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A study of clinical spectrum of HIV infection in children at a tertiary care hospital

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Abstract

Background: Pediatric HIV infection today represents a major setback to the child health. The wide clinical spectrum and paucity of relevant data from India makes early diagnosis difficult. Our aim was to study the clinical profile of pediatric patients with HIV infection. **Methods:** This cross-sectional study was conducted at a tertiary care hospital in central India over a period of 1.5 years. Children between 18 months and 15 years attending the antiretroviral therapy (ART) clinic, pediatric outpatient department or admitted in the pediatric wards, who were detected to be HIV positive (on 2 rapid tests) were enrolled. Perinatally exposed symptomatic children less than 18 months of age were also included. **Results:** Demographic data, clinical features, investigations were recorded in a pre-designed proforma. Of the 112 HIV positive children enrolled, 103 (91.96%) acquired infection through vertical transmission, 4 (3.57%) through blood transfusion, while in 5 (4.46%) the route of acquisition of infection could not be determined. 104 (92.8%) cases were symptomatic. The mean age at the onset of symptoms was 3+2.63 years (range 1 month to 12 years). The most frequent manifestations were failure to thrive, lymphadenopathy and skin manifestations. Positive correlation was found between the WHO clinical and immunologic stages; correlation coefficient was 0.275 ($p = 0.005$). **Conclusion:** Vertical transmission is the most common mode of acquiring HIV in the pediatric age group. The clinical manifestations of HIV infection are protean and mimic a number of other illnesses. A high index of suspicion would therefore help in early and appropriate diagnosis.

Key words HIV, pediatric, vertical transmission

INTRODUCTION

The global impact of the Human Immunodeficiency Virus (HIV) infection has been so dramatic and devastating that it has been described as the 'epidemic' of our century.[1] In contrast to other infectious diseases, the relatively longer incubation period, non-specificity and paucity of early symptoms, a slow evolving course and various patterns of human behavior have all contributed to the rapid spread of infection among susceptible populations.

The estimated number of people living with HIV in India was 2.39 million in 2009, of which, 36 percent were women and 4.4% children.[2] Vertical transmission accounts for 80–90% of the pediatric infection. The proportion of pregnant women receiving antiretroviral (ARV) regimen prophylactically being low (17-48% in 2009), the current vertical transmission rate is 25-30% in sharp contrast to <2% in developed world.[3] Thus, HIV in children continues to be a menace due to increasing prevalence of HIV infection in women and ineffective measures for prevention of perinatal transmission including inadequate testing, poor access to antiretroviral medications and safe breast milk substitutes. Moreover, the diagnosis of HIV infection in perinatally exposed infants poses a problem due to lack of accessibility and high cost of diagnostic facilities.[4]

Important features of HIV in children are variability in the time of symptom onset and a wide clinical spectrum.[5] In view of the varying clinical manifestation and paucity of relevant data from India, this study was conducted. We aimed to study the clinical presentation of HIV infection in children, the modes of transmission, compare the clinical profile of perinatal with transfusion acquired HIV and derive a correlation of clinical manifestation with CD4 counts.

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MATERIAL AND METHODS

This cross sectional study was conducted at a tertiary care hospital in Central India over a period of 1.5 years. Both symptomatic and asymptomatic children between 18 months and 15 years who attended the antiretroviral therapy (ART) clinic, pediatric outpatient department or admitted in the pediatric wards and confirmed to have HIV infection were included. Perinatally exposed symptomatic (having any AIDS indicator condition) children less than 18 months of age were also included. The study cleared the institutional review board of Government Medical College, Nagpur, India. After pretest counseling and written consent, their HIV status was determined by 3 rapid serological tests using different antigens or principles with the help of following kits:[6]

1.HIV Comb (J Mitra & Co. Pvt. Ltd., New Delhi)

2.Retroscreen (Qualpro Diagnostics, Goa)

3.Tridot (J Mitra & Co. Pvt. Ltd., New Delhi)

Those found reactive on Comb, were subjected to 2 other rapid tests. Those found positive with any 2 of the 3 rapid tests were declared as infected. All testing was done in accordance with manufacturers' instructions. A detailed history including demographic details, HIV status of parents and siblings, high risk sexual behavior in parents, blood/blood product transfusion in parents and child, development and immunization, time of onset of symptoms were noted. A thorough clinical examination was performed with special reference to nutritional status, presence of opportunistic or other co-infections. The details were noted in a predesigned proforma.

All children underwent the following investigations: Complete Blood Count, X-ray chest, Tuberculin test, sputum exam, liver & renal function tests, CD4 and CD8 counts [flow

cytometry using FACS count machine (Beckton & Dickinson, San Jose, USA)]. CSF exam, gastric lavage for acid fast bacilli (AFB), fine needle aspiration cytology (FNAC), blood culture, relevant imaging studies, urine and stool exam, endoscopies were done when indicated. The children were categorized using WHO criteria.

