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Original Article

Incidence and Clinical Spectrum of Opportunistic Infections among Human Immunodeficiency Virus-infected Children Aged 18 Months to 14 Years in North East India – A Hospital-based Study

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Abstract

Background: Human immunodeficiency virus (HIV) infection in children is a major public health problem. Opportunistic infections (OIs) are generally seen in children due to pre-existing immunocompromised state. OIs are an important cause of morbidity and mortality in children infected with HIV.

Objective: The objective of this study was to evaluate the incidence of OIs and clinical spectrum in HIV-infected children among the age group 18 months to 14 years.

Materials and Methods: This is a cross-sectional study conducted in a tertiary care hospital between September 2012 and August 2014. All the enrolled children infected with HIV were examined for the development of OIs after getting written informed consent from parents. Demographic details, clinical examination, and relevant investigations were done for all the children. Clinical spectrum of OIs and HIV categorization as per WHO and NACO guidelines was recorded. Data were analyzed using SPSS version 22.

Results: Out of 100 children infected with HIV, the incidence of OIs is 38%. The mean age of children was 5.4 ± 2.02 years at enrollment with female to male ratio of 1:1.2. 48.5% of children having OI was in the age group between 10 and 14 years. Tuberculosis (TB) (73.69%) was the most common OI identified followed by *Candida* (10.53%). All the OIs were treated as and when indicated. 92 children were receiving OI preventing prophylaxis as per NACO guidelines. 77% of children were underweight and 10 children need hospitalization.

Conclusion: OI in HIV-infected children is a serious health concern. There is a need for continued surveillance to assess the effort of antiretroviral therapy in the occurrence of OIs. Early identification of OI and its appropriate measures should be taken up as it can help in reducing the morbidity and mortality of HIV-infected children.

Key words: Children, Human immunodeficiency virus, Incidence, Opportunistic infections, Tuberculosis

INTRODUCTION

Human immunodeficiency virus (HIV) infection is a growing concern in the pediatric population. Approximately, 2.5 million children globally are infected with HIV at the end of the 2009.[1] Infection with HIV reduces the immune system's ability to fight infections. An opportunistic infection (OI) is an infection caused by pathogens that take various illnesses in children infected with HIV. OIs are usually responsible for causing death among the HIV infected children. Children living with HIV infection are prone to OIs due to various microbial agents. They are at risk of developing OI with fall in their CD4 counts and persistence of OI cause further fall in CD4 counts.[2,3]

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The OIs are an important factor for morbidity and mortality in children living with HIV infection. The understanding of the pathogenesis of HIV and many of the opportunistic pathogen has led to the development of variety of efficacious therapies for the infections.[4] The spectrum of OI of a particular locality should be known to prevent these infections by giving adequate prophylaxis. Prophylactic therapies are not hundred percent protective and despite improved treatment, few OIs are cured. Most of the children infected with HIV and coinfection of OIs require lifelong maintenance therapy in the absence of immune reconstitution. OI in HIV-infected children can occur in children on antiretroviral therapy (ART) as well as not on ART. Considering the importance of identifying the pathogen responsible for OI in HIV-infected children, we take up this study with the aim of knowing incidence of OI and clinical spectrum in HIV-infected children.

MATERIALS AND METHODS

An observational cross-sectional study was conducted between September 2012 and August 2014 in the Pediatrics Department of a tertiary care hospital in North East India. Children infected with HIV in the age group between 18 months and 14 years attending pediatric orthodontics pediatric dentistry and admitted in the pediatric ward were enrolled after getting approval from the Institutional Ethical Committee. A written informed consent was obtained from the parents or caregivers of each child before enrolment in the study. Children with congenital disease and malignancy were excluded from the study. A sample size of 100 was calculated presuming 50% prevalence rate of OIs in HIV-infected children with 10% margin of error on either side. Children of those parents who are willing to participate are enrolled by the sequential sampling. Strict confidentiality was maintained throughout the study period to protect the identity and record of study subjects.

