Disease in children infected with HIV in Abidjan, Côte d'Ivoire

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Abstract

***Objective*—To document the range of disease in African children infected with HIV.**

***Design*—Necropsy results in consecutive children aged 1 month or more who were HIV positive and in children who were HIV negative for comparison; IgA western blots on serum samples from children under 2 years of age who were positive for HIV-1 to test the validity of routine HIV serology.**

***Setting*—Largest hospital in Abidjan, Côte d'Ivoire.**

***Subjects*—78 children who were HIV positive and 77 children who were HIV negative on whom a necropsy was performed; their median ages at death were 18 and 21 months respectively. 36 HIV positive children and 29 HIV negative children were 1-14 months old; 42 HIV positive and 48 HIV negative children were ≥15 months old.**

***Main outcome measures*—Cause of death and prevalence of diseases confirmed pathologically.**

***Results*—Respiratory tract infections were more common in HIV positive than in HIV negative children (73 (94%) *v* 52 (68%); P<0·05), and were aetiologically heterogeneous. *Pneumocystis carinii* pneumonia was found in 11 out of 36 (31%) HIV positive children aged <15 months, but in no HIV negative children. Among older children measles was more common in HIV positive children (8/42 (19%) *v* 2/48 (4%); P<0·06). Pyogenic meningitis was present in similar proportions of HIV positive and HIV negative children aged <15 months (7/36 (19%) and 7/29 (24%)). In HIV positive children tuberculosis (1/78), lymphocytic interstitial pneumonitis (1/78), and HIV encephalitis (2/78) were rare.**

***Conclusions*—There is greater overlap between diseases associated with HIV infection and other common health problems in African children than there is in adults. Compared with adults, HIV positive children had a high prevalence of *P carinii* pneumonia and a low prevalence of tuberculosis. Measles, but not malaria, was associated with HIV infection.**

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Introduction

One million infants were infected with HIV at the end of 1993, most of them living in sub-Saharan Africa.[1] Around 25%-39% of infected African women transmit HIV to their offspring,[2] and HIV disease in children is now an important health problem in Africa.[3]

Syndromes of pulmonary infections, diarrhoea, and malnutrition are major causes of death,[4] but the causes are unknown because of the lack of a clinical infrastructure.[5] Necropsies, though concentrating on advanced disease, provide information that cannot otherwise be obtained. We report a systematic study of the diseases associated with HIV infection in children in a large west African city. At this time the prevalence of HIV infection in children in hospital was 7% (KM Vetter, 7th International Conference on AIDS in Africa, Yaounde (Cameroon), December 1992).

Subjects and methods

The study compared necropsy findings in children who died in Abidjan according to HIV seropositivity. It took place in the mortuary of the largest hospital in the city, to which most children who die in the hospital and in the community are brought. The clinical diagnoses of children who had been in hospital were limited; few laboratory or radiological investigations were performed.

To obtain a representative sample for necropsy, serological testing for HIV was performed on all children admitted to the mortuary during the eight months between August 1991 and May 1992. The age of children was determined from hospital records or, if not known, from measurement of crown-heel length and previously plotted data on age and height. A length of 56 cm indicated an age of less than 1 month [6]; the upper age and height limits were 12 years and 140 cm. Necropsies were performed on all children who could possibly have been HIV positive and on a similar number of randomly selected children of similar age and height who were HIV negative.

SEROLOGICAL TESTING

Blood samples from children in the mortuary were screened with a rapid, mixed antigen assay for HIV-1 and HIV-2, with supplemental testing by enzyme linked immunosorbent assay (ELISA), a synthetic peptide based assay, and western blotting.[7] To evaluate the reliability of routine HIV serology in detecting active infection rather than maternal antibodies in young children under 15 months old[2 8] a western blotting for IgA antibodies was performed.[9] Samples from 42 out of 51 children who were HIV-1 positive and under 2 years of age were tested (nine serum samples were not available).

NECROPSY METHODS

Complete necropsies were performed with removal of the brain. Respiratory tract lesions with giant cells or viral inclusions were evaluated for specific virus infections by immunocytochemistry for adenovirus, measles, herpes simplex 1 and 2, cytomegalovirus, and respiratory syncytial virus. HIV-1 p24 antigen was sought in brain sections of all children positive for HIV-1. In situ hybridisation for Epstein-Barr virus early RNA indicated the presence of Epstein-Barr virus.[10] Diagnosis of HIV encephalitis was based on finding multinucleate giant cells, associated with microglial nodules or leucoencephalopathy.[11]

As multiple disease was common we calculated the overall prevalence of individual lesions. We determined the main pathological cause of death, excluding malnutrition, for each child.

