

Paediatric HIV infection

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SUMMARY

HIV infection in children is a family disease, with social, economic and medical aspects that make it one of the most challenging diseases of our time. Knowledge about the factors involved in mother-to-child transmission and the natural history of the disease is gradually increasing although there is still much to understand. As the majority of children become infected through mother-to-child transmission, perinatally acquired infection will parallel increases in heterosexual transmission and the numbers of infected women of childbearing age. Current estimates of the rate of vertical transmission range from 14% to 39% in different studies. The relative proportion of transmission occurring in utero, peripartum or postpartum may vary in different localities and remains unclear. A study recently carried out in the USA showed that zidovudine given late in pregnancy, peripartum and in the neonatal period decreases HIV transmission from 25% to 8%. The clinical presentation of HIV infection in children depends in part on exposure to different infections. In developing countries the children usually present with nonspecific signs and symptoms, such as failure to thrive, chronic diarrhoea, cough and recurrent bacterial infections. Other common presentations include generalized lymphadenopathy, oropharyngeal candidiasis, dermatitis, enlargement of parotid glands and neurological problems, including delayed development.

Introduction

HIV (human immunodeficiency virus) infection in children is a family disease with social, economic and medical aspects that make it one of the most challenging diseases of our time. Knowledge about the factors involved in mother-to-child transmission and the natural history of the disease is gradually increasing, although there is still much to understand.

Magnitude of the problem

The number of children infected with HIV is increasing rapidly in countries where HIV has spread widely in adults, as most women who become infected are in the reproductive age group and the majority of children with HIV infection are infected through mother-to-child transmission. Perinatally acquired infection will therefore parallel increases in heterosexual transmission and the numbers of infected women of childbearing age. In some towns in sub-Saharan Africa up to 30% of pregnant women are HIV infected.

The World Health Organization (WHO) estimates that over one million children are infected worldwide. In Papua New Guinea (PNG) a total of 12 infected children had been reported to the STD/AIDS Unit of the Department of Health up till mid-1995. In the first 8 months of 1995 6 children were born in Port Moresby General Hospital (PMGH) to HIV-infected women.

In Uganda 24% of the children admitted to one of the hospitals in the capital, Kampala, were HIV seropositive.

Transmission

Infants and children can be infected with HIV in different ways (Table 1) but the most common mode of transmission in children is from mother to child (1). Not all children born to HIV-infected women are infected with HIV and accurate estimates of the vertical transmission rates can only be obtained from prospective cohorts of children born to infected women and followed from birth. Current estimates of the rate of vertical transmission

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TABLE 1**MODES OF TRANSMISSION OF HIV IN INFANTS AND CHILDREN**

- Vertical from mother to child:
before, during or after birth
- By contaminated blood or blood products
- By nonsterile needles or other skin-piercing
instruments
- Through sexual abuse

range from 14% to 39% in different studies. The relative proportion of transmission occurring in utero, peripartum and postpartum may vary in different localities and remains unclear. A recent evaluation of the sensitivity of PCR (polymerase chain reaction) in the neonatal period has shown that in populations where HIV-infected mothers are not

breastfeeding their babies, approximately one-third of vertically acquired HIV infection could be attributable to intrauterine transmission (2).

Breastmilk seems to play a small role especially when the mother acquires infection by blood transfusion during or soon after labour. The resulting high virus load may lead

TABLE 2**RISK FACTORS FOR PERINATAL TRANSMISSION****Maternal factors:**

- * A high maternal viral burden reflected by the presence of p24 antigen during the third trimester or at delivery gives a 3-fold increased risk of transmission
- * A CD4 count less than 400×10^6 is associated with a 3 times higher risk of transmission than a CD4 count over 700×10^6
- * The stage of disease of the mother: more advanced disease carries a higher risk of transmission
- * The presence of other infections may play a role

Infant factors:

- * Prematurity of the baby increases the risk of transmission

Other factors:

- * Mode of delivery: caesarian section carries a slightly lower risk of transmission than vaginal delivery
- * Breastfeeding (but benefits usually outweigh risks)

to transmission in the breastmilk. However, it is important to realize that in Papua New Guinea and other countries in which mortality rates from infectious disease in infancy and childhood are high, the substantial protective benefits of breastfeeding clearly outweigh, in most instances, the possible risk of transmission, and breastfeeding should be encouraged.

