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Opportunistic Infection among HIV Infected Children and Their CD4 Cell Correlates

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Abstract: *In the present retrospective study, we had analyzed the prevalence of opportunistic infections in HIV infected children and correlate the prevalence of opportunistic infections with their CD4+ T helper lymphocyte count.Total 100 Children diagnosed with HIV were enrolled. Majority of the cases were in age group 11 to 15 yrs. Males were proportionately more as compared to females. Fever was common presenting symptom along with cough diarrhea and weight loss.Persistent generalized lymphadenopathy, wasting and stunting, pallor and hepatomegaly were common signs. .Tuberculosis (pulmonary and extra – pulmonary), Herpes zoster, and oral candidiasis , were common opportunistic infections. Age and sex were not significantly associated with opportunistic infections. Opportunistic infections were significantly seen among cases who are taking anti-retroviral treatment. Among signs persistent generalized lymphadenopathy, pallor, wasting and stunting and splenomegaly were common signs associated with opportunistic infection with HIV. CD 4count was significantly low among the cases with ART.CD 4 count was significantly low among the cases with severe opportunistic infection. Because treatment of OIs is an evolving science, availability of new agents and emergence of drug resistance or clinical data on existing agents might change therapeutic options and preferences, recommendations for initiation of ART should be periodically evaluated.*

Keywords: *ART ,CD4count,Correlation, HIV, Opportunistic Infections*

I. Introduction

Children constitute 6% of global HIV disease burden. In pediatric age group the disease mortality and morbidity is high when compared to adults. Due to availability of antiretroviral therapy and improved drugs to treat opportunistic infections it has become a chronic disorder.The global pediatric HIV epidemic is shifting into a new phase as children on antiretroviral therapy (ART) age into adolescence and adulthood. The evolution of HIV into a chronic disease has greater impact on the life of a child[1].Children, that families, clinicians and policy makers at one time expected to die are living into their 20s and having children of their own[2]. Unanticipated issues such as reproductive health, higher education and career training are now urgent needs[3].
The natural history of opportunistic infections among children differs from that observed among HIV-infected adults. Many opportunistic infections in adults are secondary to reactivation of previously acquired opportunistic pathogens, which were often acquired before HIV infection at a time when host immunity was intact. However, opportunistic infections among HIV-infected children more often reflect primary infection with the pathogen. In addition, among children with perinatal HIV infection, the primary infection with the opportunistic pathogen is occurring after HIV infection is established when the child's immune system might already be compromised. This can lead to different manifestations of disease associated with the pathogen among children than among adults.

In the era before development of potent combination antiretroviral (ARV) treatment (cART) regimens, Opportunistic Infections (OIs) were the primary cause of death in HIV infected children. Current ART regimens suppress viral replication, provide significant immune reconstitution and have resulted in a substantial and dramatic decrease in AIDS related OIs and deaths in both adults and children. Despite this progress, prevention and treatment of OIs remain critical components of care for HIV infected children. Considering all the above factors , the present study was planned to estimate the prevalence of opportunistic infections in HIV infected children and correlate opportunistic infections with their CD4+ T helper lymphocyte count.

II. Aims & Objectives

1) To study the prevalence of opportunistic infections in HIV infected children (less than 15yrs)
2) To correlate the opportunistic infections with their corresponding CD4+ T helper lymphocyte count.

III. Material And Methods

The present study is a retrospective cross sectional study aimed to study prevalence of opportunistic infections in HIV infected children and correlate the opportunistic infectionswith their CD4+ T helper lymphocyte count
1. Period of the study : - July 2006 to July 2015
2. Study population: - Children diagnosed to have HIV/AIDS enrolled at D.Y. Patil medical college and surrounding areas from Pune. The confirmation of HIV status done by ELISA/Western blot. The approval of ethical committee and consent of the concerned authority was obtained to procure the data. The present study is a retrospective cross sectional study aimed to study prevalence of opportunistic infections in HIV infected children and correlate the opportunistic infections with their CD4+ T helper lymphocyte count

Place of study: - Dr D.Y. Patil hospital and research institute, Pimpri, and surrounding areas in Pune.
1. Period of the study : - July 2006 to July 2015
2. Study population: - Children diagnosed to have HIV/AIDS enrolled at D.Y. Patil medical college and surrounding areas from Pune. The confirmation of HIV status done by ELISA/Western blot. The approval of ethical committee and consent of the concerned authority was obtained to procure the data.
1. Study design: - The present study is a retrospective cross sectional study.
2. Inclusion criteria: Children diagnosed with HIV/AIDS in the age group up to 15 yrs irrespective of Anti-retroviral therapy status. All patients enrolled in this study had acquired HIV through vertical transmission.

