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Mother to child transmission of hepatitis C virus: prospective study of risk factors and timing of infection in children born to women seronegative for HIV-1

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Abstract

Objective: To determine the risk factors for and timing of vertical transmission of hepatitis C virus in women who are not infected with HIV-1.
Design: Follow up for a median of 28 (range 24-38) months of babies born to women with antibodies to hepatitis C virus but not HIV-1.
Subjects: 442 mothers and babies, of whom 403 completed the study.
Main outcome measures: Presence of antibodies to hepatitis C virus and viral RNA and alanine aminotransferase activity in babies. Presence of viral RNA, method of infection with hepatitis C, method of delivery, and type of infant feeding in mothers.
Results: 13 of the 403 children had acquired hepatitis C virus infection at the end of follow up. All these children were born to women positive for hepatitis C virus RNA; none of the 128 RNA negative mothers passed on the infection (difference 5%, 95% confidence interval 2% to 7%). 6 children had viral RNA immediately after birth. 111 women had used intravenous drugs and 20 had received blood transfusions. 11 of the infected children were born to these women compared with 2 to the 144 with no known risk factor (difference 7%, 2% to 12%).
Conclusions: This study suggests that in women not infected with HIV only those with hepatitis C virus RNA are at risk of infecting their babies. Transmission does seem to occur in utero, and the rate of transmission is higher in women who have had blood transfusions or used intravenous drugs than in women with no known risk factor for infection.

Introduction

Mother to child transmission of hepatitis C virus has been extensively studied in mothers with HIV-1 infection.[1–5] Previous reports have shown transmission rates ranging from 5.6% to 36%,[1 2 5] and the importance of HIV-1 coinfection in mothers has been repeatedly emphasised.[2 5] Little is known about the risk of mother to child transmission of hepatitis C virus or the correlates and timing of infection in children born to women who are HIV-1 seronegative. We conducted a multicentre prospective study to assess this.

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Patients and methods

Nineteen centres participated in the study. All women who came to the centres during pregnancy were tested for hepatitis C virus antibodies. Women (and their babies) with confirmed hepatitis C antibodies but negative for HIV-1 entered the study. History of blood or blood product transfusions or intravenous drug use was carefully investigated by face to face interviews with experienced paediatricians using standardised questionnaires. Information was confirmed by reviewing medical and drug addiction service records. Twelve mothers admitted illicit drug use during pregnancy. Two babies had drug withdrawal symptoms after birth. Each mother decided whether to breast feed her baby. Caesarean section was decided for obstetric reasons independent of maternal hepatitis C infection.

Blood samples were taken for measurement of alanine aminotransferase, antihepatitis C virus, and anti-HIV-1 and for hepatitis C virus polymerase chain reaction. Samples were obtained from mothers at the time of delivery and from infants at birth or as soon as possible thereafter (but within three months after birth) and then at least three times during the follow up (median 28 months, range 24-38). Cord blood was never used for testing for hepatitis C virus. The definition of breast fed or exclusively formula fed children was as previously reported.[6] Children were considered infected when hepatitis C virus RNA was detected or when antibodies to the virus persisted beyond age 2 years or reappeared after having disappeared. Alanine aminotransferase concentrations were defined as raised if they were higher than twice the upper limit of normal.

Laboratory methods

Antibodies to hepatitis C virus were evaluated by second generation enzyme immunoassay (Ortho Diagnostic System, Raritan, NJ, USA) and confirmed by western blotting (Innogenetics, Zwijndrecht, Belgium). Hepatitis C virus RNA was determined by a cDNA polymerase chain reaction with nested primers from the 5′ untranslated region of the virus.[4] RNA was evaluated in plasma and in mothers' milk (supernatant and cells).

Viral genotypes were determined with a line probe assay (Innogenetics, Zwijndrecht, Belgium), and quantitative analysis of RNA was performed by Amplicor HCV monitor (Roche Diagnostic Systems, Branchburg, NJ, USA). When alanine aminotransferase concentrations were found to be raised, additional tests were performed to exclude metabolic and viral liver disease other than hepatitis C.

