Unexplained HIV-1 infection in children — documenting cases and assessing for possible risk factors

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Background. In the year 2000 we reported possible horizontal transmission of HIV-1 infection between two siblings. An investigation of three families, each with an HIV-infected child but seronegative parents, permitted this finding. Sexual abuse and surrogate breast-feeding were thought unlikely. The children had overlapping hospitalisation in a regional hospital. Since then several cases of unexplained HIV infection in children have been reported. A registry was established at Tygerberg Children's Hospital for collection of data on the extent of horizontal or unexplained transmission of HIV in children.

Study design. Retrospective chart review.

Results. Fourteen children were identified, 12 from the Western Cape and 1 each from the Eastern Cape and KwaZulu-Natal. Thirteen (92%) had been hospitalised previously. In the Western Cape, children had been hospitalised in 8 hospitals. Ten of 13 (77%) were admitted as neonates and 9 of 13 (69%) had 2 or more admissions. Intravascular cannulation and intravenous drug administration occurred in all but 2 children before HIV diagnosis.

Conclusion. We have confirmed HIV infection in a number of cases where the source of infection has been inadequately explained. Circumstantial evidence supports but does not prove nosocomial transmission. Further studies and identification of medical procedures conducive to the spread of HIV are urgently needed.

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Children acquire HIV-1 infection through vertical transmission occurring *in utero*, during the birth process, or postnatally through breast-feeding.[1] Other well-recognised routes include contaminated blood products and sexual abuse.[2,3]

There are a number of reports from both First- and Third-World settings of unusual HIV transmission.[4-6] These include nosocomial incidents where needles had been reused and others where the cause was less obvious, but where access to a 'sharps' container was possible. HIV infection in the household was also documented.[4-6]

In a recent epidemiological survey of HIV prevalence in South Africa by the Human Sciences Research Council (HSRC), 86 HIV-positive children between 2 and 14 years of age were identified, of whom 27 were matched to a biological parent. Of 20 parents tested, only 5 (4 mothers and 1 father) were HIV-positive, suggesting by extrapolation that widespread horizontal infection was possible.[7]

Background

In 1999 we were informed of 3 HIV-infected children with seronegative parents from regional Hospital A. The possibility of sexual abuse was excluded by an experienced child abuse team. Through follow-up of the families we documented circumstances supporting horizontal transmission from an index case to his previously uninfected younger sibling.[8] We subsequently established a registry through publication in the *South African Medical Journal*, requesting information on cases of unexplained HIV-1 infection in children.[9] The Institutional Review Board of Stellenbosch University Faculty of Health Sciences approved establishment of the registry.

Voluntary counselling and testing and vertical transmission prophylaxis were introduced at Tygerberg Hospital in April 2002. Before this, infants were identified as HIV-exposed or infected only if the mother or child had been tested on clinical grounds or if a health care worker had sustained a needlestick injury.[10]

The aim of the present study was to document the circumstances around HIV-infected children with seronegative parents brought to our attention.

Methods

We conducted a retrospective study of children either from our own institution, Tygerberg Children's Hospital (TCH), or reported from elsewhere. All available medical and nursing notes were reviewed. An extensive history was taken from parents and caregivers by at least 1 of the authors in all cases from the Western Cape. Note was taken of the circumstances around the birth, especially identification of the infant at delivery and of circumstances where either surrogate breast-feeding or childhood sexual abuse (CSA) might have occurred. All patients presenting to TCH, Hospital A and Red Cross Children's Hospital (RCCH) were examined by experienced clinicians for anal or genital scarring and were referred to social services departments for expert evaluation.

Case definition

Our case definition for unusual infection was as follows: HIV infection confirmed by demonstration of either HIV-1 RNA or DNA by polymerase chain reaction (PCR) or p24 antigen by enzyme immunosorbent assay (EIA) in infants below 18 months of age or antibodies to HIV-1 by EIA if above 18 months of age, on at least 2 occasions; under 10 years of age at diagnosis; born to HIV-1 negative mothers or with previous HIV-negative serology; and no clear evidence of sexual abuse on history and examination.

Results

Sixteen children were identified. Two females were excluded. The first had a history of vaginal bleeding 4 years before presentation and although sexual abuse had been excluded through a social services investigation, we were unable to verify the information. In the second case we became aware of possible contact with an HIV-infected male from the same household.

Except for 1 case from the Eastern Cape and another from KwaZulu-Natal, all were from the Western Cape and were managed by at least 1 of the authors. Two investigators conducted telephonic interviews with the mother of the child reported from KwaZulu-Natal and with the paediatrician who referred the case from the Eastern Cape. The paediatrician had also submitted a written report, together with permission from the parents permitting our access to data.

