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"CLINICAL PROFILE OF OPPORTUNISTIC INFECTIONS IN HIV CHILDREN"

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ABSTRACT

According to the estimate of the World Health Organization, approximately 2.50 million children had been infected with human immunodeficiency virus (HIV) by the year 2011 (WHO-2011). Vertical transmission (Mother to child) is the main route by which childhood HIV infection is acquired, the risk of perinatal acquisition being about 25%. Perinatal transmission of infection accounts for 80–90% of pediatric HIVdisease. HIV infection has had exponential rise in developing countries like India, especially in urban areas. Significant literature on the clinical features of HIV infection in the pediatric age group from the rest of the world, there has been few studies from India. Also, it is possible that the spectrum of clinical profile of pediatric HIV infection in India may differ from According to the estimate of the World Health Organization; In this context the present study aims to know the clinical profile and spectrum of Opportunistic infection among HIV-infected patients. Total 73 children of more than 18 months HIV Infected children's were recruited with written conscent.All eligible children enrolled in the study were tested HIV1 and HIV2 using the ELISA tests from three different company kits as per the National AIDS Control Organization operational guidelines. Using a structured proforma secondary data were collected. Data were analyzed by using SPSS-16.50 version, Univaraite analysis and frequency matched test was employed to draw the significant inference. 39(53.42%) children of 73 cases presented with skin lesions. The commonest skin lesions were Scabies (6.84%), Pyoderma (6.84%) and Herpes zoster with Multidermatomal lesions (4.10%). Skin lesion was statistically associated with lower cd4 count at inception of HAART. Lower CD4 count was found to be more susceptible for dermatological manifestation. 30 (68.5%) cases were tuberculosis infection, 5(11.4%) suffering PCP, 4(9.1%), Esophageal Candidiasis, Cryptococcus Meningitis 2(4.3%) and recurrent pneumonias was 2(4.3%), 01 (2.3%) was Cryptosporidium. Overall prevalence of OI's among HIV infected children's were statistically significant $p<0.05$with lower CD4 count at inception of HAART. Knowledge of the clinical profile of HIV infected children is likely to help in better understanding of the disease and appropriate management.

KEYWORDS: HIV, HAART, CD4 Count, WHO, PCP, NACO, Manifestation

INTRODUCTION

National AIDS control organization, Ministry of Health and Family welfare (MHFW's), Government of India estimates that about 2.40 million Indians are living with HIV (1.93 -3.04 million) with an adult prevalence of 0.31% (2009). Children (<15 yrs) account for 3.5% of all infections, while 83% are the in age group 15-49 years. Of all HIV infections, 39% (930,000) are among women. India's highly heterogeneous epidemic is largely concentrated in only a few states — in the industrialized south and west, and in the north-east. The four high prevalence states of South India (Andhra Pradesh – 500,000, Maharashtra – 420,000, Karnataka – 250,000, Tamil Nadu – 150,000) account for 55% of all HIV infections in the country. West Bengal, Gujarat, Bihar and Uttar Pradesh are estimated to have more than 100,000 PLHA each and together account for another 22% of HIV infections in India. Though there exists significant literature on

the clinical features of HIV infection in the pediatric age group from the rest of the world, there have been few studies from India (1–18). Also, it is possible that the spectrum of clinical profile of pediatric HIV infection in India may differ from According to the estimate of the World Health Organization; In this context the present study aims to know the clinical profile and spectrum of Opportunistic infection among HIV-infected patients