Table 1 Maternal risk factors and perinatal data in 403 mother-infant couples according to presence of hepatitis C virus RNA in mothers

	RNA positive (n=275)		RNA negative (n=128)	
Maternal risk factor	No (%) of women	95% CI (%)	No (%) of women	95% CI (%)
Intravenous drug use	111 (80)	73 to 86	28 (20)	14 to 27
Post-transfusional hepatitis	20 (63)	46 to 79	12 (37)	21 to 54
No known risk factors	144 (62)	56 to 68	88 (38)	32 to 44
Delivery:				
Vaginal	213 (68)	63 to 73	101 (32)	27 to 37
Caesarean	62 (70)	60 to 79	27 (30)	21 to 40
Feeding:				
Breast	87 (64)	57 to 71	49 (36)	28 to 44
Formula	188 (70)	65 to 75	79 (30)	24 to 35

Table 2 Presence of antibodies to hepatitis C virus in non-infected children born to mothers with and without hepatitis C virus RNA

Age (months)	No (%) born to RNA positive mothers	No (%) born to RNA negative mothers	P value
3-4	230/259 (89)	82/125 (66)	0.0002
7-8	115/257 (45)	41/120 (34)	>0.05
11-12	50/258 (19)	18/119 (15)	>0.05
15-16	12/255 (5)	0/117 (0)	>0.05
19-20	0/246 (0)	0/106 (0)	>0.05

Statistical analysis

Data were processed with the SPSSX statistical package. Ages and RNA copy numbers were reported as median and range. Differences were evaluated by the non-parametric Mann-Whitney U test. Differences in frequencies were evaluated by χ^2 test or Fisher's exact probabilities. Relative risks of infection (and 95% confidence intervals) and their significance were calculated with EpiInfo Statcalc.[7] Two tailed P values were used and values below 0.05 defined as significant.

Results

Hepatitis C virus antibodies were found in 442 out of 25 654 (1.7%) women. Thirty nine (8.8%) mother-child pairs dropped out, and 403 completed the study. Medical history and clinical data did not differ in pairs who dropped out and in those who completed the study. Median follow up in the 403 children who completed the study was 28 (24-38) months. Hepatitis C virus RNA was found in 275 of 403 (68%) mothers (table 1).

All the infants had antibodies to hepatitis C virus at birth, but all those who did not have hepatitis C virus RNA lost the antibodies within 20 months (table 2). The clearance was slower in babies born to mothers with viral RNA.

Thirteen children born to the 275 women with hepatitis C virus RNA acquired the infection and became RNA positive (transmission rate 5%, 95% confidence interval 2% to 7%), whereas no child born to RNA negative mothers was infected. Six children had hepatitis C virus RNA immediately after birth. The transmission rate was higher in 20 recipients of blood transfusions (10%, 3% to 17%) and in 111 women with a history of intravenous drug use (8%, 5% to 11%) than in 144 women with no known risk factor (1%, 0.4% to 2%). The relative risk of transmission in women with no known risk of infection was significantly lower (0.17%, 0.04% to 0.73%; P = 0.0063) compared with the risk in women who had been transfused or were intravenous drug users. Twelve mothers used drugs during pregnancy. One of their infants was infected with hepatitis C virus. Two infants had drug withdrawal symptoms; neither of them was infected.

Infection occurred in nine of 213 (4%) children born by vaginal delivery and in four of 62 (6%) born by caesarean section. The relative risk of infection in children born by vaginal delivery (0.65, 0.21 to 2.05) was not significantly different from that in children born by caesarean section (P = 0.498). Six out of 87 (7%) breast fed and seven of 188 (4%) exclusively formula fed children were infected (relative risk 1.85, 0.64 to 5.35; P = 0.358). Three out of six infected breast fed children had hepatitis C virus RNA detected on the day of birth.