3. Exclusion criteria:
HIV exposed but not proven cases
Children with other immunodeficiency disorder
4. Sample size: - 100 cases
4. Research instrument (Proforma): - The proforma contains of the following information.
a) Relevant history
b) General examination
c) Systemic examination (respiratory, cardiovascular, GIT and others)
d) Laboratory investigation

Opportunistic infections were classified as:
1) Severe opportunistic infection – pulmonary and extra pulmonary tuberculosis, Pneumocystis jerovecipneumonia (PCP), and cytomegalovirus (CMV) infection.
2) Non-Severe opportunistic infection – mucocutaneous infections such as herpes zoster, pneumonia except PCP, candidial infection and ear infections such as chronic suppurative otitis media.

5. **Data analysis**: - Data was analyzed using the Statistical Package for Social Sciences (SPSS) version 16.0 software.
 Both qualitative and quantitative data analysis was performed.
A)Qualitative data:
• Frequencies were enlisted
B) Quantitative data: -
• For continuous variables Mean, Standard deviation,

IV. Results

Table 1: Age wise distribution of subjects in study group

Age (yrs	No of cases	Percentage
<6	11	11
6 – 10	36	36
11 – 15	53	53
Total	100	100

The above table shows age wise distribution of subjects in the study group. 11 were in age group < 6 yrs, 36 were in age group 6 to 10 yrs and remaining 53 were in age group 11 to 15 yrs.

Table 2: Sex wise distribution of subjects in study group

Sex	No of cases	Percentage
Male	52	52
Female	48	48
Total	100	100

The above table shows sex wise distribution of cases in the study group. 52 subjects were males and 48 subjects were females.

Table 3: Treatment (ART) wise distribution of subjects in study group

Anti-retroviral therapy(ART)	No of cases	Percentage
Yes	70	70
No	30	30
Total	100	100

The above table shows treatment wise distribution of subjects in the study group. 70 subjects were on ART and 30 subjects were not on ART.

Table 4: Symptom wise distribution of subjects in study group

Symptom	No.Of Cases	Percentage(n=100)
Fever	44	44
Cough	30	30
Loss of weight	48	48
Diarrhea	7	7

The above table shows symptom wise distribution of subjects in the study group. 44 subjects had fever, 30 subjects had cough, 48 subjects had weight loss and 7 subjects had diarrhea.

Table 5: Sign wise distribution of subjects in study group

Sign	No of cases	Percentage (n=100)
Pallor	65	65
Clubbing	6	6
PGL(Persistent Generalized Lymphadenopathy	61	61
Oral thrush	21	21
CSOM(Chronic Suppurative Otitis Media)	9	9
Wasting Stunting	64	64
Scabies	39	39
Pruritis	8	8
Hepatomegaly	67	67
Splenomegaly	37	37

The above table shows sign wise distribution of subjects in the study group. 65 subjects had pallor, 67 subjects had hepatomegaly, 64 subjects had wasting and stunting, 61 subjects had PGL (Persistent generalized lymphadenopathy), 21 subjects had oral thrush, 13 subjects had scabies, 37 subjects had splenomegaly, 9 subjects had Chronic Suppurative Otitis Media (CSOM) and 6 subjects had clubbing.

Table 6: Distribution of opportunistic infectionsamong subjects in study group

Opportunistic infection	No of cases	Percentage
Yes	26	26
No	74	74
Total	100	100

The above table shows distribution of opportunistic infection among subjects in the study group. 26 subjects had opportunistic infections and 74 subjects without any opportunistic infections.

