CURRENT TOPIC

HIV infection in children

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The World Health Organisation has estimated that 10 million adults and one million children are infected with HIV worldwide.¹ Most of these infections will have been acquired through heterosexual contact and the increasing prevalence of HIV infection among women has implications for children as vertical transmission from mother to child is the major route by which children acquire infection.

The number of children with HIV and AIDS reported in the UK is shown in table 1.² There have been no new reports of HIV seroconversion in children with haemophilia since 1985 when blood donor screening for HIV and heat treatment of freeze dried factor VIII concentrate was introduced. This information comes from a multiple of sources including the British Paediatric Surveillance Unit active surveillance scheme, whereby paediatricians are asked to report on a monthly basis any HIV antibody positive children under their care.³ Recent data from anonymous unlinked test programmes of antenatal women⁴ and newborn infants as an indirect measure of infection in pregnant women,^{5,6} suggest that HIV prevalence in Scotland ranged from 2.5 per 1000 in Edinburgh, 1.4 per 1000 in Dundee, to 0.7 per 1000 in Aberdeen.⁶ In outer London the mean prevalence was one in 1400, in the south east it was one in 16 000,⁴ whereas in inner London the prevalence in pregnant women has increased fourfold in the last two years⁵ and is now one in 500. In antenatal clinics in other parts of the country only one test in 16 000 was positive.⁴

rates of transmission have been reported from some African studies.⁸ Evidence of the effect of maternal risk factors is scarce, but it has been suggested that the presence of symptomatic HIV disease in the mother, seroconversion during pregnancy, and an increased reliance on clinical diagnosis of HIV in the children may all contribute to the observed higher transmission rates in Africa.⁸ Prospective studies have so far not been able to indentify mode of delivery (vaginal or caesarean section) as a risk factor for transmission).

Postnatal transmission of HIV may occur via breast milk.⁹ However, the additional risk to the child of a woman who is already infected with HIV throughout pregnancy is unknown, although a recent report from Zaire suggests that it is small.¹⁰ In developing countries, where bottle feeding is associated with significant mortality and morbidity, the risk of transmission of HIV via breast milk is much less than the risk of bottle feeding itself.^{11,12} Finally, it has been suggested that breast feeding may delay the onset of symptomatic disease in the child infected with HIV.^{10,13}

Diagnosis of infection

Diagnosis of HIV infection in a child can be problematic, both in the infant born to an HIV positive mother and in the older child where HIV infection may be part of a wide variety of differential diagnoses.

Children born to HIV antibody positive mothers have no manifestations of infection at birth but all will have acquired maternal antibodies via the placenta and thus test HIV antibody positive at birth. Maternal HIV antibodies persist for a median of 10 months but may be present for as long as 18 months.⁷ As antiretroviral drugs and prophylactic antimicrobials become available for early use, the need to develop reliable methods for early diagnosis of HIV infection is becoming increasingly important.

Virological tests including viral culture, p24 antigen and the polymerase chain reaction, which detects and amplifies viral genetic material, are relatively insensitive in the first three months of life.¹⁴ In addition they are costly, time consuming, and not routinely available.

Immunological abnormalities including hyperimmunoglobulinaemia, abnormal T lymphocyte subsets with low CD4 numbers,

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Vertical transmission of HIV from mother to child

Vertical transmission can occur before, during, or shortly after birth, and the relative contribution of each of these routes is unknown. The European Collaborative Study recently reported a vertical transmission rate of 13% (95% confidence interval 9 to 16%).⁷ However, higher

Table 1 HIV infected children in the UK, end of July 1991

	Born to HIV positive mother (deaths)*	Haemophilia (deaths)†	Blood transfusion (deaths)	Total (deaths)
AIDS	43 (20)	14 (8)	6 (2)	63 (30)
Infected (not AIDS)	54	73 (1)‡	9	136 (1)‡
Total	97 (20)	87 (9)	15 (2)	199 (31)