MATERIALS AND METHODS

Total 73 children of more than 18 months HIV Infected children's were recruited with written conscent.All children enrolled in the study were tested HIV1 and HIV2 using the ELISA tests from three different company kits as per the National AIDS Control Organization operational guidelines. Using a structured proforma secondary data were collected. Parents or care takers or guardians were counseled by qualified counselors regarding the disease transmission, familial history etc., Nutrition counseling were also considered and treated as a integral part of the study. The presumed mode of transmission was collected on the basis of double blinded interview with parents. Sexual behavior, history of blood transfusions and the HIV serology status of the parents. If both parents were deceased, the HIV status of the parents was obtained from available records. Children were classified into four clinical categories using the revised Centre for Disease Control and prevention classification (CDC) of 1994. Category the number of children was included and who were not symptomatic. The clinical manifestations and risk factors of enrolled children were studied. Clinical diagnosis of the presenting illness was predicted by basic investigations and special investigations. Basic investigations - Complete blood counts, Erythrocyte sedimentation rate, Mantoux test, chest x-ray, blood culture, stool culture, urine culture. Three samples of gastric aspirate for AFB and 3 samples of sputum for AFB in children > 6 years were collected. Special investigations - Cerebrospinal fluid examination, ultrasound abdomen, arterial blood gas analysis, fine needle aspiration cytology (FNAC), modified acid fast staining for Cryptococcus in stools, relevant image process index, ELISA for IgG, IgM antibodies for Toxoplasma gondii and cytomegalovirus infections were recorded. The diagnosis of Tuberculosis was presumptively and based on the history of chronic cough, weight loss, contact history, Mantoux test and chest X-ray. Pneumocystis Carinii Pneumonia was confirmed based on the history of dyspnoea on exertion or nonproductive cough of recent onset. The evidence of diffuse bilateral interstitial infiltrates on chest X-ray and arterial blood gas analysis of arterial PO_2 < 70 mmHg and no evidence of bacterial pneumonia were considered. Oral candidiasis was diagnosed by the gross appearance of white patches or plaques in the oral cavity. Diagnosis of Esophageal Candidiasis was made with history of recent onset of retrosternal pain on swallowing and presence of oral candidiasis.Cryptococcal meningitis was diagnosed based on history of headache, with cerebrospinal fluid analysis for Cryptococcus by India ink preparation and Computerized Axial Tomography scan. Cryptosporidium infection was diagnosed based on the clinical symptoms of chronic diarrhoea of more than a month and isolation of the organisms from stool samples by modified acid fast staining. Cytomegalovirus retinitis was presumptively diagnosed; when a discrete patch of retinal whitening with distinct borders, spreading in a centrifugal manner along the paths of the blood vessels was seen on fundoscopic examination. Cluster Differentiation (CD4) cells counts were done in symptomatic patients and were categorized as mild, moderate or severe suppression depending on the age group and counts. All eligible children meriting hospitalization were admitted to pediatric wards of Bowring and Lady Curzon and Vani Vilas Children's hospitals.

RESULTS

Demographic profile of parents: 25(34.2%) 48(65.7%) cases were belong rural and urban area respectively. Most of the children were registered in orphanages, whose residential places were not known. Total 73 children >18 months of

HIV Infected children's were recruited with written consent. Males and Females comprises 37(50.7%), 36(49.3%) respectively (Ratio of 1:1). Majority of the HIV +Ve children age between 2-5 years 42(57.5%). The median age was 5 years (IQR 2. 6- 14 years). Single orphan 25(34.30%), Double Orphan12 (16.40%) and both alive 36(49.30%).

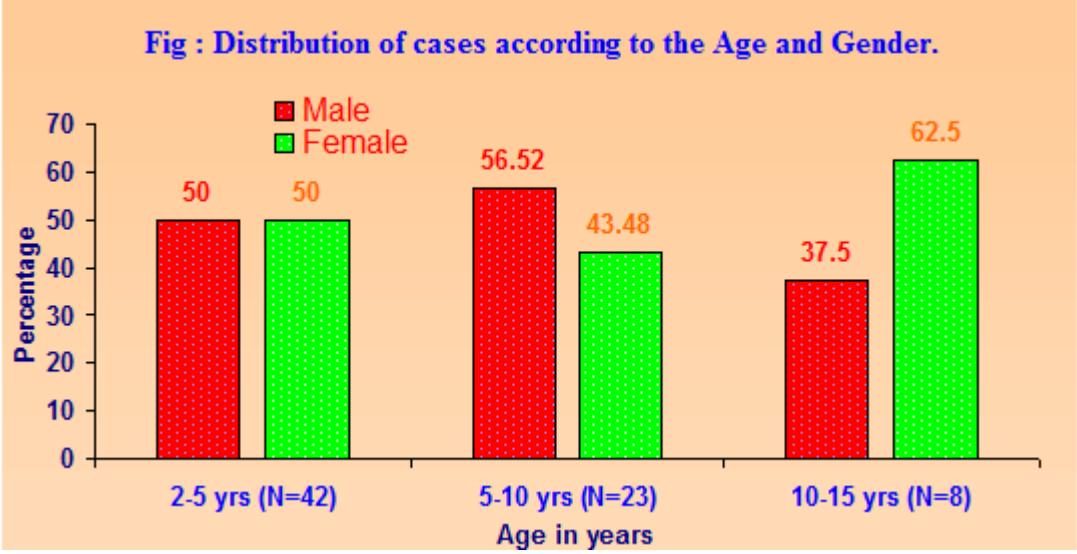

Figure 1: Distribution of Cases According To the Age and Gender

It was observed from the present study, 27(37%) children were below the 5th percentile, 11(15.2%) were between 5-10th percentile and 14(19.2%) children between 10-25th percentiles.