The diagnosis of HIV was confirmed by Elisa using two different antigens. Parents or caregivers of the enrolled children were explained regarding the development of signs and symptoms of the OIs. Demographic profile, anthropometric measurement, clinical signs, and symptoms of OIs were recorded in a predesigned proforma. Detailed history including mode of transmission and medication were recorded. The clinical and immunological status of the disease were determined according to the WHO guidelines 2006. Laboratory examination of blood, stool, urine, chest X-ray, and sputum/gastric aspirate for acid-fast bacilli (AFB) was done for each participant. The baseline value of the liver function, kidney function, and blood sugar were obtained from all the participants. The examination of skin and oral mucosa with scraping for potassium hydroxide mount preparation were done when indicated. Blood cultures and other specific investigations including imaging study were done as and when indicated depending on the clinical condition of the child. CD4 T-cell count was quantitated by standard flow cytometry technique with fluorescent activated cell sorter method.

All the OIs were treated for the specific organisms isolated. Children with tuberculosis (TB) were diagnosed and treated with antitubercular drugs 2-8 weeks before start of the ART. Children who need ART were started as per NACO guidelines. Children with severe diseases were admitted in the pediatric ward and given appropriate management. Preventive measures for children with OIs were given with prophylactic drugs as and when necessary according to NACO guidelines. Data collected were entered into the computer software, and statistical analysis was performed using SPSS version 22. Descriptive statistics were reported as means, standard deviations and percentage for categorical variables. To determine the difference between the groups ANOVA test was used. Criterion for statistical significance was set at $P \leq 0.05$.

RESULTS

A total of 100 children infected with HIV in the age group between 18 months and 14 years were enrolled for the study. There were 45 females and 55 male with a ratio of 1:1.2. The mean age of HIV-infected children at the time of diagnosis was 5.4 ± 2.02 years. The majority (84%) of HIV-infected children were in the age group 10 years and above. Mode of HIV transmission was vertical in all the cases. At the time of enrollment, 37 % children with HIV infection were in WHO clinical Stage III and only 4% children were in WHO clinical Stage IV.73 % children were anemic with hemoglobin level below 11 g/dl. Undernourished cases as per WHO growth reference chart was present in 77 % of the enrolled children infected with HIV. The majority (70%) of children did not have immune suppression while 15% of the cases had mild immune suppression with CD4 T-cell count below 500 cells/mm^3 and 10% cases had severe immune suppression (Table 1).

In this study, the overall incidences of OIs among the children infected with HIV were 38%. Out of 38 children with OIs 52.6% was male and 47.4 were female. The different presentations of OIs are represented in Table 2. Among the OIs, TB (73.69%) was found to be the most common infection followed by *Candida albicans* (10.53%). Out of 28 cases of TB, 85.2%were pulmonary TB and only 14.8% were extrapulmonary including one case of TB sinovitis (Table 3). AFB was isolated from sputum of a child with HIV infection not on ART which is shown in Figure 1.

Table 1: Baseline parameters of HIV infected children in the study population

Parameters	Number (*n*=100) (%)
Gender	
Female	45 (45.0)
Male	55 (55.0)
Age at enrollment (years)	
<10	16 (16.00)
≥10	84 (84.0)
Nutritional status	
Normal	23 (23.0)
Underweight	77 (77.0)
Children with anemia	
Hb<11 (g/dl)	73 (73.0)
Baseline WHO clinical staging	
Stage I	38 (38.0)
Stage II	21 (21.0)
Stage III	37 (37.0)
Stage IV	4 (4.0)
Baseline immunological staging	
No immune suppression	70 (70.0)
Mild immune suppression	15 (15.0)
Advance immune suppression	5 (5.0)
Severe immune suppression	10 (10.0)
Mode of transmission	
Vertical	100 (100.0)
Others	Nil
Number of hospitalization required	10 (10.0)