Alanine aminotransferase abnormalities were found in all the infected children throughout the follow up. In five children concentrations fluctuated between normal and twice normal. In the other eight children concentrations were always higher than twice normal. In two of these eight children alanine aminotransferase concentrations had peaks more than 10 times normal.

Hepatitis C virus genotypes were analysed in all RNA positive babies and their mothers. Children and their mothers had identical genotypes: four had type 1a, six had type 1b, and one each had types 2a/2c, 3a, and 4c/4d.

Presence of virus was evaluated in all the mothers whose babies became RNA positive and in 258/262 mothers whose babies did not. There was no significant difference ($z = 0.380$; $P = 0.704$) in RNA load between mothers who transmitted the virus and those who did not (3.8 (0.02 to 56) $\times 10^5$ RNA copies/ml *v* 2.4 (0.01 to 92.7) $\times 10^5$ RNA copies/ml).

Discussion

Our study shows that vertical transmission of hepatitis C virus from HIV-1 negative mothers is infrequent (5%) but possible. In utero transmission of hepatitis C virus, which has been suggested,[8] seems to occur since about half of infected babies were RNA positive immediately after birth. All the other babies were RNA positive at first examination within three months of birth, and in utero infection cannot be excluded.

The percentage of viraemic mothers among antibody positive mothers is similar to that reported in another population positive for hepatitis C virus antibodies.[9] Intermittent viraemia is known to occur, and some women who were RNA negative immediately before delivery may have been viraemic during pregnancy. However, none of their children became RNA positive. In children born to RNA positive mothers the clearance of hepatitis C virus antibodies was slower than in children born to RNA negative mothers. This reflects the lower titres of antibodies found in RNA negative mothers (data not shown). The mean titre of antibodies has been shown to be higher in viraemic patients.[10]

Although asymptomatic, all infected infants developed alanine aminotransferase abnormalities during the first year of life, as reported in other studies.[1 2 11] Enzyme concentrations peaked between the sixth and 12th month.[11]

Delivery and feeding

Previous studies have suggested that vaginal delivery is a risk factor for vertical transmission of hepatitis C virus and HIV-1 and that caesarean section may reduce risk of HIV-1 infection.[12] We found no increase in the rate of hepatitis C transmission in children born by vaginal delivery, but the power of the study and absence of elective caesarean deliveries do not allow definite conclusions.

Other authors have reported absence of infection in breast fed infants,[2] even when hepatitis C virus RNA was found in mothers' milk.[13] Our results confirm that breast feeding does not represent a risk factor within the limits of the study's power. Six of the infected children were breast fed, but in only three could maternal milk be considered as a hypothetical source of infection since the other three were RNA positive at birth. Any viral RNA that is present in milk may be inactivated in the gastrointestinal tract or the viral load may be too low to infect the baby.

Source of maternal infection

The role of the source of hepatitis C infection in mothers is still unclear. Mothers who were found to have antibodies for hepatitis C virus during routine blood tests in pregnancy and who had no history of drug misuse or transfusions seemed to have a lower probability of infecting their babies. History of intravenous drug use itself, independent of HIV-1 infection, may be an important predisposing factor for perinatal transmission of hepatitis C virus. Immunological modifications have been described in drug users[14] that could lead to an enhanced risk of vertical transmission of hepatitis C virus. Moreover, placental damage occurs in drug using mothers, which might have a role in fetal infection.[14]

Our results are based on evidence of illicit drug use during pregnancy in only a few women. Some intravenous drug users may have been overlooked, but we are confident that most were identified because of the attention given to taking histories, the use of standardised questionnaires, and cross checks with medical records and records of drug addiction services. Even if one or two of the intravenous drug users were overlooked, this would not significantly bias the results since the risk of vertical transmission was about six times higher in intravenous drug users than in women with no risk factors.

