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Original Research Article

A study of clinical spectrum of opportunistic infections in HIV infected children and its correlation with CD4 count and anti-retroviral therapy

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ABSTRACT

Background: To determine the clinical spectrum and prevalence of opportunistic infections (OIs) in HIV infected children and correlate the occurrence of opportunistic infections with their CD4 count and Anti-retroviral treatment (ART).
Methods: A total of 100 HIV infected children diagnosed with opportunistic infections were included in the study. Demographic details, clinical examination and relevant investigations were done for all the children. Clinical spectrum of OIs and HIV staging was recorded. CD4 counts were done at baseline and were repeated at 6 monthly intervals.
Results: Mean age of the patients was 7.08±3.48 years (ranging from 6 months to 15 years) at enrollment with male to female ratio of 1.2:1. Fever (91%) was a common presenting symptom followed by weight loss (74%), cough (37%), abdominal pain (29%) and breathlessness (16%). CD4 count was significantly associated with presence of opportunistic infection in the study group. Tuberculosis - pulmonary (32%) and extra-pulmonary (29%) was the most common oppurtunistic infections, followed by oral thrush (13%), Herpes zoster (10%), Molluscum Contagiosum (9%), Pneumocystis jiroveci pneumonia (3%), Parvovirus infection (3%) and Pruritic Papular Eruptions (2%). 70% children were on ART as per clinical and immunological staging of HIV.
Conclusions: Low CD4 count is significantly associated with severe opportunistic infections, therefore drop in CD4 count should serve as an alarming signal for the treating physician. High index of suspicion is required to detect opportunistic infections and therefore CD4 counts should be done more frequently to predict occurrence of OIs.

Keywords: Anti-retroviral treatment, CD4 count, HIV, Opportunistic infections, Tuberculosis

INTRODUCTION

Human Immunodeficiency Virus (HIV) infection is of grave concern in the pediatric population. As of December 2016, approximately, 1.8 million children under 15 years of age are living with HIV globally, while in India 1,50,000 children are living with HIV.[1] Significant progress has been achieved in preventing new HIV infections and in lowering the annual number of HIV related deaths. HIV-related illnesses remain one of the leading causes of death globally and are projected to continue as a significant global cause of premature mortality in the coming decades.[2] The prolonged course of untreated HIV infection is marked by a decrease in the number of circulating CD4+ T helper cells and persistent viral replication, resulting in immunologic decline and death from opportunistic infections and neoplasm.[3,4]

Opportunistic infections (OIs) are more frequent or more severe because of immune-suppression in HIV infected

persons and are the major clinical manifestations in HIV patients.[5,6] Severely immune-compromised HIV patients may develop a variety of opportunistic infections that have a significant impact on their well-being, quality of life, health care costs and their survival.[7]

The risk for the development of OIs in HIV patients depends on exposure to potential pathogens, virulence of the pathogens, the degree of host immunity and the use of anti-retroviral therapy and antimicrobial prophylaxis. Majority of these OIs are associated with an increased hazard of death in HIV patients.[7] The spectrum of OIs of a particular region should be known to prevent these infections by giving adequate prophylaxis. Many HIV infected children with OIs may require lifelong maintenance therapy in the absence of adequate immune reconstitution. Patients experiencing morbidity from opportunistic infections may have interruptions in antiretroviral therapy causing more rapid progression of HIV disease. Despite the magnitude of the problem there is paucity of data on various issues in pediatric HIV infection.

With this background, the current study was designed to know the prevalence and clinical spectrum of opportunistic infections in HIV infected children and tocorrelate the occurrence of opportunistic infections with CD4 count and Antiretroviral treatment.

METHODS

A total of 100 children infected with HIV in the age group between 6 months to 15 years attending Paediatric Centre of Excellence for HIV Care, at the Department of Pediatrics, in a tertiary care hospital were selected for the study. This observational study was started, after getting approval from the Institutional Ethical Committee and obtaining parent's written informed consent.

The history including demographic details and clinical symptoms as well as examination findings were noted in a pre-designed proforma. Children with symptoms and signs suggestive of any opportunistic infections were investigated accordingly. Symptoms included cough, breathlessness, fever, weight loss, swelling, chronic diarrhea, headache, vomiting, oral rash, loss of vision, dysphagia/odynophagia etc. Also signs such as tachypnea, cyanosis, clubbing, nuchal rigidity, localizing signs, phlecten, lymphadenopathy, vesicular rash, oral thrush, hepatosplenomegaly, etc. were investigated accordingly. Past history of Tuberculosis and ART, immunization history in relation to BCG was noted. Anthropometry of the patients noted and classified into various classes according to WHO Guidelines for malnutrition in children. Details regarding ART, CD4 counts (baseline as well as at diagnosis of opportunistic infection) were noted. Laboratory investigations on a case to case basis along with CD4 cell count were done at every six-monthly interval. Patients were graded as per WHO immunological classification as None, Mild, Advanced and Severe immunological stages depending on age appropriate CD4 levels.