The risk factors for perinatal transmission, including maternal viral burden and low maternal CD4 count, are shown in Table 2.

A study recently carried out in the USA (3) showed that zidovudine given late in pregnancy, peripartum and in the neonatal period decreases HIV transmission from 25% to 8%.

Clinical presentation

The clinical presentation of HIV infection in children depends in part on exposure to different infections as well as the treatment and care available.

The spectrum of paediatric AIDS (acquired immune deficiency syndrome) described in the classification of HIV infection in children developed by the United States Centers for Disease Control and Prevention includes opportunistic infections, severe recurrent

bacterial infections, failure to thrive, encephalopathy and malignancies. Most of these opportunistic infections cannot be diagnosed in developing countries, so this classification is mostly used in the industrialized countries.

In developing countries the children usually present with nonspecific signs and symptoms, such as failure to thrive, chronic diarrhoea, fever, cough and recurrent bacterial infections (Table 3).

WHO has developed guidelines for recognizing HIV infection in children (4). These may be used where a health worker suspects HIV infection and where testing is not available or affordable or where the child is too young for the test to be accurate. These guidelines may be helpful for clinical management of the child and to alert the health worker to possible needs of the mother for counselling and care (Table 4).

These guidelines include a combination of cardinal, characteristic and associated findings in combination with epidemiological risk factors and, if possible, laboratory evidence of HIV infection.

They are developed for clinical management, and need to be evaluated in different countries as the clinical presentations

TABLE 3

COMMON MANIFESTATIONS OF HIV INFECTION IN CHILDREN

Neurological problems
 Delay in development
 Respiratory distress with chest infection
 Enlargement of liver and spleen
 Enlargement of parotid glands
 Recurrent abscesses
 Meningitis
 Herpes zoster and herpes simplex

TABLE 4

GUIDELINES FOR RECOGNIZING HIV INFECTION IN CHILDREN

A diagnosis of HIV infection in children is made if the following are present:

* Any **cardinal** finding:

Pneumocystis carinii pneumonia (PCP), lymphoid interstitial pneumonitis (LIP), Kaposi's sarcoma, oropharyngeal candidiasis

* Two or more **characteristic** findings:

recurrent infections, herpes zoster, cytomegalovirus infection, tuberculosis, neurological problems

* One characteristic finding and two or more **associated** findings:

oral thrush, failure to thrive, skin rashes, fever longer than 1 month, diarrhoea longer than 14 days, generalized lymphadenopathy

* Three or more associated findings and any **epidemiological risk factor**:

mother tested positive for HIV, sexual abuse, history of blood transfusion, use of contaminated needles or syringes

* Two associated findings and **laboratory evidence** of HIV infection in the child

vary in different settings and diagnostic facilities are not always widely available.

A second clinical case definition which is widely used was primarily developed for epidemiological purposes and includes a combination of major and minor signs (Table 5).

This definition too needs validation in different countries, as it is rather nonspecific and has a low positive predictive value. In PNG most children with tuberculosis would fulfil the criteria and cryptococcal meningitis does not occur exclusively in the HIV-infected population.

Because HIV infection presents as common childhood problems, differential diagnosis may be difficult, but one important difference between children who are HIV infected and noninfected is that the common conditions occurring in infected children do not respond so well to standard treatment: for example, pneumonia takes longer to respond to antibiotic treatment and malnutrition does not respond so

well to adequate food intake. This should raise suspicion of underlying HIV infection.

Laboratory diagnosis

In the past few years, using new but sophisticated and expensive virological and immunological techniques, it has become possible to make an early diagnosis of HIV infection in babies born to HIV-infected women in many centres in USA and Europe. Elsewhere, the presence of passively acquired maternal antibodies, which cross the placenta and may be detected in the child up to 15-18 months of age, makes the diagnosis of infection difficult and it is often not until after this age that a definite diagnosis can be made.