Results

DEMOGRAPHIC AND SEROLOGICAL DATA

Twenty per cent (80/408) of the children admitted to the mortuary during the study were HIV positive. Overall, 155 children (78 boys, 77 girls) had a necropsy; 78 were positive and 77 negative for HIV infection. The median age at death at necropsy of children of known age was 18 months for those who were HIV positive and 21 months for those who were HIV negative (range 3 months to 8 years for both groups).

Of the 78 children who had a necropsy and were positive for HIV infection, 76 were reactive to HIV-1 and two were reactive to HIV-2. Thirteen of the 14 children aged between 15 and 24 months who were positive for HIV-1 had IgA antibodies to HIV-1 on western blotting; 22 out of 28 who were under 15 months old were IgA positive.

PATHOLOGICAL DATA

Table 1 lists the prime causes of death among the children. Table 2 shows the prevalence of malnutrition and of specific diseases. Pathological findings in HIV positive and negative children were broadly similar with certain exceptions. *Pneumocystis carinii* pneumonia, toxoplasmosis, herpes simplex infection, multinucleate giant cell encephalitis, and lymphocytic interstitial pneumonitis occurred only in children who were HIV positive. Lymphoreticular malignancies occurred only in children who were HIV negative (4/77). In children positive for HIV, lymphocytic interstitial pneumonitis[8] and opportunistic infections that defined the development of AIDS were found in 24 of the 36 (67%) children under 15 months old and in 12 of the 42 (29%) older children.

Respiratory tract diseases were the dominant causes of death in all children, particularly among those who were HIV positive (52/78 (67%) *v* 22/77 (29%); odds ratio 5·0 (95% confidence interval 2·4 to 10·5)). The causes were diverse. Pyogenic pneumonia, non-specific interstitial pneumonia, and bronchiolitis were common. Pneumocystis pneumonia was found in 11 of the 36 (31%) children under 15 months old who were HIV positive and was restricted to those under 1 year old. Measles giant cell pneumonia was more common in the older children positive for HIV infection than in the children who were HIV negative (8/42 (19%) *v* 2/48 (4%); odds ratio 5·4 (0·97 to 39·6)). Adenovirus and herpes simplex pneumonia were each seen once among children who were HIV positive. One child of 33 months who was HIV positive had lymphocytic interstitial pneumonitis associated with Epstein-Barr virus. Miliary tuberculosis was seen in one child of 18 months who was HIV positive and in two children aged 36 months and 8 years who were HIV negative. Respiratory syncytial virus was not identified in any children.

Malaria was more common in children who were HIV negative than in those who were HIV positive. Pyogenic meningitis was the cause of death in 20 children overall and was more prevalent in children under 15 months old than in older children (14/65 (22%) *v* 6/90 (7%); odds ratio 3·9 (1·4 to 11·3)). There was no difference in prevalence according to whether children were HIV positive or negative. Pyogenic infections were observed in 48 children who were HIV positive (30 children were aged 15 months or older) and in 31 children who were HIV negative (17 were aged 15 months or older).

HIV multinucleate giant cell encephalitis was found in two of the 78 (3%) HIV positive children, both of whom were over 15 months old. HIV-1 p24 antigen was present in mononuclear cells of the brain in four of the 78 (5%) children positive for HIV infection. Other specific encephalitides were restricted to children who were HIV positive: three had toxoplasmosis, one cytomegalovirus, and one measles encephalitis.

No child had giant cell hepatitis, atypical mycobacteriosis, cryptosporidiosis, Kaposi's sarcoma, progressive multifocal leucoencephalopathy, cryptococcosis, or cerebral lymphoma.

Respiratory tract disease was found at necropsy in 39 out of 43 (91%) children with a clinical diagnosis.

Table 1—*Causes of death in children at necropsy. Values are numbers (percentages) of children*

	Age 1-14 months		Age ≥ 15 months	
	HIV positive (n=36)	HIV negative (n=29)	HIV positive (n=42)	HIV negative (n=48)
Malaria	2 (6)	5 (17)	1 (2)	13 (27)
Pneumonia*	12 (33)	4 (14)	20 (48)	13 (27)
Measles	5 (14)	3 (10)	8 (19)	2 (4)
P carinii pneumonia	8 (22)	0	0	0
Meningitis	7 (19)	7 (24)	4 (10)	2 (4)
Enteritis	1 (3)	2 (7)	5 (12)	2 (4)
Other	1 (3)	8 (28)	4 (10)	16 (34)

*Excluding *P carinii* and measles

Table 2—*Prevalences of specific diseases in children at necropsy. Values are numbers (percentages) of children*