Statistical analysis

The analysis was performed using 10.0 version of statistical software SPSS. Continuous variables were summarized by using summary statistics (number of observations, mean and standard deviation) and categorical values by using frequencies and percentages. Baseline study participant characteristics were described using descriptive statistics. Parametric data if it passed the tests of normality was analyzed using parametric tests or else a non-parametric test was used for its analysis. Categorical data was analyzed using Chi-square test or Fisher's exact test.

RESULTS

The study included 100 HIV infected children diagnosed with opportunistic infections; among these 55 were males and 45 were females with male to female ratio being 1.2:1. Majority of patients (57) were in the age group of >10 years followed by (33) in the age group of 6-10 years. The mean age of the patients at the diagnosis of HIV infection in the study subjects was 7.08±3.48 years. The mean weight and height of the patients was 21.89±8.07 kg and 122.35±16.85 cm respectively. Fever was the most common complaint seen in 91% of the patients followed by weight loss (74 %), cough (37 %), abdominal pain (29%) and breathlessness (16%). Failure to thrive was seen in 20% patients on presentation. Out of total 100 cases, 27 had a previous history of opportunistic infections. Table 1 shows the number of patients with opportunistic infections at the time of study. Evidence of opportunistic infections on fundus examination was present only in 6 patients; with 4 patients having cytomegalovirus retinitis and 1 each choroid tubercle and herpetic keratitis.

Table 1: Opportunistic infections at the time of study.

Opportunistic infections	No. of patients
Pulmonary tuberculosis	32
Extrapulmonary tuberculosis	29
Oral thrush	13
Herpes zoster	10
Molluscum contagiosum	9
Pneumocystis jiroveci pneumonia	3
Parvovirus	3
Pruritic papular eruption	2
Wart	1

Out of 100 cases, 70 subjects were receiving ART. Zidovudine + Lamivudine + Efavirenz was the most common regimen used (29%) followed by Zidovudine + Lamivudine + Nevirapine (22%), Abacavir + Lamivudine + Efavirenz (7%), Abacavir + LAmivudine + Boosted Lopinavir (6%) and others (6%). Second line regimen was used in 3 patients.

As per WHO criteria, patients were divided in low CD4 counts for age group and normal CD4 counts for age group. The mean hemoglobin of the patients with low CD4 count was significantly lower compared to the mean hemoglobin of the patients with normal CD4 count (p<0.013). Mean neutrophil and lymphocyte percentage in the patients with normal and low CD4 counts were comparable. The erythrocyte sedimentation rate was significantly higher in low CD4 count group as compared to normal CD4 count group (p < 0.05), (Table 2). The total leukocyte, absolute lymphocyte and absolute neutrophil count were significantly lower in patients with low CD4 count compared to patients with normal CD4 count (p value < 0.01) (Table 2).

Table 2: Correlation of various parameters with CD4 levels.

Parameter	Normal CD4 Group (n=52)	Low CD4 Group (n=48)	p value
Hemoglobin (gm/dl)	10.59±1.507	9.7±1.994	0.013
Neutrophils %	44.71±11.517	43.23±13.724	0.562
Lymphocytes %	55.21±11.637	56.55±13.431	0.596
Erythrocyte Sedimentation Rate (mm/hr)	68.23±29.68	81.48±27.91	0.024
Total leukocyte count (per mm^3)	7346.15±2994.863	4696.38±2542.451	0.0001
Absolute lymphocyte count (per mm^3)	4067.88±2086.575	2540.69±1412.327	
Absolute neutrophil count (per mm^3)	3278.27±1386.621	2155.68±1648.863	

The prevalence of oral candidiasis and herpes zoster was significantly higher in patients with low CD4 levels as compared to patients with normal CD4 levels, (p <0.01). The occurrence of other opportunistic infection like pneumocystis jeroveci pneumonia, pulmonary and extra pulmonary tuberculosis, warts, pruritic papular eruptions, parvovirus infection and ocular opportunistic infections were comparable in patients with low CD4 levels and normal CD4 levels (Figure 1).