A summary of clinical information is shown in Table I and diagnostic evaluations in Table II. All 13 mothers (2 children were siblings) were HIV-negative. In all cases where blood products were given, the blood bank was contacted and donors were re-tested confirming the absence of HIV infection. As at least a few months had elapsed between the blood donation and re-testing, the possibility of a blood donation during the 'window' period, before development of HIV-1 antibodies, was unlikely. Maternity was confirmed by HLA genotyping in 5 cases. All mothers, and 2 caregivers, were asked about the possibility of surrogate breast-feeding. Case 3 had possible

Table I. Age, clinical and immunological classification in children at time of diagnosis of unexplained HIV infection

Characteristic	Number ($N = 14$)
Age at diagnosis (median (range))	35 months (3 - 120 months)
CD4+ T-cell count (x 10^9/l) (median (range))	909 (118 - 1 830)
CDC clinical stage	
A	2
B	9
C	3
CDC immunological stage	
1	5
2	5
3	3
No CD4 T-cell count	1

CDC = Centers for Disease Control and Prevention.

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Table II. Diagnostic HIV investigations for 14 children with unexplained HIV-1 infection and their contacts

Individuals tested	Assay (result)	Results	Number
Cases tested before			
HIV diagnosis	EIA	Negative	4
Cases at diagnosis	EIA	All positive	14
	PCR	All positive	11
Mothers	EIA	All negative	13*
	PCR	All negative	7
Fathers	EIA (all negative)	All negative	10
	PCR (negative)	Negative	1
Siblings	EIA/PCR	5 negative	6
		1 positive (case 1)	
Caregivers	EIA	Negative	2
Blood donors	Blood transfusion services	Negative	4

*Two cases were siblings.
EIA = enzyme immunosorbent assay; PCR = polymerase chain reaction.

mucocutaneous contact with non-maternal breast- milk but may have already been HIV-infected at the time.

Case reports

Cases 1 and 4

An infant (case 1) was born by normal delivery and was breast-fed by his mother. He required admission to Hospital A for meningitis at 3 years of age and again 6 months later for cryptosporidial diarrhoea. HIV infection was diagnosed but both parents and his 16-month-old sibling brother (case 4) were HIV-negative.

Case 4 presented again at 31 months of age with severe persistent otorrhoea. HIV was confirmed, while both parents remained uninfected.

The family was referred to TCH for evaluation. Phylogenetic testing showed that the brothers were infected with the same strain of virus, indicating horizontal transmission. The brothers shared a bed. Infection probably occurred as a result of the HIV-infected infant having epistaxis and chronic otorrhoea at the time that his sibling had herpes stomatitis.[8]

Case 2

An infant was hospitalised in Hospital A for a day after a home birth. He was rehospitalised at 10 months of age with disseminated tuberculosis (TB). Therapy was continued at Hospital B, a TB sanatorium. At 15 months of age HIV-1 was diagnosed at TCH because of chronic lung disease.

Case 3

This infant was delivered by emergency caesarean section at 30 weeks' gestation in Hospital A. The mother presented with antepartum haemorrhage due to placenta praevia. He required intravenous antibiotics and fluids and was fed with maternal

expressed breast-milk. At 5 months of age, expressed breast-milk from the mother's friend was placed in his ear as a remedy for persistent otorrhoea. The donor was HIV-negative during subsequent investigation. He was rehospitalised at 6 months of age for pneumonia, again needing intravenous antibiotics. At 10 months of age HIV-1 infection was diagnosed.

Case 5

This male infant with fetal alcohol syndrome and posterior urethral valves was born in Hospital C and transferred to TCH. He required multiple surgical procedures and several blood product transfusions. Multiple episodes of sepsis were documented. At 8 months of age he tested negative for HIV-1 after a health care worker sustained a needlestick injury. At 26 months he was re-tested because of generalised lymphadeno-pathy, failure to thrive and hilar adenopathy. HIV-1 antibodies were detected. The health care worker involved in the needlestick injury was re-tested and remained negative for HIV-1.

Case 6

A male infant from the Eastern Cape born at 32 weeks' gestation was hospitalised for the first 3 days of life. No procedures were documented. At 19 months of age he presented with severe pneumonia and a history of intermittent diarrhoea at which time HIV infection was confirmed.

Case 7

A male infant born at 31 weeks' gestation was cared for at TCH and in a 'step-down' nursery in Hospital C. He developed rotavirus diarrhoea, necrotising enterocolitis (managed medically), several episodes of sepsis and had multiple blood transfusions. He required a central line for intravenous access. This infant had two negative HIV-1 EIAs during the first month of life, one because the mother had a positive rapid plasma reagin (RPR) test, and a second after a needlestick injury to a health care worker. At 3 months of age he required readmission to TCH because of viral pneumonia. He was re-tested for HIV after a needlestick injury to a health care worker and had HIV antibodies. The health care worker involved in the first needlestick injury was HIV-uninfected.

