmental and familial (e.g. having HCV infected mothers) were suspected exposures among the incident cases in the older children. Risk of infection correlated with maternal HCV incidence and prevalence in the three study villages. Thus, preventive measures including focusing on reducing iatrogenic exposures, and educating mothers and others in the communities on how HCV is transmitted should be utilized to reduce HCV infection in children living in high HCV risk areas, particularly those living with HCV-infected family members.

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Figure 1. Incidence of hepatitis C virus (HCV) infection in children correlated with prevalence and incidence in women in three study villages in Menoufia Governorate, Egypt. Maternal HCV prevalence data adapted from Stoszek et al.⁸ and maternal HCV incidence data adapted from Saleh et al.⁹ IR/1000PY: incidence rate per 1000 person-years.

Information and exposure histories of individual cases of hepatitis C virus (HCV) infection in children in three study villages in Menoufia Governorate, Egypt

Table 1

Case	Age at seroconversion	Sex	Child's HCV status	Mother's HCV RNA status ^a	Exposures preceding HCV infection
1	2 months	F	Anti-HCV only	-	Ear piercing
2	6 months	F	Anti-HCV + HCV-RNA	-	None detected
3	1 year	F	HCV-RNA only	-	Ear piercing Therapeutic injections Hospitalization LBW
4	1 year	M	Anti-HCV + HCV-RNA	-	Therapeutic injections Hospitalization Blood transfusion
5	1 year	M	Anti-HCV + HCV-RNA	-	Therapeutic injections Hospitalization
6	1 year	M	Anti-HCV only	+	None detected
7	1 year	M	Anti-HCV + HCV-RNA	-	Therapeutic injections Hospitalization Hepatitis patient contact
8	1 year	M	Anti-HCV + HCV-RNA	-	Therapeutic injections LBW
9	2 years	M	Anti-HCV + HCV-RNA	-	Therapeutic injections Hospitalization Surgery Hepatitis patient contact LBW
10	2 years	M	Anti-HCV + HCV-RNA	-	None detected
11	3 years	M	Anti-HCV + HCV-RNA	+	None detected
12	3 years	F	Anti-HCV + HCV-RNA	-	None detected
13	4 years	M	Anti-HCV + HCV-RNA	+	None detected
14	4 years	F	Anti-HCV only	-	Therapeutic injections LBW
15	4 years	F	Anti-HCV only	-	None detected

LBW: low birth weight.

^a -: negative; +: positive.

Table 2

Risk factors associated with hepatitis C virus (HCV) incidence in children in three study villages in Menoufia Governorate, Egypt

Exposure	Number infected	PY	IR/1000 PY	IRR	95% CI	P-value
Village of residence						
Village B		3	2361	1.27	1	
Village A		6	1605	3.74	2.94	0.63–18.18 NS
Village C		6	1608	3.73	2.94	0.63–18.15 NS
Mother's HCV status						
RNA neg.		12	4571	2.63	1	
RNA pos.		3	686	4.37	1.67	0.30–6.18 NS
Mother's education						
No school/primary		10	1716	5.83	1	
Preparatory and higher		5	3856	1.30	0.22	0.58–0.72 0.009
Socioeconomic index score						
Low		10	1911	5.23	1	
Middle		4	2865	1.40	0.27	0.57–0.93 0.035
High		1	790	1.27	0.24	<0.01–1.70 NS
Birth weight ^a						
≥2.5 kg		8	3197	2.5	1	
<2.5 kg		4	362	11.50	4.42	0.97–16.49 NS
Mother given Rh immunoglobulin ^b						
No		6	2966	2.02	1	
Yes		3	194	15.46	7.64	1.23–35.79 0.029
Hospitalization						
No		10	5016	1.99	1	
Yes		5	539	9.28	4.65	1.24–14.94 0.022
Blood transfusion						
No		14	5521	2.54	1	
Yes		1	23	43.48	17.15	0.40–112.7 NS
Surgery						
No		14	5435	2.58	1	
Yes		1	119	8.40	3.26	0.07–21.44 NS
Ear piercing						
No		13	5017	2.59	1	
Yes		2	271	7.38	2.85	0.31–12.58 NS

PY: person-years; IR: incidence rate; IRR: incidence rate ratio; NS: not significant.

^aData are missing for three of the incident cases.

^bData are missing for six of the incident cases.