Table 7: Association between symptoms and opportunistic infections in study group

Symptom	Opportunistic Infections		Z Value	P Value
	Yes(n=26)	No(n=74)		
Fever	19 (73.08)	25 (33.78)	3.82	<0.001
Cough	12 (46.15)	18 (24.32)	1.89	>0.05
Diarrhea	1 (3.85)	6 (8.11)	0.86	>0.05
Weight Loss	11 (42.31)	37 (50)	0.68	>0.05

The above table shows association between symptoms and opportunistic infection in the study group.Among 43 subjects with fever, 19 had opportunistic infections and 23 no OIs.Among 30 subjects with cough, 12 had opportunistic infections. Among 7 subjects withdiarrhea, one had opportunistic infections. Among 48 subjects with weight loss, 11 had opportunistic infections. This within group difference was analyzed quantitatively using Z test and Z value worked out to be 3.82 for fever which is statistically highly significant ($p<0.001$) and rest are not significant statistically. ($P>0.05$).

Table 8: Association between signs and opportunistic infections in study group

Sign	Opportunistic infection		Z Value	P Value
	Yes(n=26)	No(n=74)		
Pallor	22 (84.62	43 (58.11)	2.91	<0.01
Clubbing	0	6 (8.11)	2.55	<0.05
PGL	23 (88.46)	38 (51.35)	4.34	<0.0001
Oral Thrush	5 (19.23)	16 (21.62)	0.26	>0.05
CSOM	1 (3.85)	8 (10.81)	1.33	>0.05
Wasting, Stunting	21 (80.76)	43 (58.11)	2.08	>0.05
Scabies	0	13 (17.57)	3.97	<0.0001
Pruritis	1 (3.85)	7 (9.45)	1.10	>0.05
Hepatomegaly	16 (61.54	16 (61.54	0.67	>0.05
Splenomegaly	4 (15.38)	33 (44.59)	3.19	>0.005

The above table shows association between signs and opportunistic infection in the study group. Among 65 subjects with pallor, 22 had opportunistic infections. Among 61 subjects with PGL, 23 had opportunistic infections. Among 13 subjects with scabies no one had opportunistic infections. Among 37 subjects with Splenomegaly, 4 had opportunistic infections. Among 64 subjects with wasting and stunting, 21 had opportunistic infections.Among 6 subjects with clubbing none had opportunistic infection. This within group difference was analyzed quantitatively using Z test and Z value worked out to be 2.91, 4.34, 3.97, 3.19, 2.08 and 2.55 for pallor, PGL, Scabies, Splenomegaly, wasting & stunting and clubbing respectively which is statistically significant ($p<0.001$). Rest are not significant
statistically. ($P>0.05$)

Table 9: Details of opportunistic infections among subjects in study group

Opportunistic infection	No of cases	Percentage (n=26)
Tuberculosis	9	34.62
Bronchitis	2	7.69
Community acquired pneumonia (CAP)	1	3.85
Infected Colloid Milia	1	3.85
Chronic.Parotitis	1	3.85
Cytomegalovirus (CMV) infection	1	3.85
Chronic Suppurative Otitis Media(CSOM)	1	3.85
Genital Herpes	1	3.85
Gluteal Abscesssecondary to Staph.	1	3.85
Herpes zoaster virus (HZV)infection (SKIN & Eye Lesion)	6	23.08
Oral Candiasis	3	11.54
Pneumocystis jeroveci pneumonia (PCP)	1	3.85
PityriasisCapitis	1	3.85

Details of opportunistic infections in the study group, 9 subjects had pulmonary and extra pulmonary tuberculosis, 6 subjects had HZV, and 3 subjects had oral candidiasis. Two subjects had bronchitis. One subject each had community acquired pneumonia (CAP) infected colloid Milia, chronic Parotitis, CMV infection, Chronic Suppurative Otitis Media (CSOM), Gluteal Abcess, PCP and Pityriasis capitis respectively.

Table 10: Association between CD4 count and opportunistic infection in study group

CD4 count	Opportunistic infection		Total
	Yes	No	
<200	10	1	11
200-349	7	26	33
350-499	5	16	21
>500	4	31	35
Total	26	74	100

Chi-square = 28.39, $P<0.0001$

The above table shows association between CD 4 count and opportunistic infection in the study group. Among 11 subjects with CD 4 < 200, 10 had opportunistic infections. Among 33 subjects with CD 4 count 200-349, 7 had opportunistic infections. Among 21 subjects with 350-499 CD 4 count, 5 had opportunistic infections. Among 35 subjects with CD 4 count >500, 4 had opportunistic infections. This difference within CD 4 count and opportunistic infections was analyzed using chi square test, chi-square value worked out to be 28.39 which is statistically highly significant. ($p<0.0001$)

