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ORIGINAL RESEARCH

A prospective study of vertical transmission of hepatitis C virus

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Abstract

AIM: To prospectively study the mechanism of mother to infant transmission of hepatitis C virus (HCV).

METHODS: Using a nested PCR for detection of HCV RNA and the second generation ELISA for detection of anti-HCV, 13 pregnant women who suffered from post transfusion hepatitis C (PT-HCV) and their 15 babies were studied to evaluate mother to infant transmission of HCV.

RESULTS: The total infection rate of HCV was 86.7% in the babies, including one case of clinical HCV (7.7%), three subclinical cases of HCV (23.1%), and nine inapparent cases of HCV (69.2%). The positive rates of anti-HCV and HCV RNA declined with the age of the babies, to 7.7% for anti-HCV and 15.4% for HCV RNA at the age of three years.

CONCLUSION: Babies born to mothers infected with HCV were vertically infected with HCV at a high rate, but the consequences were not serious. Four fetuses born, born through induced labor to mothers positive for anti-HCV and HCV, were all infected by HCV, suggesting that the mother to infant transmission of HCV mainly occurred in the uterus.

Key words: Hepatitis C virus; RNA; Viral; Disease transmission; Vertical

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INTRODUCTION

It is well known that mother to infant transmission of hepatitis B virus (HBV) is the main cause of chronic carrier HBV, and the vertical transmission rate of human immunodeficiency virus (HIV) is also high with grave consequences. However, the existence and extent of vertical transmission of hepatitis C virus (HCV) are still largely unclear. Serological markers (anti-HCV) indicate various rates of vertical transmission of HCV[1-3]. Recently, the polymerase chain reaction (PCR) has been developed, which has enabled more accurate and reliable studies of vertical transmission of HCV[4,5]. In this study, we prospectively followed 15 infants born to 13 mothers with post transfusion HCV (PT-HCV). The results suggest that the rate of vertical transmission of HCV is high, but that the consequences in the infants are not serious, and that the transmission occurs mainly in the uterus.

MATERIALS AND METHODS

Mother to infant transmission

Pregnant women with PT-HCV and their offspring were selected (13 mo and 15 offspring). Mothers were interviewed, and their sera were collected at three, seven and nine months during pregnancy, and at one month after delivery. Sera of infants was collected at the ages of one, three, and six months, and every six months thereafter. Parents provided informed consent for the infants.

Infection in utero

Five fetuses from five anti-HCV-positive women with induced labor and 97 fetuses from 97 anti-HCV-negative women with induced labor were studied. Liver tissue and sera of the fetuses were collected and frozen.

Serologic tests and gene amplification

Anti-HCV antibody was tested by second generation ELISA kits provided by YesBiotech Lab (C, Ns3, Ns4, Ns5) and Shenyang Huimin, Co.

Table 1 Sequences of hepatitis C virus test and genotype primers

Purpose	Code	Position	*n*	Direction	Sequences (5'-)	Target geno bp type
Test	F1	5'NC	153	Sense	GGCGACACTCCACCATGAATC	
	R1		154	Antisense	GGTGCACGGTCTACGAGACCT324	
	F3		204	Sense	ATGAGTGTCGTGCAGCCTCCA111	
	R3		203	Antisense	GTTTATCCAAGAAAGGACCCG	
Type	A	C	256	Sense	CGCGCGACTAGGAAGACTTC	
	B		186	Antisense	ATGTACCCCATGAGGTGGGC272	
	C		104	Sense	AGGAAGACTTCCGAGCGGTC	
	D1		132	Antisense	TGCCTTGGGGATAGGCTGAC57	I
	D2		133	Antisense	GAGCCATCCTGCCCTCCCCA144	II
	D3		134	Antisense	CCAAGAGGGACGGGAACCTC174	III
	D4		135	Antisense	ACCCTCGTTTCCGTACAGAG123	IV

Table 2 Temporal sequential results of hepatitis C virus RNA, anti-hepatitis C virus, and alanine aminotransferase of mothers

