Vertically transmitted HIV-1 infection in children

A report of 23 cases

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Summary

Twenty-three children with vertically transmitted human immunodeficiency virus type 1 (HIV-1) infection were seen at Baragwanath Hospital between May 1989 and April 1990. There was a marked increase in the number of cases in 1990. Infected children presented at a median age of 6 months; most commonly with lymphadenopathy, failure to thrive and respiratory complications. Serious bacterial infections occurred in 39%. Reversed helper T- to suppressor T-cell ratios were present in all but 1 of 16 children tested and hypergammaglobulinaemia and anaemia (usually normocytic) were frequently present. Some of the children have already died and the outlook for the others is bleak. With the increase of HIV infection in the heterosexual population, increasing numbers of infected children can be expected.

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The prevalence of human immunodeficiency virus type 1 (HIV-1) infection is increasing in South Africa.[1,2] The HIV seroprevalence rate in antenatal clinic attenders in Soweto has increased from 0,31% during the period March - October 1988 to 0,49% during May - October 1989 (South African Institute for Medical Research (SAIMR), Baragwanath Hospital — unpublished data). With the increased number of infected women of child-bearing age the number of vertically infected children can be expected to increase similarly. We report 23 cases that have been diagnosed at Baragwanath Hospital since our first case in May 1989.

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Patients and methods

The clinical and laboratory records of 23 infants diagnosed as having vertically transmitted HIV infection were reviewed. The children were tested for HIV on the basis of suspicious clinical features. Enzyme-linked immunosorbent assay (ELISA) serology (Abbott Recombinant HIV-1/HIV-2 EIA) was positive and this was confirmed by Western blot (SAIMR in-house transblotting; HIV-1 virolysate with commercial controls — Organon-Technika, Durham, NC, USA). All the mothers of the children were HIV-antibody positive, indicating mother-to-infant transmission. Antigen testing was not performed. T-cell subsets were performed using a Facscan Flow Cytometer (Becton Dickinson, Mountainview, California, USA).

Results

The incidence of cases of vertically transmitted HIV infection diagnosed, over the 12-month period from May 1989 is shown in Fig. 1. In the first 4 months of 1990 16 cases were diagnosed, representing 1,2% of admissions to the paediatric wards of Baragwanath Hospital. The median age of onset of symptoms was 4 months (range 19 days - 15 months) and the median age at diagnosis 6 months (range 20 days - 43 months). Eighteen of the children were male (78%). At the time of writing, 9 of the children are known to have died (median time from onset of symptoms to death 2 months), 7 are known to be alive and the rest have been lost to follow-up.

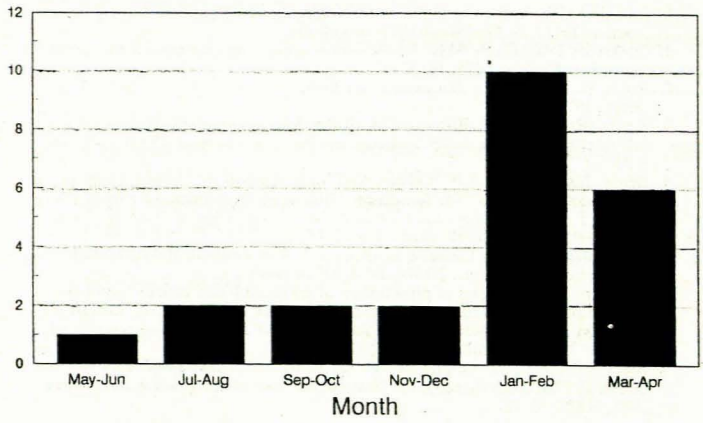

Fig. 1. Vertically transmitted HIV infection, Baragwanath Hospital, May 1989 - April 1990.

At least one of the parents of 5 children originated from beyond South Africa (viz. Zimbabwe, Malawi and Mozambique). The parents of 7 children were Soweto or Johannesburg residents. The rest of the parents came from other parts of South Africa, mostly Natal.

