Original Article

Clinical Profile and Natural History of Children with HIV Infection

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Abstract. ***Objective :*** As the HIV infection spreads in India, increasing number of children are affected. We report the clinical manifestations, the laboratory parameters and follow up of these children. ***Methods :*** We reviewed case records of all children diagnosed as pediatric HIV infection since 1995 in our department at a tertiary care hospital in north India. Since September 1999, all children with HIV infection registered in our clinic were prospectively followed up. Complete clinical and laboratory evaluation was performed at baseline and thereafter children were followed up. The children were managed according to standard treatment guidelines. ***Results :*** 109 children (82 boys, 27 girls) were diagnosed to have HIV infection. The median (range) age at presentation was 48 months (range: 0.75 months – 180 months). Eighty one (74.3%) children acquired the infection vertically. Ninety-one (83.5%) children were symptomatic at time of presentation. The common symptoms in the former were failure to thrive (81.3%), recurrent fever (73.6%), diarrhea (50.5%) and recurrent or persistent pneumonia (44%). All children had poor nutritional status at baseline. Of the 67 children who followed up, 36 were receiving antiretroviral drugs (32 received 3 drugs), while families of 31 children did not opt for antiretroviral therapy. Children receiving antiretroviral therapy showed improvement in nutritional parameters. ***Conclusion :*** Majority of children with HIV infection presented with various clinical manifestations, poor nutritional status and immunosuppression. Administration of nevirapine based antiretroviral therapy leads to improvement in growth and immune restoration. **[Indian J Pediatr 2006; 73 (3) : 201-204]**
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HIV infection has become a pandemic. At the end of 2003, it was estimated that 40 million individuals were infected globally, of which 2.5 million (6.2%) were children below 15 years of age.[1] Of the 3 million deaths due to HIV in 2003, 0.5 million (17%) occurred in children below 15 years. Ninety-five percent of the infected individuals are from in the developing countries. The estimated numbers of people living with HIV/AIDS in India by the end of 2003 were 5.1 million; of which 0.55 lakh (1.1%) were children below 15 years.[2] In the light of this trend, various authors have reported their experience regarding pediatric HIV infection in India.[3-7] Most of these studies have reported on the presenting manifestations, with little information on follow-up. We report the clinical manifestations, the laboratory parameters and follow-up of these children.

MATERIALS AND METHODS

We reviewed the case records of all children diagnosed with pediatric HIV infection since 1995 till March 2003 in our department at a tertiary care hospital in north India. Since September 1999, all children with HIV infection registered in our clinic were followed up.

In children over 18 months of age, the diagnosis of HIV infection was confirmed by three positive ELISA (enzyme linked immunosorbent assay) tests according to the WHO strategy III.[8] The three different ELISA kits used were provided by National AIDS Control Organization (NACO). Polymerase chain reaction (PCR) was used to diagnose HIV infection in children younger than 18 months age. PCR for 'gag' and 'env' regions was performed on peripheral blood mononuclear cells. The test was repeated to confirm the diagnosis. Antigen (p24) detection was relied upon for diagnosis in 3 cases.

We recorded the demographic details, clinical features at presentation, and diagnostic information. The details of management and follow-up were recorded. The presumed mode of transmission was arrived at on the basis of confidential interview with the parents regarding high risk sexual behavior in parents, history of blood transfusion in parents and child and the HIV serology status of parents.

All children underwent the following investigations: complete blood counts, serum chemistry, chest radiograph and tuberculin test (considered positive if the induration was >5 mm). CD4 counts, estimated by flow cytometry, could be done in 65 children. CD4 percentage

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was not available in many children and therefore has not been analyzed.

The children were managed as per standard guidelines for children with HIV infection.[9, 10] Children with tuberculosis were treated with two months of intensive therapy (isoniazid, rifampicin, pyrazinamide, ethambutol), followed by four to seven months of daily isoniazid and rifampicin. Antiretroviral therapy was offered to HIV-infected children with clinical symptoms of HIV infection or evidence of moderate or severe immune suppression based on absolute CD4 counts.[9, 10]

Immunizations, antitubercular prophylaxis with isoniazid, *Pneumocystis carinii* pneumonia (PCP) prophylaxis with cotrimoxazole were advised according to the available guidelines.[11, 12] Nutritional counseling was provided to all children.

RESULTS

Between January 1995 and March 2003, 109 children (82 boys, 27 girls) were diagnosed to have HIV infection. The median (range) age at presentation was 48 months (range: 0.75 months – 180 months). Thirteen children were less than 18 months of age, 43 were between the ages of 18 months and 5 years, while 48 were aged 5 years or more at presentation. Forty-four children were residents of Delhi, 21 were from Uttar Pradesh, 18 from Haryana, 9 from Bihar, and the rest from other neighboring states.