Code	Age	Disease onset date	Conception date	Pregnancy				1 month after delivery			
				C	R	A	S	C	R	A	S
1	26	Jun-90	Sep-90	+	+	+	+	+	+	-	+
1-2			Feb-93	+	-	-	-	+	-	-	-
2	29	Oct-88	Nov-91	+	+	+	+	+	+	-	-
2-2			Apr-93	+	+	-	-	+	+	-	-
3	32	Jul-89	Apr-90	+	-	-	-	+	-	-	-
4	25	Jun-90	Jul-90	+	+	+	+	+	+	-	+
5	40	Sep-90	Apr-91	+	+	+	+	+	+	-	-
6	29	May-90	May-91	+	+	-	-	+	+	-	-
7	29	Jul-90	Dec-91	+	+	-	-	+	+	-	-
8	29	May-90	Nov-92	+	+	-	-	+	+	-	-
9	31	Nov-90	Dec-92	+	+	-	-	+	+	-	-
10	31	Aug-91	Jul-93	+	+	+	-	+	+	-	-
11	22	Jun-90	Jul-93	+	+	-	-	+	-	-	-
12	22	Sep-91	Sep-92	+	+	-	+	+	+	-	-
13	27	Mar-89	Oct-92	+	-	-	-	N	N	N	N

C: Anti Hepatitis C virus; R: Hepatitis C virus RNA; A: Alanine aminotransferase; S: with clinical symptoms and signs; N: ND

Table 3 Serological markers and clinical feature of infants

Code	Mothers infected with hepatitis C virus during pregnancy			Months from conception to disease onset	Age (months) of infants																					
					1			3			6			9			12			18			24			36		
	C	R	A		C	R	A	C	R	A	C	R	A	C	R	A	C	R	A	C	R	A	C	R	A	C	R	A
1	+	+	+[1]	3	+	+	+[1]	+	+	-	+	+	-	+	+	-	+	+	-	+	+	-	+	+	-	+	+	-
1-2	+	-	-	32	+	+	-	+	+	-	+	+	-	+	-	-	-	-	-									
2	+	+	+[1]	37	+	+	-	+	+	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2-2	+	+	-	54	+	+	-	+	+	-	-	-	-	-	-	-	-	-	-									
-	+	+	-	-	-	-	-	-	-	-	-	-	-															
4	+	+	+[1]	1	+	+	-	+	+	-	+	+	-	+	+	-	+	+	-	+	+	-	-	+	-	-	+	-
5	+	+	+[1]	7	+	+	-	+	+	-	+	+	-	N	N	N	-	+	-	-	+	-	-	-	-	-	-	-
6	+	+	-	12	+	+	+	+	+	+	+	+	-	+	+	-	-	+	+	-	+	-	-	-	-	-	-	-
7	+	+	-	17	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
8	+	+	-	30	+	+	-	N	N	N	+	+	-	N	N	N	-	-	-									
9	+	+	-	25	+	+	-	+	+	-	+	+	-	N	N	N	-	-	-									
10	+	+	+	23	+	+	-	+	+	-	+	+	-	-	-	-												
11	+	+	-	37	-	-	-	-	-	-	-	-	-	-	-	-												
12	+	+	-[1]	12	+	+	+	N	N	N	N	N	N	-	-	-	-	-	-									
13	+	-	-	29	+	+	-	N	N	N	N	N	N	-	-	-	-	-	-									

C: Anti Hepatitis C virus; R: Hepatitis C virus RNA; A: Alanine aminotransferase; N: ND; [1]: Symptom and sign of hepatitis.

RT-nested PCR[6] was used for the HCV RNA PCR test, and the primers were from the 5′ untranslated region of the HCV genome. For the genotype PCR, the primers were from the core region[7] (Table 1).

HBsAg screening kits (RPHA) were provided by the Institute of Beijing Biological Products, and the conformative reagents were provided by the Beijing Sihuan Factory.

Definition of hepatitis and HCV infection

Clinical cases of HCV. were defined as patients who were positive for anti HCV, who had elevated alanine aminotransferase (ALT) level, and who had symptoms and signs of hepatitis.Subclinical HCV cases were defined as patients who were positive both for HCV RNA and anti HCV and who had elevated ALT, but who did not have symptoms and signs of hepatitis. Inapparent cases of HCV were defined as patients positive both for HCV RNA and anti HCV, but who had normal ALT levels.Anti-HCV antibody passive transfer cases were defined as newborns who were positive for anti HCV antibody initially, but subsequently anti HCV negative. Infection with HCV in utero was defined as the detection of HCV RNA in the liver tissue or heart blood of a fetus.

RESULTS

Infection of mothers

Between 1988 and 1990, we recruited 13 mo aged 22 to 40 years (mean: 28.6 ± 4.6 years) who suffered from PT-HCV. None of these mothers were infected with HBV. Table 3 shows the mothers' sera markers of HCV. During pregnancy, five cases had clinical HCV, one had subclinical HCV, six had unapparent HCV, and three were only anti HCV positive. All mothers had normal ALT levels at one month after delivery, but two cases still had symptoms and signs of HCV.