Table 11: Association of CD4 count with severity of opportunistic infections in study Group

Opportunistic infection	N	CD4count		Z Value	P Value
		Mean	SD		
Severe	11	191.1	132.6	4.20	<0.05
Non-severe	15	434.9	395.5		
No	74	569	445.8		

The above table shows Association of CD 4 count with opportunistic infections in the study group. Mean CD 4 count among severe opportunistic infections was 191.1 (S.D. ±132.6), among non-severe opportunistic infections Mean CD 4 count was 434.9 (S.D. ±395.5). Mean CD 4 count among no opportunistic infections group was 569 (S.D. ±445.8). This mean difference of CD 4 count is analyzed quantitatively within group using Z test, Z value worked out to be 4.20 which is statistically significant. ($p<0.05$).

V. Discussion

The children constitute 6% of global HIV disease burden[4].Before the availability of antiretroviral therapy, median survival after diagnosis of AIDS was 12 to 18 months. In the era before development of potent combination antiretroviral (ARV) treatment (cART) regimens, OIs were the primary cause of death in HIV-infected children [5]. In this study it was observed that out of 100 HIV positive children, prevalence of opportunistic infections was 26% (TABLE no 6). The similar prevalence rate was observed in a study conducted by Iroezindu MO et al. Out of 339 patients, 76 had OIs giving an overall prevalence of 22.4%6[6].Another cross sectional study conducted by Moges and Kassa, included 423 patients HIV Positive Patients who were on ART in the age group 5 to 7 years.The overall prevalence of OIs in the above study participants was 42.8%[7].In a study conducted by Rachita Dhurat et al (2000), they found prevalence of opportunistic infection was 50%[8]. The differences in the prevalence rates among the current study and different studies can be attributed to the sample size, different geographic and demographic profiles In this study, majority of children were in the age group of 11-15yrs followed by 6-10yrs.Only 11 cases were below 6yrs (Table no 1). Sex wise distribution showed 52% was males and 48% were females (TABLE no 2). Similar findings were observed in a study conducted by Rajesh R et al (2013). They enrolled 1982 HIV positive children, among them 59% were males and 40% were females[9].

Fever was common symptom among the subjects followed by cough, weight loss and diarrhea (Table no 4). Majority of children in this study had pallor, PGL, wasting & stunting and hepatomegaly when compared to clubbing, oral thrush, CSOM, scabies, pruritis and splenomegaly (TABLE no 5). Prakash Poudel et al (2014) investigated the clinical, laboratory, epidemiological profiles and outcome in human immunodeficiency virus (HIV) infected Nepalese children. Fever, lymphadenopathy, hepato-splenomegaly, skin eruptions and oral lesions were common presenting features[10]. Virat Sirisanthana (1996) described the demographic and clinical characteristics of symptomatic vertical HIV-infected children. On the first admission signs and symptoms of non-specific findings of HIV infection such as hepatosplenomegaly, generalized lymphadenopathy, failure to thrive, oral thrush, chronic fever and chronic diarrhea were present.[11]. Rachita Dhurat et al studied the modes of transmission of pediatric HIV infection, to categorize clinical manifestations and to compare clinical spectrum of perinatal with transfusion acquired HIV infection. Among the 55 children enrolled, they observed most common presenting signs and symptoms were hepato-splenomegaly, failure to thrive, unexplained fever, parotitis, gastroenteritis and generalized lymphadenopathy. These studies are in confirmation with the current study.

Fever was significantly associated with opportunistic infection in the current study group.

In our study, the most common opportunistic infections (OI) were pulmonary and extra pulmonary (CNS, abdomen) tuberculosis (35%) followed by Herpes zoster (skin and eye lesion) 23% and oral candidiasis (12%). Other opportunistic infections were bronchitis, community acquired pneumonia (CAP), infected colloid Milia, chronic Parotitis, CMV infection (ventriculitis and retinitis), CSOM, Gluteal Abcess, PCP and Pityriasis capitis (TABLE no 9). In a study by Dhungel BA et al (2008), Tuberculosis (30%) was found to be most common OI followed by candidiasis (14%). Pulmonary tuberculosis (21.14%) was more common than extra pulmonary tuberculosis (8.92%) which is similar to the findings observed in the current study[12]. Damtie D et al (2013) assessed the prevalence and CD4 correlates of OIs among adult HIV-infected patients attending at Gondar University Hospital. The sample size was 360 HIV-infected patients. Tuberculosis, oral candidiasis and chronic diarrhea were the leading OIs encountered by HIV-infected patients[13].