Tuberculosis was diagnosed on the basis of symptoms, history of adult contact, radiology, Mantoux text, sputum & gastric lavage for AFB and FNAC from lymph node. Pneumocystis jeroveci (carinii) pneumonia (PCP) was diagnosed by clinical and radiological findings & response to co-trimoxazole. Recurrent lower respiratory tract infection (LRTI) was defined as > 2 episodes in one year or > 3 episodes over any period of time.[7] The siblings and parents whose HIV status was not confirmed were also screened by rapid tests after informed consent. Our social counselor offered pre- and post-test counseling to parents. Total confidentiality of all participants and results was maintained.

RESULTS

Total 112 children with HIV infection were enrolled in the study. Age of the children ranged between 2 months and 12 year 6 months. Male to female ratio was 1.66. 49.1% cases were fully immunized, 38.4% were partially immunized, whereas the status in 12.5% was not known. Of the 224 parents, HIV status could be confirmed in190 (106 mothers and 84 fathers) through testing or past records. History of death due to HIV related disease was present in 61 parents - 18 mothers and 43 fathers. History of high risk sexual behavior was forthcoming from 28 fathers.

Vertical mode of transmission was presumed in 103 (91.96%) children on the basis of mothers having positive HIV serology. Prevention of parent to child transmission (PPTCT) intervention was carried out in 4 of these. Three were given replacement feeding and rest were breast fed in infancy. Blood transfusion was the possible mode in 4 (3.57%) cases. Two had thalassemia and two had sickle cell disease. All of them had received at least one transfusion more than 3 months before diagnosis. The route of acquisition of infection could not be determined in 5 (4.46%) children. Of these children, one was from orphanage, in 2 cases the parents were not available for testing and the parents of 1 child had died due to chronic illness (probably HIV related). These children had not previously received any transfusions. History of sexual abuse was not forthcoming from any.

104 children (92.8%) were symptomatic at the time of presentation. The mean age at the onset of symptoms was 3+2.63 years (range1 month to 12 years). The age group 1-5 years had the largest proportion of children (51.92%). (Table 1) The most frequent manifestations were failure to thrive, lymphadenopathy and skin manifestations especially pyoderma & papular urticaria. (Table 2) Hematological manifestations were seen in 45 children (Table 3). Of these, 36 (34.6%) had anemia (Hb <8 gm %) and 2 had thrombocytopenia (without bleeding manifestations). Of the respiratory manifestation, bacterial pneumonia was seen in 20 patients. Seven of them had recurrent LRTI. Two had pleural effusion; however, pleural fluid did not reveal any organism. PCP was presumptively diagnosed in 4 children. Microorganism couldn't be isolated in any. Twelve children were diagnosed to have pulmonary TB. Mantoux test (induration ≥ 5mm) was positive in 4 patients. Sputum or gastric aspirate for AFB was positive in 2 patients.

Gastrointestinal manifestations were found in 22 (21.2%) patients, recurrent/chronic diarrhea being the most frequent. USG abdomen showed hepatosplenomegaly in 15 and mesenteric lymphadenopathy in 2. Deranged liver function tests were seen in 3 patients. Stool examination revealed cryptosporidia in 3, microsporidia in 2, fungal spores in 2, candida in 2, Ecoli in 1 and V. cholera in 1. CNS manifestations were seen in 26 patients: developmental delay in 15, microcephaly in 11, cerebral atrophy (CT Brain) in 1 and meningitis in 1. No patient with cardiovascular or renal manifestation or malignancy was found.

Thirty seven children had recurrent bacterial infections in the form of pneumonia, pyoderma or suppurative otitis media. Tuberculosis was seen in 21 patients. Twelve had pulmonary, 5 had TB lymphadenitis, 3 had pulmonary with lymph node involvement and 1 had miliary TB . Candidiasis, cryptosporidiosis, PCP, H. zoster & Chicken pox were found less commonly. (Table 4)

The categorization of patients as per WHO clinical staging was as follows: Stage 1: 8 (7.14%), stage 2: 31 (27.68%), stage 3: 38 (33.93%), stage 4: 35 (31.25%). CD4 counts were done in 105 patients. 19 (18.1%) patients showed no significant immunosuppression, 31 (29.52%) had mild suppression, 30 (28.57%) had advanced whereas 25 (23.81%) had severe immunosuppression. Positive correlation was found between the WHO clinical and immunologic stages; correlation coefficient was 0.275 ($p = 0.005$).