Infection of infants

Of the 15 infants (5 male, 9 female), seven were followed up for three years, six for one year, and two for nine months. The infection rate of HCV was 86.7% (13/15), and two infants (13.3%) were negative both for anti-HCV antibody and HCV RNA. Among the 13 infected infants, one (7.7%) had clinical HCV, 2 (23.1%) subclinical infection, and 9 (69.2%) inapparent HCV infection (Table 3). Table 4 summarizes the characteristics of anti-HCV antibody and HCV RNA during follow-up. The seroconversion rate was 100% before three months, with some starting to turn negative at six months, and the rate decreasing toy 33.3% at 18 mo. Anti-HCV was persistently positive in one infant over 36 mo (16.7%). The detection rates of HCV RNA were the same as that of anti-HCV antibody before 9 mo, but were 66.7% at 18 mo and 33.3% at 36 mo. We did not find cases of anti-HCV antibody passive transfer only, or re-positive cases after negative conversion.

The genotypes of 10 HCV RNA positive infants born to nine HCV RNA positive mothers were all of genotype Ⅱ.

Table 4 Serological profiles of infants during follow-up

Month(s)	Number	Anti hepatitis C virus antibody +		hepatitis C virus RNA +	
		Number	%	Number	%
1	12 (13)	12 (13)	100.0 (100.0)	12 (13)	100.0 (100.0)
3	9 (11)	9 (11)	100.0 (100.0)	9 (11)	100.0 (100.0)
6	10 (11)	9 (10)	90.0 (90.9)	9 (10)	90.0 (90.9)
9	11 (13)	6 (6)	54.5 (46.2)	5 (5)	45.5 (38.5)
12	12 (13)	3 (3)	25.0 (23.1)	5 (5)	41.7 (38.5)
18	6 (13)	2 (2)	33.3 (15.4)	4 (4)	66.7 (30.8)
24	6 (13)	1 (1)	16.7 (7.7)	2 (2)	33.4 (15.4)
36	6 (13)	1 (1)	16.7 (7.7)	2 (2)	33.3 (15.4)

Infection of HCV in uterine

Four fetuses from women who underwent induced labor were positive for both anti-HCV antibody and HCV RNA in cord and heart sera, and their liver tissues were HCV RNA positive as well. However, a fetus from a woman who was positive only for anti-HCV was uninfected with HCV, and the sera and liver tissues were all negative for anti-HC V and HCV RNA.

DISCUSSION

In this prospective study, we used a nested PCR for HCV RNA detection and a second generation ELISA for anti-HCV detection. The results suggest that the vertical transmission rate of HCV is high (86.7%). This vertical transmission can lead to clinical HCV, subclinical HCV, and inapparent infection. These results are consistent with the results reported by Thaler[4]. Our results also showed that the types of clinical manifestations and the duration of HCV RNA was related to the conditions of mothers in pregnancy.

Infants born to mothers with clinical HCV had a high rate of clinical HCV. Their HCV RNA and anti-HCV antibody could persist for a long time-as much as three years in 2. Furthermore, the clinical manifestations types of infants were related to the clinical manifestations of their mothers. One baby born to a mother who had acute HCV during pregnancy had clinical HCVs, with persistent viremia up to three years, but three babies whose mothers were had chronic or inapparent HCV during pregnancy showed inapparent infection and their HCV RNA and anti-HCV disappeared in six to nine months. The results suggest is indicated that mothers with acute hepatitis C transmit HCV to their babies at a high rate.

The grave consequences of vertical transmission of HBV are well known. The rate of vertical transmission of HCV is higher in our study, but mainly (69.2%) resulted in inapparent HCV, the virus was cleared in one year in most cases, and only a few (15.4%) were persistently positive for 3 years. These results suggested the consequence of HCV vertical transmission are not as serious as those associated with vertical HBV transmission. Unlike the transmission of HBV, the transmission of HCV mainly occurs in uterus. (1) The infants were all positive for anti-HCV antibody and HCV RNA at one month after delivery. (2) The detection rates of anti-HCV and HCV RNA decreased with with age. And (3) All of fetuses from For mothers with induced labor who were positive for anti HCV and HCV RNA, all of their fetuses were positive for anti-HCV and HCV RNA in heart sera, and one of those fetuses was HCV RNA positive in liver tissue.

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