Careful review of medical records makes underestimation of women who received blood transfusions unlikely. In mothers who had post-transfusional hepatitis a high viral load has been proposed as a possible risk factor for vertical transmission.[1] On the other hand, other authors could not find a correlation between infection in children and maternal viraemia.[2 5] Our data suggest that there may be a higher risk of vertical transmission in mothers with a higher viral titre, but the results were not significant. Previous reports showed that tests using branched DNA-1 detect viral RNA of types 2 and 3 with a lower efficiency than RNA of type 1.[15] Recently, similar differences in detection efficiency have been described for methods based on polymerase chain amplification such as the one we used.[16] Our results may therefore underestimate viraemia in mothers with non-type 1 infection. However, underestimation would be present to the same extent in mothers whose babies did and did not become infected. We conclude that viraemia does not seem to be an important risk factor in vertical transmission of hepatitis C virus and that other variables (possibly related to the source of infection[17]) may enhance the risk of transmission.

Genotype

Most of the mothers of infected children in our study had genotype 1b and 1a. The hepatitis C virus genotype pattern in the mothers of infected babies is similar to that found in a population of Italian adults with chronic hepatitis.[18] A study of patients with normal liver function, however, reported a predominance of genotype 2a.[19] Given the low rate of virus transmission the effect of

Key messages

- Little information exists on vertical transmission of hepatitis C virus in women not infected with HIV
- This study in a large unselected population of infants born to HIV-1 negative mothers suggests that intravenous drug use itself is an important risk factor for transmission of hepatitis C virus
- Maternal post-transfusional hepatitis is also an important risk factor for infection of infants
- Viral genotype, maternal viraemia, type of delivery (vaginal delivery or caesarean section) and breast feeding do not seem to be risk factors
- In utero transmission of hepatitis C virus has been suggested by RNA positivity on day of birth in some infected children

genotype cannot be easily separated from other maternal factors in transmission of hepatitis C virus.

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Contributors: MR initiated and coordinated the formulation of the primary study hypothesis, discussed core ideas, designed the protocol, and participated in clinical evaluation of patients, and analysis and writing of the paper. CA initiated and coordinated the formulation of the primary study hypothesis, discussed core ideas, designed the protocol, performed part of the laboratory tests, and participated in analysis and writing of the paper. FM and EN participated in the design and execution of the study, particularly data collection and documentation, interpreted the data, and contributed to the paper. MM discussed core ideas, participated in the protocol design, performed laboratory tests, participated in the analysis and interpretation of the data, and contributed to the paper. AV initiated the research and participated in study design, analysis, interpretation of the data, and writing the paper. MdeM participated in study design, data documentation, and statistical analysis, discussed core ideas, and contributed to writing the paper. All the authors gave their final approval to the revised version. Alison Evans gave statistical help, and Sergio Nanni, Wigi Sgarra, and Paolo Parigi gave technical help. MR is the study guarantor.

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Science commentary

Science commentary: Behaviour of hepatitis C virus

Hepatitis C virus was identified in 1989 in the United States. Parenteral and sexual transmission is responsible for most hepatitis C infection worldwide. There is a difference in carriage rate between hepatitis B and C. For example, over 80% of people infected with hepatitis C virus become chronic carriers compared with up to 20% of those infected with hepatitis B virus.

One possible explanation for this difference between the two viruses is that hepatitis C evades the immune system more easily than hepatitis B because it mutates more rapidly. This theory is supported by the observation that one person may be infected by several subtypes of hepatitis C simultaneously. Vaccine development will prove difficult for the same reason.

Fetomaternal transmission of the two viruses also differs. In mothers infected with hepatitis B virus the vertical transmission rate may be over 90%. The immaturity of the neonatal immune system at least partly accounts for this inability to mount an immune response sufficient to clear the virus. With hepatitis C virus, however, which has recently been shown to be present in the uterine muscle as well as in blood, vertical transmission is only about 6% (but higher if the mother is HIV positive).

The difference may be partly accounted for by the factors that influence infectivity of the two viruses. Hepatitis B is much more likely to be transmitted from mother to infant if there is a high concentration of the virus in the mother's blood. This explains the ethnic differences that are observed—for example, the transmission rate is over 70% in Chinese women but less than 10% in white women. This ethnic difference does not seem to apply to hepatitis C infection.