Eighty-one (74.3%) children acquired the infection vertically. In 21 (19.3%) children, blood/blood product transfusion was the possible mode of transmission. The route of acquisition of infection could not be determined in 7 children; the parents were seronegative and the child had not previously received any blood/blood product. Of the 81 children with presumed vertical transmission, mothers of 13 were possibly infected by transfusion either during a surgical procedure or delivery; in all these cases, the fathers of the children were seronegative and history of high-risk behavior in the mothers was not reported. In the rest, history of high-risk sexual behavior was forthcoming from the father. None of the children had received any prophylaxis for prevention of parent to child transmission.

Most children (60.6%) were diagnosed in our clinic on the basis of clinical suspicion. 26.6% children were identified by screening when HIV seropositive parents requested for the screening of their children. Fourteen children were referred to us after a diagnosis of HIV infection was confirmed elsewhere.

In 98 children, the diagnosis of HIV infection was based on ELISA. Only two of these children were less than 18 months; the mothers of these children were seronegative, ruling out perinatal transmission. Polymerase chain reaction was used to confirm the diagnosis in 8 children, while antigen detection was used in 3 children.

Fathers of 18 children had succumbed to their illness, while mothers of 12 had died due to HIV infection/AIDS.

Ninety-one (83.5%) children were symptomatic at the time of presentation; 18 were asymptomatic. The common symptoms in the former were failure to thrive (81.3%), recurrent fever (73.6%), recurrent diarrhea (50.5%) and recurrent or persistent pneumonia (44%) (Table 1). Lymphadenopathy, hepatomegaly, pallor and splenomegaly were the commonest clinical findings (Table 1). Six children had features of encephalopathy at presentation. Twenty-nine children had tuberculosis, and 10 of them had miliary/disseminated disease. Mantoux test was positive (>5 mm) in only 4 children. Lymphoid interstitial pneumonitis (LIP) was suspected in three children.

TABLE 1. Clinical Features of HIV Infected Symptomatic Children (n=91)

Clinical sign/symptom	No. (%) positive
Failure to thrive	74 (81.3)
Fever	67 (73.6)
Recurrent/Persistent LRTI	40 (44)
Recurrent diarrhea	46 (50.5)
Lymphadenopathy	61 (67)
Hepatomegaly	58 (63.7)
Oral Candidiasis	24 (26.4)
Splenomegaly	40 (44)
CNS involvement	6 (6.6)
Bronchiectasis	10 (11)

All children had poor nutritional status at baseline. The median (95% confidence interval) weight for age 'z-score' was –2.35 (₴.68, –2.09), height for age 'z-score' –2.68 (-3.15, –2.38), weight for height 'z-score' –1.01 (-1.19, –0.62), and body mass index 14.81 (14.34, 15.35).

Forty-one (37.6%) children had features of clinical category C, while category A features were present in 34. Reports of CD4 counts were available in 65 children; 26 had severe immunosupression, while 15 had normal counts (Table 2). CD8 counts were available in 49 children; 43 of these had CD4: CD8 ratio of less than 1, while only 2 children had a ratio of more than 2.

Forty-eight children had hemoglobin of less than 10g/dl. Albumin: globulin ratio was reversed in 37 out of 60 children where values were available.

The mean follow up was 7.7 $\pm$ 13.5 months (range:0-72 months). Forty-two children did not follow up at all; in the other 67 children, the mean follow-up was 12.6 $\pm$ 15.4 (range: 0.25- 72 months). Of these 67 children, 36 were receiving antiretroviral drugs (32 received 3 drugs), while families of 31 children did not opt for antiretroviral therapy.

The mean age at which ART was initiated in children was 73.3 $\pm$ 40.1months (range 15- 164 months). The mean age at presentation of the children who were started on ART was 64.92 $\pm$ 34.59 months (range: 14- 142 months). The mean age at presentation of children who received

TABLE 2. Classificaton of Children with HIV Infection

Clinical category (n = 109)		Immune category Category*	(n = 65)
N	18 (16.5%)	No immunosupression	15 (23.1%)
A	34 (31.2%)	Moderate immunosuppression	24 (36.9%)
B	16 (14.7%)	Severe immunosuppression	26 (40%)
C	41 (37.6%)		

*Reference[13]

ART compared with that of children not receiving ART was similar (p=0.09). There was a difference in the age at presentation and the age at start of ART for various reasons: some patients had TB at presentation and we completed the antitubercular therapy before starting ART; some families took some time for arranging funds for ART.

The most commonly used regimen was a combination of stavudine, lamivudine and nevirapine. The fixed drug combinations for use in adults were adminstered after determining the most appropriate fraction to satisfy the dosing requirements.

Pneumocystis carinii prophylaxis was started in 60 children. Eight children were advised prophylaxis against recurrent bacterial infections. Twenty-nine children with tuberculosis received ATT. Eight children received anti-fungal prophylaxis.

The mean follow-up in children who came after first visit was 12.6± 15.4 months (range 0.25- 72 months). The mean (range) follow-up in children who did not receive ART was 6.7 ± 8.6 (0.24- 44) months, while that in children receiving three drug ART was 17.5 ± 18.5 (0.5- 72) months.