Table 1: Distribution of Symptoms (n = 73)

Symptoms	Number	Percentage	CI-95%	P-Value
Fever	58	79.5	57.63-60.12	0.001**
Cough	49	67.1	48.22-50.15	0.003**
Loss of appetite	47	64.4	46.50-48.22	0.001**
Weight loss	29	39.8	27.03-30.16	0.002**
Ear discharge	27	37	26.03-28.15	0.004*
Diarrhoea	14	19.9	13.68-15.26	0.051ns
Dysphagia	4	5.5	3.06-5.33	0.632ns

****, Significant at 0.05 level**

Symptoms were recorded for each follow up event and OPD admitted cases. Various symptoms was noticed and fever was accounted (79.50%, p=0.001), Cough 67.10% p=0.003, Loss of appetite 64.40% p=0.001, weight loss 39.80 p=0.002, ear discharge 37.0%, p=0.004,Diarrhoea 37.0% p=0.051 and Dysphagia was 19.90% p=0.632. Fever, cough, loss of appetite, weight loss ,ear discharge are significantly associated with HIV infection and lower CD4 count presented in Table (1).

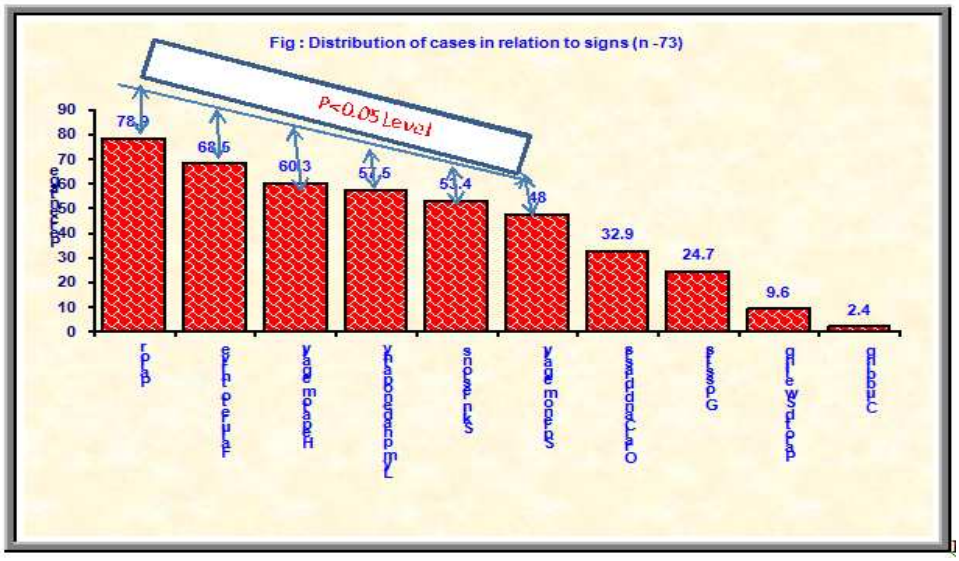

Figure 2: Status of Different Sign

Pallor 57(78.1%), failure to thrive 50(68.5%), hepatomegaly 42(60.3%), lymphadenopathy 42(57.5%) and skin lesions 39(53.4%) were the predominant signs observed in the present study.

Table 2: Distribution of Cases According to Skin Lesions. (N -73)

Skin Lesions	Number	Percentage	P-value
Scabies	05	6.84	p>0.05
Pyoderma	05	6.84	p>0.05
Herpes Zoster, Multi dermatomal	03	4.10	p>0.05
Periporitis	02	2.73	p>0.05
Fungal infection of right toe	01	1.36	p>0.05
Molluscum Contagiosum	01	1.36	p>0.05
Seborrhea	01	1.36	p>0.05
Others	21	28.76	P<0.05
Total	**39**	**53.42**	**P<0.05**

