High risk of HIV-1 infection for first-born twins

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To examine the epidemiology and natural history of mother-to-infant transmission of human immunodeficiency virus type 1 (HIV-1), especially genetic and intrapartum exposure factors, we obtained data on twins and triplets born to women infected with the virus.

40 investigators in nine countries contributed demographic, clinical, and epidemiological data on 100 sets of twins and 1 set of triplets. Among the 66 evaluable sets, HIV-1 infection was more common in first-born than in second-born twins (p = 0.004). In 22 sets, only one twin was infected (18 first-born, 4 second-born). 50% of first-born twins delivered vaginally and 38% of first-born twins delivered by caesarean were infected, compared with 19% of second-born twins delivered by either route. HIV-1 infection status tended to be concordant in more monozygotic (14 of 17 sets) than dizygotic (26 of 43) sets, but the frequency and clinical signs of HIV-1-related disease were similar in only 3 of the 10 sets with both children infected.

These findings suggest that some infants may be infected in utero before labour but that a substantial proportion of HIV-1 transmission occurs as the first twin encounters the cervix and birth canal. Such measures as cleansing of the birth canal and caesarean delivery before membrane rupture might reduce the risk of transmission for infants born to HIV-1-infected women and should be the subjects of controlled clinical trials. Caesarean section should not be regarded as a wholly preventive measure, however, since substantial proportions of both first-born and second-born twins delivered in this way were infected.

obstetricians, and infectious disease specialists. Contributors were asked to provide demographic, clinical, and epidemiological data on sets of HIV-1-infected women and their twin or triplet offspring. No names or other identifying information were obtained. The definition of HIV-1 infection was framed to include all children with an HIV-1-related disorder at any age or persistence of HIV-1 antibodies beyond age 15 months. Before that age, clinically well seropositive children, in addition to those who died without AIDS, were said to have indeterminate HIV-1 status. Absence of HIV-1 infection was defined as absence of antibodies and clinical disorders beyond age 12 months. The HIV-1 status in most infected and uninfected children was assessed by several laboratory tests, such as p24 antigen assays, HIV-1 cultures, or polymerase chain reaction with HIV-1 primers and probes. We used the Centers for Disease Control (CDC) classification system for HIV-1-related clinical disorders. Zygosity was clinically assessed for most twin sets.

Birthweights were compared by standardisation to the first-born twin (twin A). Similar results (not shown) were obtained with standardisation to the weight of twin B.

Data were analysed by McNemar's test for the matched twin pairs. The relation of the twins' HIV-1 status to zygosity was evaluated by pairwise concordance, conditional on infection of at least one twin, and the kappa (κ) statistic (standard error). Log-linear models were used to assess potential risk factors for HIV-1, adjusting for the correlation of infection status within twin pairs.

### Results

Data on 100 sets of twins and 1 set of triplets born to HIV-1-infected women were contributed to the registry by May 1, 1991. The 101 sets included 78 from the USA, 6 from France, 4 each from the Congo and the UK, 3 each from Italy and Spain, and 1 each from Australia, Puerto Rico, and Switzerland. Clinical studies on 2 of these sets have been reported previously. 35 sets lacked complete infection data: HIV-1 status was indeterminate for 62 children, 6 were infected, and 2 were uninfected. The table shows the HIV-1 status of the 66 sets with complete infection data. By matched-pairs analysis, HIV-1 infection was significantly more common in twin A than in twin B (p = 0.004).

HIV-1 infection was diagnosed in 16 of 32 (50%) first-born twins delivered vaginally and 10 of 26 (38%) delivered by caesarean, compared with 6 of 32 (19%) and 5 of 26 (19%), respectively, second-born twins. By matched-pairs analysis, twin A had a significantly higher risk of infection than twin B with vaginal delivery (p = 0.006) but not with caesarean delivery (p = 0.13). After adjustment for the high correlation between twins, the distribution of HIV-1 infection within sets was similar with vaginal and caesarean delivery (table). All 6 babies in the 3 sets with the first twin delivered vaginally and the second by caesarean were very small (birthweight 790–1380 g). Both twins of 1 of these sets were infected, and in another, only twin B was infected. Data on when the membranes ruptured were not available.