Case 8

A male infant born at 32 weeks' gestation in Hospital D was hospitalised for 2 weeks. He required readmission several times from 5 months of age for pneumonia and gastroenteritis. He also had severe upper airway obstruction due to enlarged adenoids. He was transferred to TCH intensive care unit after intubation for severe upper-airway obstruction. Antibodies to HIV-1 were detected.

Case 9

A 9-year-old girl was admitted to TCH with a pleural effusion.

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TB was diagnosed after a diagnostic thoracocentesis. She was transferred to Hospital C for 3 weeks. She presented 1 year later with a mild gastrointestinal upset. She tested positive for HIV after a needlestick injury to a health care worker.

Case 10

A term infant from KwaZulu-Natal was ventilated for 1 day because of respiratory distress. In the year preceding diagnosis of HIV-1 infection, she had repeated hospitalisations for impetigo, pneumonia and tonsillitis. Antibodies to HIV-1 were detected at 6 years of age.

Case 11

At 3 years of age this girl was admitted to Hospital E with TB meningitis. She received intravenous antibiotics and was negative for HIV-1 (history from the mother). Three years later she had a tonsillectomy at Hospital C. At 8 years of age she presented to TCH with generalised lymphadenopathy and had antibodies to HIV-1.

Case 12

This baby was born at term by vaginal delivery. On day 2 of life she was admitted to RCCH with haematocolpos requiring surgical intervention. At 3 months of age she was readmitted with severe pneumonia. HIV infection was diagnosed.[11]

Case 13

This term male infant was admitted to RCCH with prune-belly syndrome shortly after a normal vaginal delivery. He was readmitted at the age of 4 weeks with pneumonia. At 6 months he presented with pneumonia and hepatosplenomegaly. HIV infection was diagnosed.[11]

Case 14

A set of twins was born by vaginal delivery at TCH. At the age of 1 month, twin A was admitted to RCCH with gastroenteritis and presumed sepsis. His mother was tested for HIV infection and was negative. He was discharged after 41 days, but readmitted at the age of 4 months with hepatosplenomegaly and pneumonia. TB was diagnosed and he was referred to a community clinic for treatment. At the age of 7.5 months he was readmitted to RCCH with pneumococcal meningitis, at which time HIV infection was diagnosed.

Possible transmission in health care facilities

Hospitalisation preceded the diagnosis of HIV-1 infection in 13 of 14 cases. Hospitals included several regional and two tertiary institutions in the Western Cape. Both cases outside of the Western Cape were from the private sector. Possible risk factors for nosocomial transmission are summarised in Table III.

Table III. Admission data and possible risk factors for nosocomial transmission of HIV in cases with documented hospitalisation

Admission data and possible risk factors	Number (N = 13)
Single admission < 14 days	2
Single admission > 14 days	2
Two or more admissions	9
Neonatal admission	10
Intensive care unit admission	6
Blood transfusion	4
Intravenous access	12
Scalp vein access	2
Intravenous antibiotics	12
Surgical procedures*	3
Possible expressed breast-milk	10

*Two urogenital procedures and 1 tonsillectomy.

Outcome

Four patients died and 1 was lost to follow-up. Three patients do not yet require antiretroviral therapy and the rest are receiving triple therapy. Two of these have severe end-organ disease, 1 with chronic lung disease and the other with spastic quadriplegia.

Discussion

We have documented a number of cases of HIV infection in which the means of transmission was not clear. Any study of this nature faces the serious difficulty of establishing possible events and transmission risks of HIV, which occurred a long time before diagnosis of HIV, especially in a health facility. This study is an attempt to make sense of these incomplete data, to encourage further research and to make suggestions to decrease the risks in children admitted to hospital.

Maternity was confirmed through linkage analysis in 5 patients. CSA is extremely difficult to exclude. Perineal lesions associated with CSA may not be evident after a few months and occasionally even after a few days in approximately half of all cases. Many medical procedures such as haemoglobin and blood glucose monitoring at birth and routine childhood immunisation are poorly documented.

During the neonatal period and early infancy there is also a risk of giving HIV-infected expressed breast-milk. There is no record that the donor of expressed breast-milk correlated with the recipient. The amount of HIV in breast-milk is comparable to that in plasma and the virus remains stable at room temperature for at least 16 hours.[12] That some of the children from our survey received expressed breast-milk in hospital suggests an opportunity for inadvertently giving contaminated

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milk to an uninfected infant. Single or multi-user breast pumps could become contaminated between use (Gert Kirsten, Department of Paediatrics and Child Health, Stellenbosch University — personal communication). As much care should be taken with administration of expressed breast-milk as with blood products to ensure correct identification of donor and recipient. Guidelines for correct procedures for management of expressed breast-milk and care of breast pumps were implemented in 2002.[13,14] Surrogate breast-feeding is also not easy to exclude as one relies entirely on the history of the caregiver.