Alcohol intake and obesity are both thought to be associated with more severe hepatitis C, although the exact interaction is unknown. Advanced liver disease, for example, is far worse in people infected with hepatitis C who also have a high alcohol intake than in those with a low intake. About half of patients with hepatitis B infections respond to interferon compared with 15% with hepatitis C. Ongoing trials of interferon and antivirals together may prove more fruitful. Although infection with hepatitis C virus does not necessarily cause abnormal liver function, precirrhotic damage confirmed by biopsy is one reason for starting treatment with interferon.

Abi Berger *Science editor, BMJ*

Deliberate self harm: systematic review of efficacy of psychosocial and pharmacological treatments in preventing repetition

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Abstract

Objective: To identify and synthesise the findings from all randomised controlled trials that have examined the effectiveness of treatments of patients who have deliberately harmed themselves.
Design: Systematic review of randomised controlled trials of psychosocial and physical treatments. Studies categorised according to type of treatment. When there was more than one investigation in a particular category a summary odds ratio was estimated with the Mantel-Haenszel method.
Setting: Randomised trials available in electronic databases in 1996, in the Cochrane Controlled Trials Register in 1997, and from hand searching of journals to 1997.
Subjects: Patients who had deliberately harmed themselves shortly before entry into the trials with information on repetition of behaviour. The included trials comprised 2452 randomised participants with outcome data.
Main outcome measure: Repetition of self harm.
Results: 20 trials reported repetition of self harm as an outcome variable, classified into 10 categories. Summary odds ratio (all for comparison with standard aftercare) indicated reduced repetition for problem solving therapy (0.73; 95% confidence interval 0.45 to 1.18) and for provision of an emergency contact card in addition to standard care (0.45; 0.19 to 1.07). The summary odds ratios were 0.83 (0.61 to 1.14) for trials of intensive aftercare plus outreach and 1.19 (0.53 to 2.67) for antidepressant treatment compared with placebo. Significantly reduced rates of further self harm were observed for depot flupenthixol versus placebo in multiple repeaters (0.09; 0.02 to 0.50) and for dialectical behaviour therapy versus standard aftercare (0.24; 0.06 to 0.93).
Conclusion: There remains considerable uncertainty about which forms of psychosocial and physical treatments of patients who harm themselves are most effective. Further larger trials of treatments are needed.

Introduction

Prevention of suicide is now included in health policy initiatives in several countries, and reduction in suicidal behaviour, both fatal and non-fatal, is part of the Health for All targets of the World Health Organisation.[1] In the United Kingdom, reduction in the number of suicides is a central theme in the government's Health of the Nation strategy for England.[2] There is, however, a considerable lack of information as to which preventive strategies are effective.[3] Improvement of outcome after deliberate self harm is an important focus because at least 1% of patients presenting to general hospitals in the United Kingdom after deliberate self harm kill themselves within a year and 3-5% do so within 5-10 years. A history of multiple episodes of deliberate self harm is a particular risk factor.[4] Higher rates of suicide after deliberate self harm have been reported from other countries.[5 6] About half of all people who kill themselves have a history of deliberate self harm, an episode having occurred within the year before death in 20-25%.[7 8]

It would be difficult to investigate the effectiveness of intervention strategies after deliberate self harm in terms of subsequent actual suicides because extremely large populations of patients would be required. Repetition of deliberate self harm is, however, a reasonable proxy measure because of its strong associations with suicide. It is also in itself an important outcome because it occurs frequently,[9 10] indicates persistent distress, and results in considerable healthcare costs. Deliberate self harm is common in Europe[11] and in other parts of the world,[12 13] especially in young people. Recent marked increases in rates of deliberate self harm in the United Kingdom,[14 15] with a currently estimated 140 000 hospital referrals in England and Wales,[10] have highlighted the need for effective aftercare strategies.

Descriptive reviews of treatment outcomes in patients who deliberately harm themselves have been

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