HIV-1 infection was slightly but not significantly more common in dizygotic than in monozygotic twins. HIV-1 status was concordant (both infected or both uninfected) in 14 of 17 monozygotic sets (κ = 0.56 [0.22]), compared with 26 of 43 dizygotic sets (κ = 0.16 [0.25]). Pairwise concordance was 50% (3 of 6) in monozygotic sets compared with 26% (6 of 23) in dizygotic sets. Discordance...
in birthweight seemed to be associated with a greater likelihood of HIV-1 infection when twin B was lighter, and the distribution of HIV-1 status in these sets differed significantly from that in sets with similar birthweights (p = 0.04, table). When at least one twin was infected, pairwise concordance was only 11% (1 of 9) for sets with similar birthweights, compared with 33% (2 of 6) when twin A was more than 10% lighter and 70% (7 of 10) when twin B was more than 10% lighter.

There was no significant association between the likelihood of HIV-1 transmission and gestational age, mother’s race, or mother’s transmission category and the distribution of HIV-1 status in these sets. A greater likelihood of HIV-1 transmission and gestational age was more than 10% lighter. Similar birthweights, compared with 33% (2 of 6) when twin A was infected, significantly from that in sets with similar birthweights. When at least one twin was infected, concordance sets (4 twin A, 1 twin B). By contrast, all offspring were uninfected in the 11 sets with caesarean delivery. For the remaining 3 sets, the route of delivery was not known, and 2 were vaginal/caesarean deliveries that resulted in 1 twin B infection. 13 sets were ascertained because of an HIV-related clinical diagnosis in at least one twin: 4 were concordant and 9 discordant (8 twin A, 1 twin B); by definition, none was concordant uninfected. Infection by route of delivery was similar—2 concordant infected sets and 4 discordant infected sets (all twin A) were vaginally delivered, and 2 concordant infected and 5 discordant sets (4 twin A, 1 twin B) were delivered by caesarean.

3 of the 9 sets of infected twins were reported to have similar HIV-1-related disorders, including 1 set with mildly symptomatic (CDC stage P2A) disease and 2 sets with Pneumocystis carinii pneumonia diagnosed within a month in both twins. AIDS was diagnosed in both twins in 3 other sets, but age at initial diagnosis differed in the siblings by 9–30 months, and only 1 pair had the same opportunistic infection. 1 of these pairs of twins had mild disease (CDC stages P1B and P2A), whereas in the other 2 sets the first-born twins were CDC stage P2A and the second-borns had AIDS diagnosed at ages 29 and 79 months, respectively. Discordance in HIV-1-related disorders seemed not to be related to zygosity. The triplets were all infected with HIV-1: triplets A and B had CDC stage P2A disease, and triplet C, who died aged 8 years, had oesophageal candidiasis, HIV-1-related encephalopathy, and extensive necropsy-proven Kaposi’s sarcoma.

**Discussion**

This analysis shows that birth order, route of delivery, and relative birthweights are associated with discordance in transmission of HIV-1 to twins. The risk of transmission was highest with first-born vaginal delivery (50%), followed by first-born caesarean delivery (38%), and then second-born delivery by either route (19%). These results will be difficult to confirm without additional sets of twins and further follow-up of those already registered. If accurate, however, the findings lead to two biologically important conclusions. Firstly, HIV-1 transmission to some infants probably took place at the time of delivery, since factors related to delivery affected the risk of infection. Secondly, it may be possible to reduce the risk of vertical transmission, since the risk of infection was much lower for twin B than for twin A, especially with vaginal delivery. If the factors were understood, they might be amenable to change by modified obstetric techniques.