Of the 103 children who had acquired the infection vertically, 95 were symptomatic. The mean age at the onset of symptoms was 2 years 9 months + 2.20 yrs (range 2 months to 12 years). The most common manifestations were failure to thrive, lymphadenopathy and skin involvement. Of the 4 children who acquired the infection through blood or blood products 2 had thalassemia. One was asymptomatic for HIV while the other had pulmonary and extrapulmonary (lymph node) TB. Two children had sickle cell disease. One of them had pulmonary TB and, the other had bacterial pneumonia. The mean age at onset of symptoms was 9 years 7 months + 1.10 yrs (range 8 yr. 6 months to 11 years). Anti retroviral therapy was instituted in 82 of these children.

DISCUSSION

Pediatric HIV infection is assuming alarming proportions in developing countries, especially in urban India.[7] Vertical transmission remains the primary route of transmission accounting for 91.9% of cases in this study and supported by the findings of previous studies.[1,8-11] In developed countries, vertical transmission has virtually been eliminated (≤2%) with good prenatal care, antiretroviral prophylaxis, safe delivery practices and widespread availability and safe breast milk substitutes.[12] PPTCT is a cost effective way of reducing the incidence of pediatric HIV infection and significant progress in this area has been made in the past several years.[13] However developing countries still have a long way to go.

The second most common source of infection is through blood and blood products; 3.57% in the present study and 10-39% in earlier studies.[1,10,11,14] Mandatory screening of donated blood for HIV antibodies was brought in force since 1993 which has resulted in gradual fall in the transfusion acquired infections.[14] However, transmission may occur from an infected donor during window period.[15] This emphasizes the importance of regular screening of transfusion dependant patients and prudent use of blood and blood products. No case of transmission by

Table 1: Age at Onset of Symptoms (N=104)

Age	Number of children	Percentage
< 1 year	31	29.81
1 – 5 years	54	51.92
> 5 years	19	18.27

Table 2: Clinical Manifestations of HIV Infected Symptomatic Children (N=104)

Signs/symptoms	Number	Percentage
Failure to thrive	62	59.6
Lymphadenopathy	62	59.6
Skin manifestation	62	59.6
Pyoderma	29	27.9
Scabies	4	3.8
Papular Unticaria	28	26.9
Chicken Pox	2	1.9
H. Zoster	3	2.9
M. Contagiosum	2	1.9
Supp. Otitis Media	34	32.7
Recurrent/Persistent LRI*	31	29.8
Recurrent URI	29	27.8
Hepatomegaly	22	21.2
Tuberculosis	21	20.2
Recurrent Diarrhea	19	18.3
Prolonged fever > 1 month	16	15.4
Splenomegaly	16	15.4
Wasting	12	11.5
Parotitis	12	11.5
Oral thrush	7	6.7
Clubbing	5	4.8

*** > 2 episodes in one year or > 3 episodes over any period of time**

sexual route was found in this study and history of sexual abuse was also not forthcoming from any. Moreover, sexual debut was not expected as the oldest child in our study was 12 yr 6 months. Sehgal et al reported 3.1% of children infected by heterosexual route. This could be attributed to adolescents comprising 24% of their study polulation.[14] These cases highlight the changing values and lifestyle in Indian adolescents and emphasize the need for health education for adolescents.

Most (51.92%) children presented between 1-5 years similar to earlier study.[1] The median age at presentation was 2 years;

Table 3: System Specific Manifestations

	Number	Percentage
Hematological	45	43.3
Anemia*	36	34.6
Leucopenia	7	6.7
Thrombocytopenia#	2	1.9
Respiratory	36	34.6
Bacterial Pneumonia	20	19.2
Pulmonary TB	12	11.5
Pneumocystis Carinii	4	3.8
Lymphoid Interstitial Pneumonia	-	0.0
CNS	26	25.0
Developmental Delay	14	13.5
Microcephaly	11	10.6
Meningitis	1	1.0
Gastrointestinal	22	21.2
Recurrent/Chronic Diarrhea	19	18.3
Parasitic	5	4.8
Fungal	4	3.8
Bacterial	2	1.9
Hepatitis	3	2.9
Oropharyngeal candidiasis	-	0.0
Abdominal Tuberculosis	-	0.0
Cardiovascular	-	0.0
Renal	-	0.0
Malignancy	-	0.0

*** Hb<8gm%,#Platelet<1.5lac/cumm**

Table 4: Opportunistic Infections in HIV Positive Children

Opportunistic infection	Number of patients	Percentage
Recurrentbacterial infections	37	35.6
Tuberculosis	21	20.2
Candidiasis	7	6.7
Pneumocystis Carinii (PCP)	4	3.8
Cryptosporidiosis	3	2.9
Herpes Zoster	3	2.9
Chicken Pox	2	1.9

other studies reported 3.2-4.5 years.[8,15] This could be related to the timing of transmission: children infected in-utero having faster disease progression than those infected during delivery.[16]
A combination of high virus burden and immunologic naiveté contributes to quicker progression of disease in children as compared to adults.[1,16] Moreover, the patterns of disease expression differ among children and also from those in adults.[17] Infected children have wide spectrum of clinical signs and symptoms as reported in literature.[18,19] A high index of suspicion is therefore necessary for early diagnosis.