HIV: Human immunodeficiency virus, Hb: Hemoglobin

Table 2: Different infections among HIV infected children with presentation of OI

Infection	Number of children (*n*=38) (%)
Mycobacterium tuberculosis	28 (73.69)
Candidiasis	4 (10.53)
Cryptosporidium	1 (2.63)
Streptococcus pyogenes	1 (2.63)
Salmonella typhi	1 (2.63)
Escherechia coli	1 (2.63)
Herpes zoster	1 (2.63)
Scabies	1 (2.63)

HIV: Human immunodeficiency virus, OI: Opportunistic infection

Table 3: Spectrum of TB in HIV infected children at presentation

Site involve	Number of children (*n*=28) (%)
Pulmonary TB	23 (82.15)
TB lymphnode (peripheral)	2 (7.14)
TB meningitis	1 (3.57)
Milliary TB	1 (3.57)
Osteoarticular (synovial)	1 (3.57)

HIV: Human immunodeficiency virus, TB: Tuberculosis

All the TB cases were treated with antitubercular drugs as per recommended treatment regimes for HIV-infected children (WHO 2010). For children receiving treatment for TB, initiation of ART is defer for 2-8 weeks. Among the study population, one child presented as cryptosporidial diarrhea (Figure 2). OIs with one case of scabies and one case of herpes zoster (Figure 3) were diagnosed based on clinical examination. All the OIs were treated with appropriate medications as and when indicated. 10 children needed hospitalization and 3 children expired. 85% of the children infected with HIV were receiving ART as per NACO guidelines.

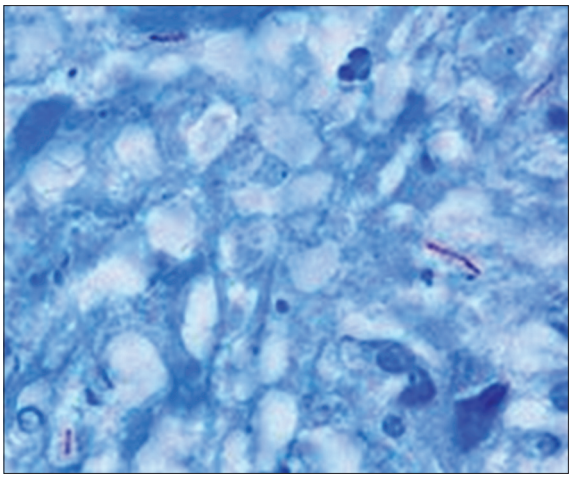

Figure 1: Acid-fast bacilli isolated from sputum of 8-year-old male child not on antiretroviral therapy

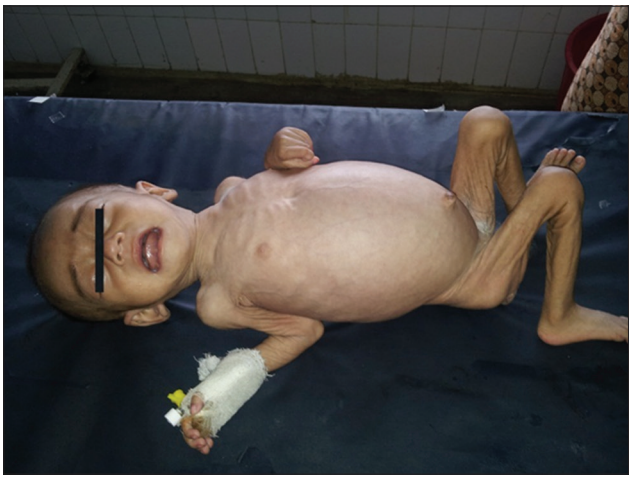

Figure 2: Female, 2-year-old undernourished child not on antiretroviral therapy presenting as *Cryptosporidium* diarrhea