In a study conducted by Moges and Kassa, they observed that among 423 HIV infected children, the commonest type of OIs among HIV patients on ART were oral candidiasis 50(11.8%), followed by chronic diarrhea for greater than 1 month 42(9.9%) and tuberculosis 41(9.7%). The prevalence of Pneumocystic pneumonia was 2.8%, severe bacterial pneumonia 3.1%61. This is in confirmatory with the current study, the prevalence of PCP and bacterial pneumonia was 3.8%. In a study conducted by Iroezindu MO et al, the most common opportunistic infections were- candidiasis 8.6% followed by TB 7.7%. The less commonopportunistic

infections were dermatitis 5.6%; chronic diarrhea, 1.5%; and sepsis 1.5%. Bacterial pneumonia was diagnosed in 0.9% of patients, cryptococcal meningitis, herpes zoster, genital herpes, and genital warts were each diagnosed in 0.6% patients. Similar findings was observed in a study conducted by Prakash Poudel et al , they observed most common opportunistic infections was Tuberculosis (16.0%), followed by chronic otitis media (12.0%), bacterial pneumonia (9.3%) and oropharyngeal candidiasis (6.7%). The findings observed in the current study are similar to studies conducted in India and different from other parts of the world. It can be interpreted that geographical variations are important in the manifestations of OI in HIV infected children. These findings are important in policy making and distribution of resources.

Coming to the association between CD4 count and OIs, it was observed that CD 4 count was significantly associated with presence of opportunistic infection in the study group. Among 26 subjects with opportunistic infection 4 had CD 4 count >500, 7 had CD 4 count 350-499, 5 cases had CD 4 count 200-349 and 10 subjects had CD 4 count < 200 (TABLE no 10). In a study conducted by Jaivinder Yadav et al (2014), on HIV children, they concluded that the severity and frequency of opportunistic infection and its complications in pediatric patients with HIV increased with fall in CD4 count. Similar results were observed in the current study, 90.9% of children with opportunistic infections had CD4 count less than 200[14]. In study conducted by Gisler V et al (2014) similar findings was observed. They observed patients with CD4 >500/µL, chronic HIV infection was the main immune-compromising condition to cause the AIDS-defining opportunistic infections (ADOI). Overall chronic HIV infection with a CD4 count >500/µL was the likely explanation for the ADOI in only 14%. Other attributable explanations for ADOI are primary HIV infection (10%), unmasking of inflammatory immune response syndrome (IRIS) in 2% cases, etc[15].

On further analyzing the information, it has been observed that patients with severe opportunistic infections had low mean CD 4 count and was significantly correlated. Mean CD 4 count among severe opportunistic infection was 191 and among non-severe opportunistic infection were 434 (Table no 11). Similar findings were observed in a study conducted by Ekta & Aroma (2015), they screened the HIV seropositive patients for OI in relation to their CD4 counts in a tertiary care hospital. Among them 38 (47.5%) patients were positive for OI. There were 13.6% patients presenting with infections having a CD4 count of below 200cells/µL. In their study it has been observed that cryptosporidiosis (23.68%), tuberculosis (5.92%), and CMV infection, PCP, isosporiasis and cryptococcosis were 2.96%.

VI. Conclusion

In the current study, the prevalence of opportunistic infections was found to be 26%. Out of many opportunistic infections in our study the most common were tuberculosis followed by herpes zoster (skin and eye lesion), and oral candidiasis. 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. Lower the CD 4 count more the severity of the opportunistic infection. It has been observed that low CD4 count is significantly associated with severe opportunistic infections. Fever was common presenting symptom along with cough, diarrhea and weight loss. Persistent generalized lymphadenopathy, wasting and stunting, pallor and hepatomegaly were common signs. 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 it is evident that a dipping of CD4 count should serve as an alarming signal for treating physician. CD4 count should be done more frequently to predict onset of OI and need for ART.

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