	Age 1-14 months		Age ≥ 15 months	
	HIV positive (n=36)	HIV negative (n=29)	HIV positive (n=42)	HIV negative (n=48)
P carinii pneumonia	11 (31)	0	0	0
Pyogenic pneumonia	12 (33)	11 (38)	21 (50)	13 (27)
Non-specific interstitial pneumonitis and bronchiolitis	9 (25)	7 (24)	5 (12)	7 (15)
Lymphocytic interstitial pneumonitis	0	0	1 (2)	0
Tuberculosis	0	0	1 (2)	2 (4)
Measles	5 (14)	3 (10)	8 (19)	2 (4)*
Malaria	3 (8)	5 (17)	3 (7)	18 (38)†
Enteritis	10 (28)	4 (14)	13 (31)	10 (21)
Pyogenic meningitis	7 (19)	9 (31)	4 (10)	3 (6)‡
Cerebral toxoplasmosis	2 (6)	0	1 (2)	0
HIV encephalitis	0	—	2 (5)	—
Cytomegalovirus infection	16 (44)	3 (10)	8 (19)	2 (4)‖
Adenovirus infection	0	1 (3)	1 (2)	0
Severe malnutrition	17 (47)	6 (21)	26 (62)	14 (29)‖
All respiratory tract infections	36 (100)	21 (72)	37 (88)	31 (65)

*P < 0·06, HIV positive *v* HIV negative children (both aged ≥ 15 months).
†P < 0·05, HIV positive *v* HIV positive children (both ages).
‡P < 0·05, children < 15 months *v* children ≥ 15 months (both groups).
‖P < 0·05, HIV positive *v* HIV negative children (both ages).

Pyogenic meningitis was underdiagnosed: nine out of 14 (64%) cases found at necropsy were unsuspected. Among the 30 children diagnosed as having malnutrition, disease was diverse and not related to HIV seropositivity. All had pathological evidence of severe malnutrition. Of two children clinically diagnosed as having tuberculosis, one had miliary tuberculosis and the other lymphocytic interstitial pneumonitis.

The causes of death in the seven children who were HIV-1 positive but IgA negative were pneumocystis pneumonia (three), cytomegalovirus pneumonitis (one), desquamative interstitial pneumonia (one), toxoplasma encephalitis with HIV-1 p24 antigen in mononuclear cells (one), and pyogenic meningitis (one).

Discussion

In Africa infant mortality in children born to mothers infected with HIV is increased by 15%-26%[4 12]; mortality at 5 years in children infected with HIV is projected to be 50%-75%.[3] Although clinical reports emphasise the importance of pulmonary infections, diarrhoeal diseases, and malnutrition,[4 5 13 14] this is the first study that we know of that compares disease at death in a representative sample of African children according to HIV seropositivity.

Despite the lack of virological evidence of HIV infection in children under 15 months old, most such children seemed to be genuinely infected. Significant differences existed between the diseases among HIV positive and negative children in the youngest age group (inclusion of children under 15 months old who had only maternal antibodies would have weakened these differences). A high rate of IgA antibodies to HIV (79%) was found in children of this age who were seropositive on routine serology; necropsies showed diseases that were indicative of AIDS in most children who were positive for HIV but negative for IgA.

CAUSES OF DEATH

Respiratory diseases were the predominant causes of death in children infected with HIV and were aetiologically heterogeneous. A prevalence of 31% for pneumocystis pneumonia in children infected with AIDS who were under 15 months old contrasts with that of 3% described in adults positive for HIV at necropsy in Abidjan[15]; to our knowledge, no other published data on paediatric pneumocystosis associated with HIV infection in Africa exist. In industrialised countries 43% of children with AIDS have pneumocystis pneumonia, the median age of presentation is under 6 months, and mortality is high.[16 17] Surprisingly, the frequency of pneumocystis pneumonia associated with HIV infection in young children in Abidjan is comparable with that in North America and Europe.

Measles is a major cause of death in west Africa, mainly affecting children aged 6-18 months.[18] Unvaccinated children under 9 months old who are HIV positive are at increased risk of acquiring measles,[19] and mortality from measles in children infected with HIV is higher.[20] We found an increased prevalence of measles, predominantly with pulmonary disease, in children aged 15 months and older who were infected with HIV, suggesting an increased susceptibility to severe measles disease in this group.

COMPARISON WITH OTHER STUDIES

Three conditions were surprisingly uncommon in children infected with HIV[4]: lymphocytic interstitial pneumonitis, HIV encephalitis, and tuberculosis. In industrialised countries lymphocytic interstitial pneumonitis has a benign prognosis and presents at an average age of 29 months.[21] The prevalences of HIV encephalitis and identifiable HIV-1 antigen in brain were 3% and 5% respectively, compared with rates of 38% for HIV encephalitis in studies in industrialised countries.[11] Selection bias towards inclusion of children with encephalopathy in other studies and early mortality in African children may account for some of this discrepancy. Our cross sectional study cannot provide evidence for a bimodal clinical evolution of HIV disease in children as observed elsewhere,[22] but it is striking that pathological evidence of HIV encephalitis was rare while pneumocystis pneumonia was common, both these syndromes being predictive of early death in industrialised countries.[22]

Other studies in Africa have reported the prevalence of HIV to be 12%-37% in children with tuberculosis.[23 24] Of the 78 children who had a necropsy, only one (1%) had tuberculosis, in contrast to the overall prevalence of tuberculosis of 38% in adults dying of HIV infection in Abidjan.[15] With an annual risk of tuberculosis infection of about 2% in many African countries, most children infected with HIV will die without having been exposed to *Mycobacterium tuberculosis*, and this organism is not as important an opportunistic agent for children as for adults with HIV infection.