*Deaths in brackets are included in the figures before them.
†Only children who are under 15 years of age as of July 1991 are included.
‡One child died of a non-HIV related cause.

and an inverted CD4:CD8 ratio may suggest infection,⁷ but the normal range of these parameters is poorly defined in infants, and such tests lack specificity. In the European Collaborative Study clinical manifestations that discriminated infected from uninfected children born to HIV positive mothers included oral candidiasis, persistent parotitis, and Gram negative septicaemia or pneumonia.⁷ Non-cryptosporidial diarrhoea, lymphadenopathy, fever, and hepatosplenomegaly were relatively non-specific.

In summary, although to date there is no single test that can definitively diagnose infection in the early months of life, by using a combination of virological and immunological tests with clinical examination at regular intervals in the first months of life, it is usually possible to obtain an indication as to whether or not a child is infected.

In the older child, the diagnosis of HIV may be suggested by a wide spectrum of symptoms and signs, many of which are non-specific (table 2). If the paediatrician decides that a child should be tested for HIV infection, informed consent should be obtained from the parents. The issue of pretest counselling is one which many paediatricians find inhibiting because of the distress it causes parents. However, by testing the child, the mother is also being tested, and it is important to discuss the implications of a positive test with the parents before embarking on testing. It is rare that a parent refuses to have a child tested if the child is symptomatic.

Natural history and characteristic manifestations of HIV

The natural history of children infected by transfusion or coagulation factors may differ from that of vertically infected children in both the duration of the incubation period and clinical pattern of disease. In the former group, the time from infection to the onset of AIDS is shortest in infants and older adults and longer in children, adolescents, and young adults.¹⁵ In addition, lymphocytic interstitial pneumonitis (LIP), which effects 30–50% of vertically infected children, appears to be less common in children with haemophilia.^{16 17} Thus in both these respects, the disease in children with haemophilia appears more closely to resemble that of adults.

Table 2 Manifestations of HIV disease

AIDS indicator diseases
Opportunistic infections
LIP
HIV encephalopathy
Severe recurrent bacterial infections
Severe failure to thrive
Malignancy
Other manifestations of HIV infection
Persistent/recurrent oral candidiasis
Persistent parotitis
Persistent diarrhoea
Persistent hepatomegaly/splenomegaly
Persistent generalised lymphadenopathy
Thrombocytopenia
Severe/recurrent varicella infection
Nephropathy
Cardiomyopathy

Approximately one third of children with vertically acquired HIV infection develop severe disease in the first year of life. The remainder have a more slowly progressive course, although nearly all show some manifestations of infection (clinical or immunological) by 12 months of age.⁷ In retrospective cohorts of children presenting to hospital with HIV disease, determinants of prognosis included both age at diagnosis and presenting symptoms.^{18 19} Thus children presenting under 1 year of age with opportunistic infections (mainly *Pneumocystis carinii* pneumonia) or HIV encephalopathy had a poorer survival than those presenting at an older age with bacterial infections or LIP. The highest incidence of *P carinii* pneumonia is in the first few months of life and this may be the first indication that a child is infected; it is associated with a high mortality rate.²⁰

Neurological disease due to HIV presents with regression of developmental milestones and/or progressive motor signs, often commencing with a spastic diplegia. The reported prevalence of neurological abnormalities in HIV infected children is higher in USA (50–90%)^{21 22} than in Europe (20–30%).^{7 19} This may be due in part to methodological differences in patient recruitment, but also to cocaine use in mothers of infected children in USA. The European studies reported abnormalities only after the development of immunosuppression and other severe manifestations of HIV or AIDS.

Recurrent bacterial infections, especially with polysaccharide encapsulated bacteria, have been reported to occur more frequently in children with HIV infection,²³ but there is no evidence that viral respiratory infections occur more commonly.