DISCUSSION

The introduction of highly active ART (HAART) in HIV-infected children has led to their better survival, but with increasing spectrum of OIs. There is a lack of data on OIs developing among HIV-infected children in our region. The identification of pathogens responsible for OI is very important in managing the HIV-infected children. The results of this study show that the overall incidence of OIs is 38% which demonstrates increase of OIs in HIV-infected children since the introduction of ART. In a study done by Gona *et al.* about the incidence of opportunistic and

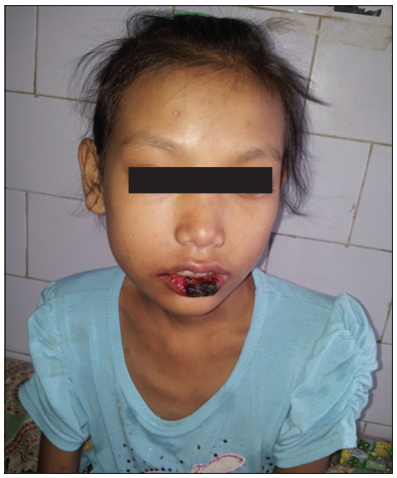

Figure 3: Female, 12-year-old child not on antiretroviral therapy with Herpes labialis

other infections in HIV-infected children in the HAART Era, the OI rates is 14% only and found to be lower than those reported in the HAART Era.[5]

In 2000, the pediatric AIDS clinical trials group (PACTG) repeated a meta-analysis of 3331 HIV-positive infants and children who were enrolled in 13 PACTG studies conducted before treatment with HAART had become available to determine the rates of various HIV-associated infectious complications.[6] In their study, pneumonia and bacteremia were the most common bacterial infections reported. In this study, TB infection were found to be the most common OI (73.69%) followed by *Candidiasis*. Sterling *et al.* noted that TB is the most common OI in children infected with HIV and most HIV-infected patient with TB have relatively advanced HIV disease.[7] According to pediatric ART guidelines 2013, there is involvement of extra pulmonary sites in 14% of TB infection in children with HIV and this finding is near to the finding of this study (17.85%). Increase incidence of extrapulmonary TB has been also observed recently, constituting approximately 20% of the TB cases among children with HIV infection.[8] In another study done at Gautemale Sub-Saharan Africa, TB infection is found to be the most common OI among HIV-infected individual.[9] Increasing levels of co-infection with TB and HIV in children have been reported from countries with epidemics. Infection with HIV is a strong risk factor for progression from latent to active TB. HIV-infected children with TB represent a deadly co-morbidity. Another study done by Biswas *et al.* found that the incidence of pulmonary TB in HIV-infected children was 42.85% which is very high.[10] As immune competence decreases in HIV-infected patients, the incidence of atypical presentations increases, including high proportions of patients with extrapulmonary disease and disseminated TB.[11]

In this study, one case of TB sinovitis was found among the extrapulmonary TB. TB sinovitis is a repeatedly missed diagnosis when diagnosis is delayed. Knee joint involvement is a relatively rare manifestation of extrapulmonary TB, but the number of patients is increasing among the TB infection. Although osteoarticular TB is reported in 1-3% of patients with TB, the knee joint involvement of TB is not common in children.[12,13] Wanjari *et al.* reported a case of TB sinovitis in seropositive adult with HIV.[14]

Among this study group, the overall prevalence of underweight were 77%. Padmapriyadarsini *et al.* have observed 63% prevalence of underweight among children infected with HIV in South India.[15] The relative frequencies of specific OIs may vary in different countries and even in different areas within the same country.[16] 20% of AIDS defining illnesses in children are recurrent bacterial infections caused primarily by encapsulated organisms such as *Streptococcus pneumonae* and *Salmonella*.[17] Repeated common infection occurs in 10 cases of this study population. Before combination ART era, serious bacterial infection was the most commonly diagnosed OIs in HIV-infected children with an event rate of 15 per 100 child-year.[18]