We speculate that passage through the birth canal, an exposure of equal intensity in singleton and twin A deliveries, may lead to many, but not all, vertical HIV-1 infections. Although one study of singleton infants born to HIV-1-infected mothers recorded no difference in transmission by routes of delivery, five others have reported non-significantly lower transmission rates with caesarean than with vaginal delivery. Few of these reports provide data about important covariates, such as the indication for caesarean and time since membrane rupture.

Hepatitis B virus (HBV) data from Hong Kong support our birth-canal hypothesis. Among mothers who were carriers of HBV surface antigen (HBsAg), transmission increased with the length of first-stage labour when HBsAg was present in cord blood. In addition, HBsAg was detected in 96% of the vaginal fluid samples and 90% of samples of newborn infants’ gastric fluid, a combination that was associated with HBV infection detectable by age 3 months but not by age 1 month. HBsAg was found in only 26% of the amniotic fluid samples but was associated with HBV infection detectable as early as age 1 month. Thus, maternal-fetal transfusion by way of cord blood and oral ingestion of infectious vaginal fluid may account for a substantial proportion of the HBV transmissions. Twin deliveries have not been studied in large numbers for discordance in maternal-fetal transmission of HBV or other infections. Discordant transmission of herpes simplex virus or cytomegalovirus has been reported in a few twin sets.

Our study suggests that mixing of maternal and fetal blood is not the sole (and may not be the main) mechanism of HIV-1 transmission during delivery. Firstly, although attached to the placenta for a shorter time, twin A was at higher risk of infection than was twin B with vaginal delivery. Secondly, even with caesarean delivery twin A was at higher risk of infection than was twin B. Generally the lower twin in the uterus is delivered first by caesarean section. The time from rupture of membranes was long (data not available), the lower twin would have greater exposure to potentially infectious cervical and vaginal blood and mucus. Herpes simplex virus can ascend the genital tract to infect a singleton baby during labour if the membranes have been ruptured for longer than 4 h, which negates the benefit of caesarean delivery. Ascending group B streptococcus infection in utero has also been reported. Twin A also is accessible for fetal scalp monitoring, but preliminary data (not shown) do not suggest that it is a likely route of infection.

The route by which second-born twins become infected merits further attention. Our observation of a higher rate of concordant infections with lower birthweight in twin B suggests that transmission occurred well before delivery in twin B and at delivery in twin A. Although the risk for early infection must be similar for both twins, HIV-associated lower birthweight would be more difficult to detect in first-born twins if a substantial proportion were infected during passage through the birth canal. Johnson and colleagues reported that, in singleton pregnancies, infected infants had lower birthweight than did those who were not infected.

The risk of HIV-1 transmission by breastfeeding has not been established, but breastfeeding is the main mode of...
transmission of human T-lymphotropic virus type I to infants. It is possible that differences in feeding methods for twins A and B produced the observed discordance in HIV risk. However, most of the mothers in our study were intravenous drug users in developed countries, among whom breastfeeding is discouraged and seldom used because of potential exposure of the infants to drugs or HIV-1. Thus, breastfeeding probably had little effect on our analysis of twin pairs.

Because this is a retrospective study of a special population, the possible effects of selection or ascertainment bias or misclassification must be considered. Overall, HIV-1 infection was found in 32% of the twins or triplets born to infected women, which is within the range noted in prospective cohort studies of singletons.1-7 The true prevalence in twins is likely to be lower, as shown by an 11% transmission rate in the 32 sets that were ascertained as a consequence of the mother’s HIV-1 diagnosis. Nonetheless, the associations in the full data set seem valid. There were no infections among the 11 maternally ascertained sets delivered by caesarean. Moreover, among the 18 sets with vaginal delivery there were 3 twin-A-discordant sets and only 1 twin-B-discordant set. Missclassification of birth order is possible but would be more likely with caesarean than with vaginal delivery,28 and we verified birth order for most of the discordant sets by repeated correspondence and record review. In addition, we used matched-pairs analyses that are not affected by the ascertainment methods used.