Failure to thrive, lymphadenopathy and skin manifestations were the most frequent manifestations in this study. Papular urticaria, common in our patients, has been described as one of the initial manifestations of HIV infection in Haitian adults and children.[10] Other clinical features like otitis media, hepatomegaly, lower respiratory infections, tuberculosis were similar to those reported earlier from developing and developed countries.[1,10,15] The slightly higher number of children with failure to thrive as compared to that in developed countries is accounted for by the poor socio-economic status, malnutrition, associated secondary infections etc. Clubbing, which is a less frequently reported sign was found in 4.8% of our children. Clubbing has been described in association with underlying tuberculosis, recurrent LRTI and lymphoid interstitial pneumonia in HIV infected children.[14]

The HIV pandemic has had a major impact on the epidemiological dynamics of TB.[20] The risk of active TB in children with HIV is 5-10 times higher than those without HIV.[21]
Twenty one (20.19%) patients in the present study were diagnosed to have TB. Previous studies have reported the frequency of TB in the range of 11-67.5%.[1,8,10,15,22] Mantoux was positive in 4 children. Mantoux positivity being variable, establishing the diagnosis of TB in these children becomes difficult.[8,22,23] In the presence of HIV infection, extrapulmonary & disseminated forms of tuberculosis are more common.[13] While HIV infection increases the risk of TB, the reverse is also true.[21,23-24] Moreover, both these infections have overlapping symptomatology. Hence, the tuberculosis and HIV/AIDS programs will need to collaborate to deliver a more effective response to TB/HIV.

Despite recent advances in early diagnosis of HIV infection, new antiretroviral therapies, and improved understanding of the cellular immunity of young children, life threatening infections continue to abound. Recurrent bacterial infections (35.6%) and TB (20%) were found commonly in our children. Oral thrush, cryptosporidiosis, PCP, H Zoster were found less commonly. Earlier studies have reported tuberculosis, oral candidiasis, recurrent diarrhea and PCP as common opportunistic infections.[8,22,25] Opportunistic infections are responsible for a considerable proportion of morbidity, mortality in pediatric HIV infection. Prophylactic regimens can be used to prevent a number of these infections.

Microbiological confirmation of diagnosis of tuberculosis and PCP was not always possible, and diagnosis was often presumptive, based on clinical criteria and response to treatment. As in other studies from India, bacterial pneumonia occurred more frequently than PCP.[1,10] This may reflect the greater importance of bacterial infections in tropical countries as well as limited diagnostic facilities for diagnosis of PCP. In developing countries where definitive diagnosis using broncho-alveolar lavage or lung biopsy are seldom feasible, early therapy based on presumptive criteria may prevent one of the major causes of death in infants.

The mean age at presentation was 2 years 9 months in vertically transmitted children and 9 years 7 months in those infected with blood or blood products. The incubation period for vertically transmitted HIV is less than for transfusion acquired HIV.[26] Literature reports lymphoid interstitial pneumonia to be more common in the vertically infected group, and encephalopathy in the transfused group,[27] though this finding was not observed in our study.

Significant correlation was found between the WHO clinical stage and the immunological status of the patients. Shah found no significant correlation between CD4 count, CD4% & HIV viral load with different clinical manifestations of HIV in children,[28] while other studies reported a positive correlation.[29,30] Total Lymphocyte count has also been shown to serve as a surrogate marker for CD4 count in resource-limited areas.[31] These studies suggest CD4% as a reliable marker of progression of HIV infection and as a measure of relative risk of developing opportunistic infections. It could serve as a determinant for initiation of antiretroviral treatment in HIV infected children.

A limitation of this study was inability to compare the profile of patients with perinatal and transfusion acquired infections due to inadequate number of children in the latter group. Increased knowledge of the unique features of transfusion acquired HIV may greatly assist in improving care of these patients. Moreover lack of PCR facility hindered diagnosis of asymptomatic children < 18 months. Improved diagnostic facilities, PPTCT intervention and prompt ART are needed to bring down the burden of the disease.

CONCLUSIONS

Vertical transmission being the primary route of HIV infection in children, screening of antenatal mothers and anti-retroviral prophylaxis can substantially reduce the incidence of pediatric HIV. Blood transfusion still appears to be an important mode of transmission, emphasizing the need for judicious use and stringent screening of blood products, and routine screening of transfusion dependant patients. The clinical manifestations of HIV infection are protean and mimic a number of other illnesses. Many children had advanced disease, indicating delay in diagnosis. A high index of suspicion would therefore help in early and appropriate diagnosis. However, we are a long way from winning the battle against this malady.

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