All study children on screening for hepatitis found a case of viral hepatitis B infection. Hepatitis B virus and C virus infection are common in HIV-infected patient due to their overlapping mode of transmission. In this study, the second most common OI was due to *C. albicans* (10.53%) affecting oral cavity extending to pharynx. A study from North India done by Misra *et al.* reported that TB as the most common OI (71%) followed by *Candidiasis* (39%).[19] Infection with *Cryptosporidium* was significantly associated with HIV infection.[20] 32% cases of diarrheal illnesses were revealed in this study children and *Cryptosporidium* infection was found in one children. In a study done by Asnake *et al.* shows that the prevalence of diarrhea in HIV-infected children were approximately 55%.[21] Although protozoal infection like *Toxoplasma* can be associated with HIV infection, no such case was found among the enrolled children infected with HIV.

In a study done by Sharon *et al.*, severe bacterial infection was observed among children infected with HIV.[22] In this study, out of 6 cases of bacterial infections, one case of *Salmonella* typhi and another case of *E. coli* infection were found. There was one event of Herpes zoster infection in our study. In a study done by Moore and Chaisson, the incidence of Herpes zoster in HIV-infected person was decrease compare to other OIs.[23] Less serious bacterial infections such as otitis media and sinusitis were particularly common in untreated HIV-infected children.[24]

In this study, out of 85 cases of children with HIV on ART OI were found in 30.6% whereas among the children with HIV not on ART 73.33% were having OIs. These findings suggest that ART if started early after the diagnosis of HIV can prevent the development of OIs, thus reduces the morbidity and mortality. The risk of developing an OI for a person receiving potent ART is highest during the initial months of therapy, and this patient should be follow-up closely during this critical period.[25] However new HAARTs are boosting the blood absolute CD4 T cell counts of many patients with AIDS and are decreasing the prevalence of AIDS-related OIs.

In this study, the CD4 cell count was lowest among the age group 10-14 years and the OIs were most commonly present between these age groups (52.63%). A study done by Nathalie *et al.* shows that more number of children with OIs than children without OIs had a CD4 percentage of less than 15% at the time of HAART initiative at enrollment.[26] This study shows that lower the immunological status higher is the incidence of OI in HIV-infected individual. In a study done by Gomber *et al.* observed that OIs were more common in children with higher degrees of immunosuppression.[27] The immunologic stage is a stronger independent predictor of short-term risk than long-term risk suggests that CD4 cell level reflects current disease stage more than it predicts future disease.

In this study, 92 cases of the study population are receiving OI preventive prophylaxis. Although current practice for determining the timing and initiation of prophylactic therapies relies chiefly on CD4 count, the occurrence of specific AIDS defining OIs in patients with HIV infection should also be taken into account in making-decision regarding prophylaxis strategies.[28] The introduction of ART in children has dramatically improved survival and quality of life in children living with HIV infection by reducing OIs.[29] The incidence of many OIs is decreasing primarily because of advances in HIV-related therapy. However, OIs are still occurring, especially when patients access care late during the course of disease. Even after accessing care, children with HIV infection may develop OIs because of lack of prescription for prophylaxis, AR drug resistance or poor adherence to therapy. Early diagnosis and prompt treatment of OIs definitely contributes to increased life expectancy among infected patients, delaying the progression to AIDS.[30] The understanding of the pathogenesis of HIV and many of the opportunistic pathogens has led to the development of a variety of efficacious therapies for these infections. In this study, we did not analyze the potential impact of the use of vaccines to prevent OIs and follow-up studies were not included.

CONCLUSION

The OIs are an important cause of morbidity and mortality in children infected with HIV. However, few data are available regarding the overall prevalence, incidence and clinical correlates associated with OIs in the pediatric HIV population. Knowledge of the most common OI of those geographical areas will help in implementing the preventive measures against that pathogen. Our findings demonstrate that HIV-infected children continue to develop OI in spite of ART and preventive OI prophylaxis. Further studies are necessary to isolate OIs and other related infections with improvement in resources for OI investigations. Measures should be taken up to closely monitor the children infected with HIV to find out the development of OIs.

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