This means that a positive ELISA test, which tests for IgG antibodies, in an infant born to an HIV-positive mother does not necessarily mean that the child is infected. The child may only test positive because of the presence of maternal antibodies. A Western

TABLE 5**WHO CLINICAL CASE DEFINITION FOR PAEDIATRIC AIDS****Major signs:**

- Weight loss or abnormally slow growth
- Chronic diarrhoea of more than 1 month duration
- Prolonged fever of more than 1 month duration

Minor signs:

- Generalized lymphadenopathy
- Oropharyngeal candidiasis
- Repeated common infections
- Persistent cough
- Generalized dermatitis
- Confirmed maternal HIV infection

Definition:

Paediatric AIDS is suspected in a child presenting with at least 2 major signs associated with 2 minor signs in the absence of known causes of immunosuppression, such as cancer, malnutrition or other recognized aetiologies

blot test is not conclusive either, as this also tests for IgG antibodies.

A definite diagnosis of HIV infection in an infant needs techniques which test directly for the presence of virus, such as virus culture, polymerase chain reaction (PCR) or p24 antigen, tests which determine antibody production by the child, such as IgA or IgM, or tests which demonstrate in vitro production of HIV antibodies by the child's own cells. Usually a child is considered infected when 2 of these tests have been positive. Negative tests do not rule out infection.

The detection of IgA antibodies is a sensitive and specific diagnostic test by 6 months of age; the assay is simple, reproducible and relatively inexpensive and may provide a tool for early diagnosis of HIV in infants throughout the world.

Without a definitive virological diagnosis, the regular monitoring of immunoglobulins, CD4:CD8 ratio and clinical signs helps to establish the HIV status of the child.

In PNG only IgG antibody testing is available, so it is not possible to make a definitive diagnosis of HIV infection before the child is approximately one and a half years old.

Where sophisticated testing is available children who show no early clinical evidence of HIV infection or evidence of virus by culture, PCR or antigen testing and are antibody negative on at least 2 samples can be considered uninfected.

Management

The management of HIV-infected children differs greatly in different parts of the world,

TABLE 6

MANAGEMENT OF HIV-INFECTED CHILDREN

- * Treat infection as early as possible, using standard treatment guidelines
- * Maintain good nutrition -
 - advise on breastfeeding
 - advise on feeding a child with a poor appetite
- * Early diagnosis and treatment of suspected tuberculosis for all family members
- * Oral rehydration therapy during diarrhoea episodes to prevent dehydration
- * Regular growth monitoring
- * Immunize as usual -
 - the only contraindication is BCG to a child with AIDS
- * Give pain relief when necessary
- * Treat the child as normal -
 - playing with other children, schooling etc
- * Support for the family, especially for the mother

depending on available facilities. HIV-infected children can be managed in hospitals but are mostly cared for at home in their own communities.

Management in the USA and Europe includes the use of antiretroviral drugs such as zidovudine, which is standard antiretroviral therapy for children with symptomatic disease. No efficacy studies have been performed in children, although data from open-label studies suggest benefit in children with symptomatic disease, particularly in those with encephalopathy. Other antiretroviral drugs which are being used are didanosine (ddI), dideoxycytidine (ddC) and combinations of drugs.

Other treatment includes prophylaxis against *Pneumocystis carinii* infection for all HIV-infected children if an early diagnosis can be made – cotrimoxazole remains the drug of choice; and intravenous immunoglobulin, which may provide some protection against a wide range of bacterial and viral infections.

These measures are not all possible in PNG but this does not mean that we cannot do anything. Most HIV-related illnesses are caused by common infections which can be prevented or treated. However, they often last longer than in HIV-negative children and do not respond so well to standard treatment. The points which are important in care in PNG are summarized in Table 6.

One special aspect of management and care is the support for the family, especially for the mother, to help in coping with their complex psychological and social needs. The child may be the first family member to be diagnosed and parents may have to face the prospect of being tested. Mothers often feel an enormous sense of guilt at having infected their child. There is still tremendous stigma attached to a diagnosis of HIV and support is needed. Illness may affect the economic situation of the family. It is important to realize that whilst HIV infection cannot be cured in any country, care for patients and their families can be effectively given in resource constraint settings such as

PNG (5). Adequate care is essential to improve the quality of life.