Meningitis was a common cause of death in both HIV positive and negative children. The relative lack of malaria among HIV positive children reflects the high mortality under 2 years of age from diseases related to HIV infection.

CONCLUSIONS

In summary, overlap exists between the clinicopathological presentations of HIV disease and other common health problems in African children. Recognition of HIV disease is difficult and the usefulness of a verbal necropsy in distinguishing the cause of death in children dying of diseases related to HIV infection is questionable.[25] Although respiratory infections and malnutrition dominate the clinical picture, the underlying pathological conditions are varied, and *P carinii* pneumonia is common. Differences between the diseases of AIDS in industrialised and African countries seem less extreme in children than in adults.[15]

Specific chemoprophylaxis against pneumocystis pneumonia, investigation and treatment of specific opportunistic infections, and use of antiretroviral drugs are impossible in most African health facilities. The data suggest that vaccination programmes,

Key messages

- There are few data on the diseases associated with HIV infection in children in Africa
- In regions with a poor clinical infrastructure necropsy provides information that cannot be obtained otherwise
- This survey of children aged under 1 month to 12 years who died in Abidjan, Côte d'Ivoire, found that a fifth were positive for HIV infection with a median age at death of 18 months
- Almost a third of HIV positive children under 15 months old had *Pneumocystis carinii* pneumonia, a rate similar to that found in affected children in industrialised countries but much higher than the rate in affected adults in Abidjan
- Measles was more common in children who were HIV positive, suggesting that vaccination would be a feasible intervention

especially against measles, should be pursued vigorously. For all children the management of acute respiratory infection, malnutrition, and enteric disease requires strengthening, as does the appropriate management of malaria and meningitis.

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Conflict of interest: None.

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Single or multiple daily doses of aminoglycosides: a meta-analysis

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Abstract

***Objective*—To assess relative efficacy and toxicity of aminoglycosides given by single daily dose compared with multiple daily doses.**

***Design*—Meta-analysis of 21 randomised trials identified through MEDLARS (1966 to January 1995). Data were overviewed with fixed effects and random effects models and with meta-regression analysis.**

***Subjects*—Total of 3091 patients with bacterial infection, most without pre-existing renal disease.**

***Interventions*—Patients were randomised to receive aminoglycosides once daily or multiple times daily with similar total daily dose.**

***Main outcome measures*—Clinical failure of treatment, nephrotoxicity, ototoxicity, and mortality.**

***Results*—Single daily dose regimen produced a non-significant decrease in risk of antibiotic failures (random effects risk ratio 0·83 (95% confidence interval 0·57 to 1·21)). Benefit of once daily dosing was greater when the percentage of pseudomonas isolates in a trial was larger. Once daily administration reduced risk of nephrotoxicity (fixed effects risk ratio 0·74 (0·54 to 1·00)). Similar trends were noted for patients with febrile neutropenia and for children. There was no significant difference in ototoxicity between the two dosing regimens, but the power of the pooled trials to detect a meaningful difference was low. There was no significant difference in mortality.**

***Conclusions*—Once daily administration of aminoglycosides in patients without pre-existing renal impairment is as effective as multiple daily dosing, has a lower risk of nephrotoxicity, and no greater risk of ototoxicity. Given the additional convenience and reduced cost, once daily dosing should be the preferred mode of administration.**

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Introduction

Aminoglycosides have potent activity against Gram negative bacilli and are often used to treat infections caused by these species, especially when resistance to beta lactam antibiotics is suspected. However, use of aminoglycosides is limited by concerns about toxicity, primarily nephrotoxicity and ototoxicity. The drugs are usually administered intravenously in two to four doses a day in patients with normal renal function. A once daily dose is more convenient and has been proposed to be an equally effective and potentially less toxic mode of administration.[1-4]

Numerous randomised trials have compared a single daily dose with multiple doses of aminoglycosides in hospital inpatients. Although a few studies showed one or the other regimen to be of superior merit,[1,5] most found no significant difference in efficacy or toxicity between the two regimens. Individual trials, however, have been of relatively small size, and their power to detect a significant difference in outcome was low. Thus, although there is evidence from in vitro and animal studies to suggest that administering aminoglycosides once daily is advantageous, the validity of