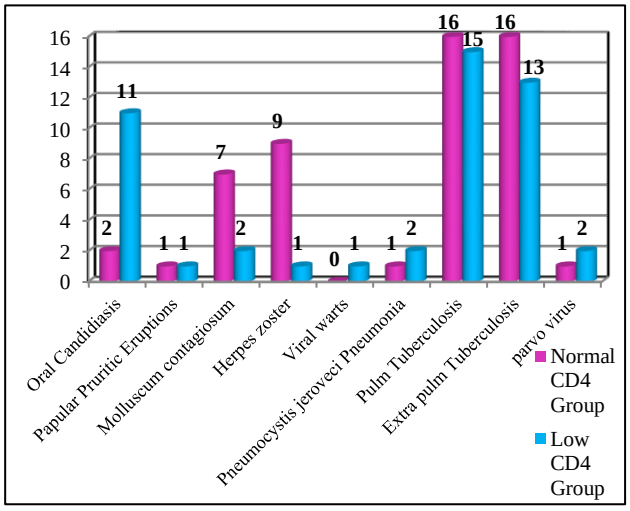

Figure 1: Correlation of prevalence of opportunistic infection with CD4 levels.

DISCUSSION

In present study, mean age of patients at diagnosis of HIV infection was 7.08 years. It was similar to study done by Sehgal et al [8] but this was significantly lower as compared to the study conducted by Ferrand et al.[9] 36% patients had weight less than 3 SD, 27% had weight between 3 SD and 2 SD, 25% had weights between 2 SD and 1SD, 9% had weight between 1SD and median while, 3% had weight more than median which shows the effect of HIV on the nutritional status of the child. However, 42% patients had height less than 3 SD, 33% had height between 3 SD and 2 SD, 14% had heights between 2 SD and 1 SD, 6% had height between 1SD and median, while 5% had height more than median which shows the effect of chronic illness like HIV on the growth of the child. The weight and height distribution of study subjects were compared with other studies.[10,11]

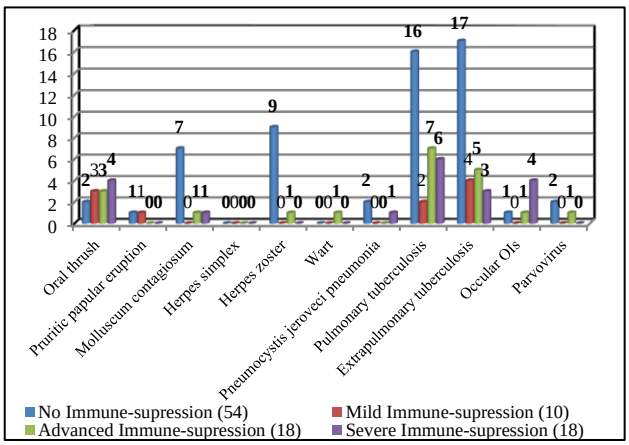

Figure 2: Correlation of various opportunistic infections with who immunological staging.

Fever (91%) was a common symptom among the subjects followed by weight loss (74%) and failure to thrive (20%). Oral thrush was present in 10% of patients. Few other presenting complaints were breathlessness (16%), abdominal pain (29%), rash (21%), difficulty in swallowing (14%), chest pain (10%) and ocular symptoms (3%). Tuberculosis was the most common

opportunistic infection in our study and this was similar to the study of Madhivanan P et al and Shah SR et al.[12,13] Among the HIV infected children in the study by Rajasekran S et al tuberculosis was diagnosed in 63.1%.[14] Variation in tuberculosis occurrence has been noted in several Indian studies. The lower occurrence of tuberculosis in our study was probably due to better ART program in our centre. Other opportunistic infections were oral thrush (13%), herpes zoster (10%), molluscum contagiosum (9%), pruritic papular eruptions (2%), pneumocystis carinii pneumonia (3%) and parvovirus infection (3%). Ocular involvement was present in 6 % of patients with 4 patients having cytomegalovirus retinitis and 1 each having choroid tubercle and herpetic keratitis. Our study correlated with different studies.[12-15]

As per WHO clinical staging, majority of patients (39% each) were belonging to stage 3 and stage 4. 22% were in stage 2. None of the patients were in stage 1. As per WHO immunological classification, advanced and severe immunosuppression was present in 18 patients each. 10 patients were having mild immunosuppression while 54 patients were not having significant immunosuppression. 77 % of patients in stage 2, 43.7 % of stage 3 and 51.7 % of stage 4 were not having significant immunosuppression. While advanced to severe immunosuppression was present in 48.7 % of patients in stage 3 and 35.5 % of patients in stage 4. These findings were different from other studies.[16,17] This difference could be explained by high prevalence of extrapulmonary tuberculosis in children in our study. Majority of our patients with extrapulmonary tuberculosis (51.7%) did not have significant immunosuppression, though as per clinical classification extrapulmonary tuberculosis is a stage 4 disease. CD4% declined with deterioration of WHO clinical stage of the disease.