Zygosity may have been misclassified for some of the sets of the same sex, since blood typing or other laboratory studies to confirm the clinical impression of genetic identity were not done in the monzygotic sets. However, the proportion of twins reported as monzygotic (28%) is similar to that expected for a predominantly black population.29 Concordance in HIV-1 infection status between twins was higher for monzygotic than for dizygotic twins, and this difference was almost significant by conservative kappa statistics.

Concordance in monzygotic twins suggests that genetic factors may affect an infant’s risk of becoming infected with the mother’s strain of HIV-1. Monzygotic twins also have a greater likelihood of vascular communications,26 but more than 3 monzygotic discordant infected sets would be expected if fetofetal transfusion were common. When both twins (or all three triplets) were infected, there was little concordance of AIDS and HIV-1-associated clinical disorders within either monzygotic or dizygotic sets. For future studies, we hope to characterise viral isolates from twin pairs and to confirm zygosity for the same-sexed twins. We plan a more rigorous statistical analysis of clinical disease progression as the study population grows older.

In addition to genetic factors, we propose that passage through, or at least proximity to, the birth canal is an important contributor to intrapartum transmission to HIV-1. During labour and vaginal delivery, twin A encounters the main barrier and most of the trauma, whereas twin B usually follows rapidly. It seems plausible that the mucous membranes of twin A may have greater exposure to potentially infectious secretions and blood than those of twin B, especially during dilatation of the cervix and passage through the birth canal. With vaginal delivery, twin A may “clean out” the birth canal, permitting twin B passage through the canal relatively free of virus. Our results suggest that caesarean delivery may be helpful if it can be done before the membranes rupture. However, 19% of our caesarean-delivered second-born twins were infected, so caesarean delivery is not panacea. Unless our data are independently confirmed, ideally in a controlled clinical trial, caesarean section should not be considered standard practice for HIV-1-infected women. In addition, we suggest a randomised, placebo-controlled trial to assess the efficacy of cleansing the birth canal, provided that irritation of the infant’s skin and mucous membranes can be kept to a minimum. If such an easy and cheap intervention were shown to reduce HIV-1 transmission, it would be well suited for all areas of the world.

REFERENCES


Stressful life events and Graves’ disease

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The role of stressful life events in the onset of Graves’ disease (toxic diffuse goitre) is controversial. However, the numerous early clinical reports that supported such an association were not adequately controlled and specificity of the diagnosis could be questioned. Later studies have not shown a causal relation, but these studies were small, did not have proper controls, or epidemiological methods were inappropriate. To assess possible associations between life events, heredity, social support, and Graves’ disease, we have done a population-based case-control study in a defined area with about 1 million inhabitants.

Over 2 years, 208 (95%) of 219 eligible patients with newly-diagnosed Graves’ disease and 372 (80%) of all selected matched controls answered an identical mailed questionnaire about marital status, occupation, drinking and smoking habits, physical activity, familial occurrence of thyroid disease, life events, social support, and personality. Compared with controls, patients claimed to have had more negative life events in the 12 months preceding the diagnosis, and negative life-event scores were also significantly higher (odds ratio 6·3, 95% confidence interval 2·7–14·7, for the category with the highest negative score). Individuals who had relatives with thyroid disease (especially first-degree and second-degree relatives) were more likely to have Graves’ disease (3·6, 2·2–5·9). Slightly more patients than controls were divorced (1·8, 1·0–3·3) and reported a less frequent intake of alcohol (0·4, 0·2–0·8). When results were adjusted for possible confounding factors in multivariate analyses, risk estimates were almost unchanged.

These findings indicate that negative life events and hereditary factors may be risk factors for Graves’ disease.


Introduction

The cause of Graves’ disease (diffuse toxic goitre) is largely unknown. Hereditary factors linked to the HLA

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