We have no knowledge of the HIV status of health care workers who cared for the patients, but although HIV transmission to patients is probably unlikely it has occasionally been reported.[15] Also, we did not document other possible risks such as dental procedures, scarification and body piercing.[16-18]

In the majority of these children, nosocomial transmission of HIV is a possibility. Brody *et al*.[19] and Gisselquist and colleagues[20] presented epidemiological evidence linking the spread of HIV infection in Africa to medical procedures. Reports have linked the spread of the Ebola virus with re-use of needles and syringes in underresourced African hospitals.[21]

To the best of our knowledge, needles and syringes are not re-used in South Africa. We have, however, witnessed the re-use of razor blades after brief immersion in chlorhexidine (Hibitane) solution for shaving infants' scalps before inserting intravenous cannulae. When a medication is administered intravenously to more than 1 patient a single syringe might be used, especially in the setting of a heavy workload and budgetary constraints. Intravascular lines are flushed with heparinised saline from multi-use vials after infusion of medication or withdrawal of blood. Health care workers could re-use syringes after attaching a new sterile needle when withdrawing saline, thus potentially contaminating the multi-use vial. One investigator witnessed such an incident, which has also been reported elsewhere in stressful situations.[22] HIV-1 adheres to erythrocytes, which are far more numerous than CD4+ T cells, thus increasing the range of cells that could transmit HIV.[23]

We have observed that clinical notes can become bloodstained after the leakage of blood from open-ended capillary tubes. Occasionally, patient linen is bloodstained. Although transmission through this route is unlikely, it reflects a failure to appreciate the seriousness of exposure to blood. HIV-1 decays slowly in whole blood and complete decay of infectivity in plasma may take up to 7 days.[24,25]

It is also possible that a re-usable device for percutaneous administration of bacille-Calmette-Guérin (BCG) vaccine may have inadvertently contributed to the spread of HIV. BCG is routinely administered to neonates within 1 - 2 days of birth. Before 1996, a re-usable tool was used for percutaneous

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administration. This device had strict guidelines for sterilisation between usage, either by autoclaving or immersing in gluteraldehyde.[26] This instrument was replaced by a disposable tool in 1996, and by intradermal injection with disposable syringes in 2000. While there is no evidence that sterilisation practices were not strictly adhered to, the re-usable tool created a risk of abuse, especially if there were insufficient tools available on a particular day. Even after the phasing out of the re-usable instrument, 1 of the authors noted their presence in some immunisation facilities (Neil Cameron — personal observation).

Equipment such as endoscopes may be re-used after sterilisation with gluteraldehyde.[27] Although the sterilisation process should be monitored regularly, this is often not done (S Mehtar — personal communication). The mechanical cleaning of equipment before autoclaving or cold sterilisation is also important for adequate sterilisation, but is often inadequately performed. Mucus and blood has been found in ventilator tubing, threads of catheter mounts and inside face masks (S Mehtar — personal communication). While anecdotal observations may be difficult to link with infection, they reflect the lack of expertise in this field. Even 70% ethanol, a commonly used disinfectant, has impaired ability to sterilise when applied to inadequately cleaned surfaces.[28]

The risk of transmission of HIV-1 to household contacts is estimated to be 0.2 - 0.7 infections per 100 years of contact.[29] In the only epidemiological investigation of horizontal transmission in Africa, Mann *et al*.[30] compared household contacts of recently hospitalised HIV-infected subjects with contacts from an orthopaedic ward in Kinshasa, Zaire. In the former, HIV-1 infection was present in 4.8% of non-spouse household contacts versus 1.6% in control households. Although not considered to support household spread, a reappraisal suggested that household spread was possible.[29] The risk, although small, increases if there is more than 1 HIV-infected person in a household and could be exacerbated by overcrowding and lack of indoor piped water. These conditions are more likely in African settings than in developed countries.

Conclusions

We have documented a number of cases of unexplained HIV infection in children, many of which may have been nosocomial. Although we cannot prove this, we feel that there is sufficient evidence to investigate this possibility. Epidemiological studies are necessary to document the extent of unexplained HIV infection in children in resource-poor settings.

There is an urgent need to re-evaluate and improve infection control practices in health care settings. Procedures for safe administration of expressed breast-milk should be widely disseminated. Infection control should receive high priority for

adequate funding so that personnel are continually trained and procedures regularly monitored.

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