Prognosis

The prognosis depends on several factors, such as age of presentation, severity of AIDS diagnosis and the availability of health care and drugs to treat opportunistic infections. When the age of presentation is looked at there seem to be two patterns of disease progression to AIDS. During the first year of life severe immunodeficiency associated with serious infections or encephalopathy occurs in approximately 20% of infected children. The remaining 80% have a slower progressive disease, similar to that observed in adults. In a New York study an estimated 14% of infected children progressed to AIDS in the first year and 11-12% annually thereafter.

The mortality varies in different studies. In the European Collaborative Study, mortality in HIV-infected infants was 15% and mortality by the age of 5 years was 28% (6). Data from Zaire (7) have shown that HIV-infected children have a 0.26 risk of death by the first birthday and 0.44 by the third birthday. Other estimates are that, worldwide, 40% of HIV-infected children die before their first birthday.

HIV-affected children and their families

HIV infection is a family disease and does not only affect the infected children and adults but also the noninfected children and family members. Noninfected children have an increased mortality rate because of the deteriorating health of the mother. WHO estimates that more than 5 million children will have lost their mother or both parents to AIDS by the year 2000. After their parents' deaths, children can lose their rights to the family land or to the house. Without education, work skills or family support, children may end up living on the streets and are then especially vulnerable, become sexually active and are at high risk of HIV infection.

Families face increased poverty and stress because adults are forced to leave their paid employment or may be unable to farm the land because of sickness. Women may be ill as well as caring for sick family members and looking after young children. Girls in particular often

become carers for sick relatives and younger brothers and sisters. The extended family members, especially grandmothers, need to look after their orphaned grandchildren and may be unable to meet the costs of extra food and school fees.

Different organizations try to help in different ways, such as organizing support for grandmothers who are looking after orphans, school fee programs and community support. These programs have to be carefully designed to prevent discrimination between AIDS orphans and children disadvantaged because of other reasons or between adopted AIDS orphans living with a family and the biological children of the adopting parents.

Support groups for HIV-infected persons have been developed which play an important role in the care of the HIV-infected persons themselves and also in AIDS control programs since many of these people are also valuable health educators in their own communities.

REFERENCES

- 1 **Gibb D, Wara D.** Paediatric HIV infection. *AIDS* 1994;8(Suppl 1):S275-S283.
- 2 **Dunn DT, Brandt CD, Krivine A, Cassol SA, Roques P, Borkowsky W, De-Rossi A, Denamur E, Ehrnst A, Loveday C, et al.** The sensitivity of HIV-1 DNA polymerase chain reaction in the neonatal period and the relative contributions of intra-uterine and intra-partum transmission. *AIDS* 1995;9:F7-F11.
- 3 **Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'Sullivan MJ, Van Dyke R, Bey M, Shearer W, Jacobson RL, Jimenez E, O'Neill E, Bazin B, Delfraissy JF, Culnane M, Coombs R, Elkins M, Moya J, Stratton P, Balsley J, for the Pediatric AIDS Clinical Trials Group Protocol 076 Study Group.** Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. *N Engl J Med* 1994;331:1173-1180.
- 4 **World Health Organization.** Guidelines for the Clinical Management of HIV Infection in Children. WHO Document WHO/GPA/IDS/HCS/93.3. Geneva: WHO, 1993.
- 5 **Appropriate Health Resources and Technologies Action Group (AHR TAG).** AIDS Action. The International Newsletter on HIV/AIDS Prevention and Care, Asia-Pacific Edition, Issue 27, Apr-Jun 1995.
- 6 **Peckham C, Gibb D.** Mother-to-child transmission of the human immunodeficiency virus. *N Engl J Med* 1995;333:298-302.
- 7 **Ryder RW, Nsuami M, Nsa W, Kamenga M, Badi N, Utshudi M, Heyward WL.** Mortality in HIV-1-seropositive women, their spouses and their newly born children during 36 months follow-up in Kinshasa, Zaire. *AIDS* 1994; 8:667-672.