The clinical features present at the time of diagnosis are shown in Table I. The most common presenting features were failure to thrive and lymphadenopathy. Although some of the children did not have lymph nodes > 1 cm in size they were thought to have increased numbers in and involvement of unusual sites, such as epitrochlear and axillary areas. This was noted before the diagnosis of HIV was confirmed. Neurodevelopmental abnormalities were noted in 7 infants; 4 had developmental delay, 2 were abnormally floppy and 1 had developmental delay and was spastic. Four cases presented with 'mild' kwashiorkor and HIV infection was suspected because of wasting and lymphadenopathy. No cases of *Pneumocystis carinii* pneumonia were diagnosed. However, tracheal aspirates were obtained in only a few children and no children have undergone bronchoscopy or lung biopsy. No malignant disease was found.

TABLE I. CLINICAL FEATURES ON PRESENTATION OF 23 HIV-INFECTED CHILDREN

	No. present	%
Lymphadenopathy	**19**	**83**
Failure to thrive (or weight loss/malnutrition)	**19***	**83**
Cough	**17**	**74**
Hepatomegaly	**16**	**70**
Oral thrush	**15**	**65**
Diarrhoea	**15**	**65**
Splenomegaly	**13**	**57**
Respiratory distress	**10**	**43**
Fever	**10**	**43**
Recurrent serious bacterial infections	**9**	**39**
Neurodevelopmental abnormalities	**7**	**30**
Seborrhoeic dermatitis	**3**	**13**
Dysmorphism	**3**	**13**

* Includes 4 infants with kwashiorkor.

Bacterial infections

Nine of the children (39%) presented with serious bacterial infections. These included septicaemia in 3 (1 had three separate episodes caused by *Staphylococcus aureus*, *Salmonella* sp. and *Shigella*), lobar pneumonia in 2 (1 of whom grew *Streptococcus pneumoniae* on blood culture), prolonged or recurrent suppurative otitis media in 3 (1 of whom was only 20 days old) and 1 child with recurrent meningitis (*Haemophilus influenzae* type b) and recurrent septicaemia (*H. influenzae* and *S. pneumoniae*). *Mycobacterium tuberculosis* was isolated from a tracheal aspirate of a 7-month-old infant.

Viral infections

Viral bronchopneumonia was confirmed in 2 cases. One had serological evidence of influenza type B and measles virus was isolated from a tracheal aspirate of the other. This child was 1 month old, had no skin rash and died of respiratory failure. One child was positive for hepatitis B surface antigen (and e antigen) and cytomegalovirus was grown from the urine of 2 other children.

The HIV ELISA and Western blot tests were positive in all 23 infants and their mothers. Of 10 fathers, who were tested soon after the presentation of their children, 5 were HIV-positive. There was some evidence of abnormal immune function in all the children. T-cell subsets were performed in 16 children and 15 of these were abnormal. Fourteen of these 15 cases had raised immunoglobulin G (IgG). Thus 14/16 patients, in whom tests of both cellular and humoral immunity were performed, fulfilled the US Centers for Disease Control (CDC) criteria for HIV infection in children under 15 months of age.[3] The 7 patients, who did not have tests of cellular immunity, all had raised IgG levels.

Details of laboratory and radiological findings are presented in Table II. Total lymphopenia was rare. Fifteen of 16 children had reversed helper T- to suppressor T-cell ratios (i.e. T4/T8 < 1) but only 4 had absolute T4 counts of $< 1\,000 \times 10^6/l$. Of the children known to have died, only 1 had a low T4 count. All children tested ($N = 17$) had elevated levels of β_2-microglobulin. Most of the children were anaemic; 30% had microcytosis (with low serum iron) and the rest normocytic anaemia.

Lung infiltrates were seen in 70% of children of whom only 63% had signs of respiratory distress. The causes of these infiltrates were not determined in most cases but it was suspected that many of these were due to lymphoid interstitial pneumonitis (LIP). In some cases there was clinical improvement with standard antibiotic treatment, although the lung infiltrates rarely improved.

TABLE II. LABORATORY AND RADIOLOGICAL FEATURES ON PRESENTATION OF 23 HIV-INFECTED CHILDREN

	No.	%
White cell count > $15{,}0 \times 10^9/l$	**7**	**30**
Anaemia*	**21**	**91**
Haemoglobin < 8 g/dl	**8**	**35**
Platelets < $150 \times 10^9/l$	**3†**	**13**
Raised gammaglobulin*	**19**	**83**
Raised IgG†	**22**	**96**
Chest radiography		
Lung infiltrates	**15**	**68**
Hilar adenopathy	**6**	**27**
	Median	Range
Lymphocytes ($\times 10^9/l$)	**6,7**	**0,3 - 15,2**
Helper T cells ($\times 10^6/l$)	**1299**	**10 - 2639**
Helper T/suppressor T cells (T4/T8)	**0,3**	**0,01 - 1,4**
Beta 2-microglobulin (mg/l) (normal < 3 mg/l)	**4,6**	**3,1 - 6,1**

* Above/below the limits of normal for age.
† 2 children septicaemic.