We compared the median weight for age 'z-scores' at baseline with that of the last follow up. In children not on any ART, the value changed from –2.30 (-2.7, -1.96) to –2.21 (-3.3, -1.76), while for those on ART, this changed from –2.55 (-2.86, -2.16) to –1.9 (-2.4, -1.1); both these changes were statistically not significant. Similarly, in children not on any ART, the median height for age 'z-scores' changed from –2.72 (-3.35, -2.31) to –3.08 (-3.5, -2.67), while that in children receiving ART changed from –2.53 (-3.3, -2.2) to –1.19 (-2.67, -0.56); these changes were not statistically significant. However, weight for height in children receiving three drug ART improved from –1.11 (-1.46, -0.8) to 0.08 (-1.06, 0.38) [p=0.012].

The freqencies of LRTI, acute gastroenteritis, requirement for antibiotics and hospitalization in children who followed up were lower in children receiving antiretrovirals but the differences were minimal and not statistically significant (p>0.05).

The mean ± S.D. CD4 counts changed from 745.4 ± 473/ mm^3 at baseline to 372 ± 111.5/ mm^3 at last follow-up in children who did not receive any ART (p=0.06). In children receiving ART, the mean CD4 counts at baseline were 576.5± 644.4/ mm^3, and these improved to 614 ± 455.7/ mm^3 at last visit (p=0.66).

Sixty-seven children were followed up after first visit. Of these, in the group receiving ART, one child died during the follow-up and two children were lost to follow-up. In children not on ART, 2 children died and 7 were lost to follow-up. Of the 36 children receiving ART, 2 developed herpes zoster, 2 varicella, 2 chronic diarrhea and 1 encephalopathy during follow-up. Of the 31 children not on ART, one child developed tuberculosis (rate: 6 per 100 child-years of follow up), 2 herpes zoster and one had encephalopathy during follow-up. One child was suspected to have LIP on follow-up.

DISCUSSION

Children have faster progression of the the disease because of immunological immaturity. The clinical course of vertical HIV-1 infection is highly variable, but before the widespread use of antiretroviral therapy, two general patterns of survival were described. Approximately 10% to 20% of infants experienced rapid progression of disease and died of AIDS–related complication by 4 years of age. The mean survival time for the remaining 80-90% infected children was approximately 9-10 years.[13]

In the present study, majority of children were symptomatic. The common clinical manifestations of HIV infection such as failure to thrive, recurrent pneumonia, recurrent diarrhea, hepatomegaly, generalized lymphadenopathy and oral candidiasis are similar to those reported in studies of HIV-infected children in both Western[14, 15] and tropical countries[16, 17] and in recent reports from India.[3-7]

Most of the children in the present series had advanced disease, as indicated by clinical features, malnutrition and profound immunosupression, which indicated delayed diagnosis. This was despite numerous previous contacts with the health-care system. Therefore, a high index of suspicion is necessary for early diagnosis. Recurrent infections, poor intakes and HIV infection itself can lead to severe wasting. Growth failure is a poor prognostic factor in HIV-infected children.[18]

It was not possible to document the etiologic agents of pneumonia including *P. carinii* in majority of the patients; most children received empirical anti-bacterial and anti-PCP therapy. Lymphoid interstitial pneumonitis (LIP), a common feature of pediatric AIDS, was suspected in three children. Merchant *et al* reported that nearly 12% children had chronic lung disease, mostly due to LIP.[6] However,

Verghese *et al* reported figures of 2.6% similar to ours.[5]

Nearly 50% of patients who were followed up in the AIIMS could not afford antiretroviral therapy due to high cost of therapy that has to be sustained lifelong, and were offered supportive care alone. With the use of antiretroviral therapy there had been some improvement in the nutritional status of children as determined by weight for height. This aspect has been studied and similar results have been shown by other authors also.[19-21] There is improvement in the quality of life of these patients with antiretroviral and supportive therapy.

We used CD4 counts alone for assessing the impact of ART, as clinical criteria for assessing the same are not available. Our data shows drop in the CD4 counts on follow-up in children not receiving any ART, while in the ones who received ART, these were maintained at almost the same level. The mean age of the 2 groups was comparable. The CD4 counts decline with age. Decrease in CD4 counts in children not receiving ART over a short follow-up period and maintenance over a longer period of follow-up in those who received ART, do suggest that with the use of ART, there is prevention of decline in CD4 counts.

We also studied the rates of common infection in these children on follow-up. Though the rates were a bit lower in children receiving ART, the differences were minimal. This may partially be due to relatively short follow-up and also the fact that all children were receiving appropriate supportive care.

There is need for better understanding of the clinical presentations of these patients and for early diagnosis and appropriate management. While highly active antiretroviral therapy (HAART) may be out of reach for most families, nevirapine based regimen may be affordable by quite a few. Currently, the government is making efforts to provide the drugs free of cost to HIV-infected patients. Pediatric formulations will be needed to benefit children. There is need for supportive care and good and regular follow-up of these patients; this may help in reducing morbidity in these patients and improve the quality of life.

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