Out of total cases, 70 cases were receiving ART which was comparable to findings by Alarcon JO et al.[11] Most of the patients in our study were on ART. Mean duration of ART was 20.04 months. Majority of patients were started on 1st line ART while 3% were on 2nd line ART. In the study by Candiani TMS et al 83.6% of the HIV infected children were on 1st line ART.[18]

Correlation of various hematological parameters with CD4 levels, found that the mean hemoglobin of the patients with low CD4 count was significantly lower compared to mean hemoglobin of patients with normal CD4 count, ($p<0.05$). The mean lymphocyte percentage in patients with normal and low CD4 count was comparable. The neutrophil count in our study in individuals with normal CD4 count was higher as compared to patients with low CD4 count and this was similar to the study of De Santis et al.[19] Also another study has pointed out that there was a significant positive correlation between absolute neutrophil count and CD4 count.[20] This means that as the CD4 count decreases the neutrophil count also decreases. The exact mechanism by which neutropenia occurs in patients with HIV is unclear. Studies have suggested direct effects of HIV causing increased apoptosis in neutrophils as well as premature phagocytosis of bone marrow cells, which may account for the observed neutropenia.[21] The erythrocyte sedimentation rate was significantly higher in low CD4 count group compared to normal CD4 count ($p <0.05$). ESR is a marker of infection and inflammation; patients with low CD4 count are associated with increased infections resulting in higher ESR levels.

Coming to the association between CD4 count and prevalence of various opportunistic infections, it was observed that CD4 count was significantly associated with presence of opportunistic infection in the study group. The incidence of pulmonary tuberculosis in the normal CD4 count group (30.77%) and low CD4 count group (31.25%) were comparable, this was similar to study by Yadav J et al.[22] HIV infection is associated with lower immunity leading to increased incidence of tuberculosis. The largest increase in tuberculosis has occurred in locations and demographic groups with the highest HIV prevalence, which suggests that the epidemic of HIV is atleast partially responsible for the increase of tuberculosis.[23] There is evidence that immune responses in tuberculosis and in other infection induce cytokines that enhance the replication of HIV and this drives the patient into full blown AIDS. The occurrence of oral thrush in the low CD4 count (22.92%) was higher than the normal CD4 count group (3.85%) ($p <0.01$), this finding was compared with the study of Yadav J et al.[22] The prevalence of herpes zoster was more in normal CD4 count group (17.31%) compared to the low CD4 count group (2.08%), ($p <0.01$) which was different from other studies.[11,24] This difference could be explained by variation in age group of study population wherein because of better immunity, children with normal CD4 levels get reactivation of herpes zoster. Thus, higher prevalence of herpes zoster was observed in normal CD4 patients in older children. The prevalence of other opportunistic infection like pneumocystis jiroveci pneumonia, molluscum contagiosum, wart, pruritic papular eruption, parvo infection and ocular opportunistic infections were comparable in patients with low CD4 levels and normal CD4 levels.

Correlation of various opportunistic infections with clinical stages as per WHO demonstrate that the prevalence of oral thrush was more in stage 3 (20.51%) as compared to stage 2 (9.09%) and stage 4 (5.12%). Molluscum contagiosum as well as herpes zoster was more prevalent in patients with stage 2. Pulmonary tuberculosis was more prevalent in stage 3 while extrapulmonary tuberculosis is a stage 4 defining condition. Correlation of various opportunistic infections with immunological stage shows that oral thrush and ocular OI were more prevalent in patient with advanced and severe immunosuppression.[3,4] Most of the patients with molluscum contagiosum and herpes zoster were not having significant myelosuppression. 16 patients of pulmonary tuberculosis (out of 32, i.e. 50 %) and 17

patients (out of 29, i.e. 58.6%) were having no significant immunosuppression. Our findings were different from other studies.[16,17] This difference could be due to better screening for pulmonary and extrapulmonary tuberculosis where high index of suspicion and clinical correlation is necessary irrespective of CD4 counts.

CONCLUSION

Out of many opportunistic infections in our study the most common were tuberculosis followed by oral thrush and herpes zoster. We conclude that CD4 count is significantly depressed in opportunistic infection. It has been observed that CD4 is a protective factor as evident from lesser number of opportunistic infections in children with CD4 count more than 500 cells/mm^3. Lower the CD4 count more the severity of the opportunistic infection. Fever was a common presenting symptom along with weight loss, cough, abdominal pain and breathlessness. The clinical signs and symptoms can be used as the predictors of Opportunistic infections in HIV infected children and thereby helpful in getting CD4 counts of these children. Hence the CD4 estimation is considered the backbone of AIDS control program in developing nations. It has been studied as a marker of progression of HIV infection and as a measure of relative risk of developing opportunistic infection.

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