LIP is a slowly progressive chronic lung disease, characterised by reticulonodular infiltrates on the chest radiograph. The aetiology is unclear, but could involve Epstein-Barr virus²⁴ or HIV itself; further study is required. Despite abnormalities on the chest radiograph, the child may be asymptomatic initially with no abnormal findings on auscultation. Later shortness of breath, hypoxia, and digital clubbing may develop, although children rarely die of LIP alone. A definitive diagnosis is based on a lung biopsy specimen, but a presumptive diagnosis can be made from the characteristic chest radiograph appearances after other causes of interstitial pneumonitis have been excluded. However, differentiating LIP from other lung disease such as tuberculosis, bacterial infection, and *P carinii* pneumonia is not easy and it is prudent to perform a baseline chest radiograph in any HIV infected child to avoid later diagnostic difficulties.

Surrogate markers for disease progression

In children, markers of progression of disease have been less extensively studied than in adults. CD4 (T helper) lymphocyte counts are age dependent, being higher in infancy, and values have not yet been clearly defined in normal children. Although p24 antigenaemia was not shown to predict progression to AIDS in the first 12 months in the European Collabor-

ative Study,⁷ other studies have suggested otherwise.¹⁴ Further research in this area is required as such surrogate markers would be valuable as endpoints in clinical trials, particularly for treatments used in early HIV infection or asymptomatic children.

Management

FOLLOW UP OF THE CHILD BORN TO AN HIV POSITIVE MOTHER

Where a child is born to an HIV positive mother, the paediatrician should ideally have met the mother before the child is born to discuss issues such as breast feeding and difficulties with early diagnosis. The baby should be examined in the neonatal period and virological and immunological investigations performed. In addition, a urine and serum sample should be tested for cytomegalovirus to exclude congenital infection, and where maternal hepatitis B carrier status is unknown, hepatitis B status should be determined. At this time discussion about informing the general practitioner and health visitor if they do not already know should take place. Most mothers recognise the value of this, but are afraid that the information will be further disseminated to others. Good liaison between community and hospital personnel with discussion about confidentiality issues is important. In some circumstances the possibility of shared care with a specialist centre may be considered. Finally, as HIV may affect a number of family members, family centred care where all members of the family can receive medical and social care and follow up needs consideration. The role of 'family clinics' is likely to increase in the future.

Infants should be followed up at regular intervals of three months to identify any early manifestations of disease or immunosuppression and to determine the child's infection status. The mother, general practitioner, and health visitor should be aware that every referral is important if the baby becomes unwell, especially with respiratory symptoms suggestive of *P carinii* pneumonia.

MANAGEMENT OF THE CHILD WITH HIV INFECTION

The mainstay of management is close follow up in a multidisciplinary setting with prevention of infections by prophylaxis and vaccination, prompt treatment of bacterial and opportunistic infections, and if necessary, early nutritional support to prevent failure to thrive.

VACCINATIONS

The baby should receive all routine vaccinations including measles vaccination, at the normal time, and hepatitis B vaccine when indicated. It is preferable to give killed rather than live polio vaccine, because of the theoretical risk of transmitting live polio virus to other immuno-compromised family members. No adverse effects have been observed from either measles or live polio vaccines in HIV infected children. If the baby proves to be infected, vaccination against haemophilus and meningococcus is advisable. It has been demonstrated that asymptomatic children with HIV infection produce satisfactory antibody responses to measles vaccination but these may decrease with declining immune function,²⁵ so that immunoglobulin prophylaxis may be required after contact with measles or chickenpox. BCG should not be given to HIV symptomatic children, but there have been no adverse effects reported from giving it in the neonatal period to children subsequently found to be HIV infected.²⁶