Discussion

After the first diagnosed case of vertically transmitted HIV-1 infection in May 1989, a dramatic increase has been seen in the number of HIV-infected infants at Baragwanath Hospital. This is due partly to a true increase in incidence but also partly to an increased awareness of the illness in our department and consequently an increased number of children being tested.

Because of the transplacental transfer of antibodies, which can persist for up to 12 - 15 months,[3,4] the confirmation of infection in infants below this age can be problematical. The CDC has laid down criteria for the diagnosis of HIV infection in children.[3] For children under 15 months of age all three of the following criteria should be fulfilled: (*i*) positive HIV serology; (*ii*) typical symptoms; and (*iii*) laboratory abnormalities of both cellular and humoral immunity. Where tested, most of the children in our study fulfilled these criteria. However, 2/16 children had abnormalities of either cellular or humoral immunity but not both and thus did not fulfil the third-mentioned criterion. In our earlier cases T-cell subsets were not performed but all these children had evidence of abnormal humoral immunity (hypergammaglobulinaemia and/or raised IgG). We are of the opinion that abnormalities of either humoral or cellular immunity together with the first two criteria mentioned above are adequate evidence of HIV infection. This is particularly relevant in areas where T-cell function tests are not available.

The children in this series usually presented under the age of 1 year (median 6 months). Only 1 child was over 2 years at the time of diagnosis. This is in keeping with experience elsewhere.[5-7] In a large study from Miami,[8] in which children were followed up from birth, 57% of children presented at < 1 year and 23% at > 2 years of age. Our cases were of a younger age than in this report but the mean age of onset in any area can be expected to increase with time.[8,9] The marked preponderance of male infants in this series is unexplained.

The most common presenting features in our children were lymphadenopathy, failure to thrive and respiratory symptomatology. This is similar to other studies.[5-7,10] We have been especially impressed with the frequency of lymphadenopathy, not only because of the size of the lymph nodes but more because of their number and location. The finding of epitrochlear and numerous axillary glands (in addition to numerous inguinal and cervical lymph nodes) was common.

Serious bacterial infections were also relatively common and included septicaemia, meningitis, lobar pneumonia and suppurative otitis media. This last finding is not included in the CDC definition of serious bacterial infections[3] but we have included these cases because they were persistent or occurred at a very young age. Lung infiltrates were often present and, although we suspect that most of these were due to LIP, this was not histologically proven.

Four patients presented with kwashiorkor, which was thought to be 'mild', and because of significant lymphadenopathy and wasting HIV infection was suspected. One can speculate as to whether the kwashiorkor in these cases was primarily nutritional or was precipitated by the HIV infection.

The most frequently abnormal laboratory investigations were reversal of the helper T-/suppressor T-cell ratio, and elevated β_2-microglobulin and IgG levels. Low absolute helper T-cell numbers and total lymphopenia were uncommon even in children who subsequently died. Other common laboratory abnormalities included hypergammaglobulinaemia and normocytic anaemia. These findings are typical,[5,7,11,12] but anaemia, although common,[13] is often not emphasised.

Once illness has manifested itself, the prognosis is extremely bleak. Studies with a longer follow-up report a median survival after presentation of 9 - 38 months.[8,14-16] Our follow-up period is at present too short to determine life expectancy but a number of the infants died within 2 months of presentation.

Based on our experience, we recommend that HIV testing be performed on any child who has any of the following conditions that is otherwise unexplained: (*i*) generalised lymphadenopathy; (*ii*) hepatosplenomegaly; (*iii*) failure to thrive; (*iv*) recurrent or persistent respiratory 'infection'; (*v*) severe or recurrent oral thrush; (*vi*) recurrent serious bacterial infections; and (*vii*) hypergammaglobulinaemia or raised IgG levels.

HIV infection is on the increase in South Africa and we hope this report will heighten awareness and recognition of this infection in children.

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