Prophylaxis

P CARINII PNEUMONIA

Prophylactic treatment for *P carinii* pneumonia has not been evaluated in children with HIV infection. Extrapolating from adult data and from studies of *P carinii* pneumonia prophylaxis in children with leukaemia, co-trimoxazole (Septrin, Wellcome) given three times weekly is the drug of choice. However, in vertically infected children the incidence of *P carinii* pneumonia is high early in life, often before a definitive diagnosis of infection can be made. For example, six of the eight children reported with *P carinii* pneumonia in the UK developed the disease in the first six months of life, and six have died (C Davison, personal communication). Furthermore, whereas in adults *P carinii* pneumonia is rare if the CD4 count is above $0.2 \times 10^9/l$, it can occur in children with CD4 lymphocytes over $1.0 \times 10^9/l$. Guidelines for *P carinii* pneumonia prophylaxis in children, based on CD4 counts, have been recently issued (table 3).²⁷ Where such tests are not available, prophylaxis should be considered in any infected infant. For older children, phase I studies of pentamidine administration, using a modified Respigard II nebuliser, are commencing in the USA.

BACTERIAL INFECTIONS

Theoretically, immunoglobulin treatment provides passive antibody to protect against a wide range of infections. A recent US multi-centre, placebo controlled trial of monthly immunoglobulin reported a decreased incidence of bacterial infections, particularly invasive pneumococcal disease and clinically diagnosed acute pneumonia, but no reduction in mortality.²³ The authors commented that these results should not be interpreted as indicating that all children with HIV infection should receive immunoglobulin. Further evaluation is required to identify those children most likely to benefit. In the mean time, the risk of

Table 3 Guidelines for prophylaxis against *P carinii* pneumonia in paediatric HIV infection²⁷

Age	CD4 count ($10^9/l$)	
1-11 Months	<1.50	
12-23 Months	<0.75	
2-6 Years	<0.50	
>6 Years	<0.20	
Drugs		
Co-trimoxazole	{ Trimethoprim 150 mg/m ² Sulphamethoxazole .750 mg/m ²	Daily or three times weekly
Pentamidine	300 mg via Respigard II nebuliser	Monthly
Dapsone	1 mg/kg	Daily

bacterial infection in an individual child must be weighed against the disadvantages of frequent hospital attendance and regular insertion of cannulae. It is possible that daily co-trimoxazole prophylaxis, in addition to preventing *P. carinii* pneumonia, may be a useful prophylaxis against bacterial infections.

Antiretroviral therapy

The only antiretroviral drug currently available for treatment of children with HIV infection is 3'-azido-3'-deoxythymidine (AZT), although dideoxyinosine (DDI) and dideoxycytosine (DDC) are being evaluated in phase I studies in USA. AZT inhibits viral reverse transcriptase activity and has been shown to prolong life in symptomatic adults. It has also been shown to slow disease progression in asymptomatic adults with CD4 lymphocytes below $0.5 \times 10^9/l$.²⁸ There have been no studies of its efficacy in children but phase I and II studies in symptomatic children have suggested an increase in weight and well being and an improvement in HIV encephalopathy.²⁹ The criteria for commencement of treatment with AZT and at what dose remain unclear and practices vary widely. For this reason, a multicentre trial to answer these questions about AZT is to commence in Europe in the near future. This would be rapidly followed by other studies comparing monotherapy with combinations of antiretroviral drugs as well as trials of prophylactic drugs.

Conclusion

The prevalence of HIV infection in women and children is increasing and paediatricians need to become familiar with the disease. Although in the UK the size of the problem is still limited, the number of infected children is increasing. Now is the time to consider the organisation of services to provide regular, coordinated follow up of children born to HIV positive mothers as well as other family members. The issue of early diagnosis needs to be addressed, and collaboration with other European centres is needed to set up clinical trials for evaluation of antiretroviral and antimicrobial prophylactic treatments. Although some HIV infected children develop severe disease early in life, in many disease progression is slow. There is no evidence of casual transmission of HIV occurring in the school or playgroup setting³⁰ and children with HIV can attend as normal children do. Paediatricians need to be involved in dispelling the stigma and fear which surrounds this disease and enable children and their families with HIV to live as full lives as possible.

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