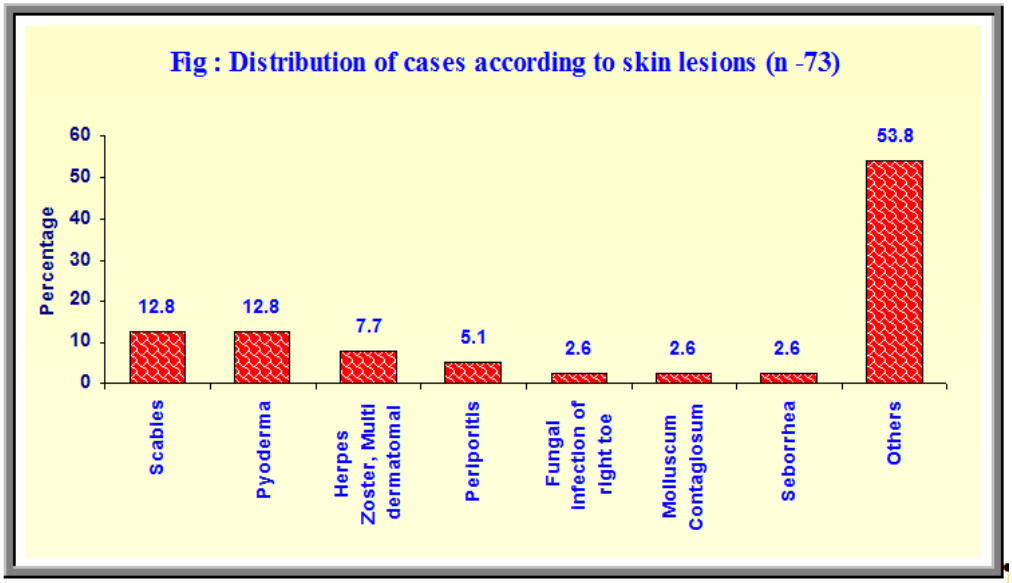

Figure 3: Distribution of Cases Based on Skin Lesions

39(53.42%) children of 73 cases presented with skin lesions. The commonest skin lesions were Scabies (6.84%), Pyoderma (6.84%) and Herpes zoster with Multidermatomal lesions (4.10%). Skin lesion was statistically associated with lower cd4 count at inception of HAART. Lower CD4 count was found to be more susceptible for dermatological manifestation.

Table 3: Distribution of Cases according to Centre for Disease Control and Prevention Classification (CDC) (n-73)

Clinical Staging			
CDC	**Frequency**	**Percent**	**P-Value**
Category- N	30	41.2	P<0.05
Category -A	12	16.4	p>0.05
Category -B	10	13.6	p>0.05
Category -C	21	28.8	P<0.05
Total	**73**	**100**	**P<0.05**

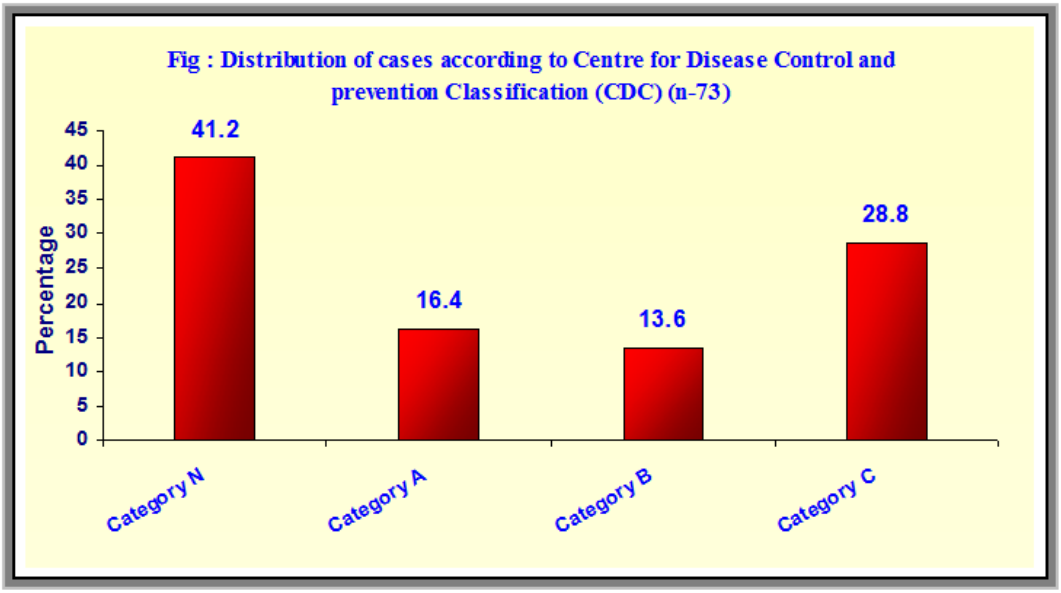

Figure 5: Cases Distributed According to CDC

The number of cases with different clinical staging was classified inaccordence with Centre for Disease Control (CDC) and prevention classification Categories ,category I was found to be 12 (16.4%), Cat -II,10(13.6%) 2 and 21(28.8%) was category III respectively. Cat I and Cat II were statistically significant (p<0.05) presented in Table (3)

Table 4: Distribution According to the Opportunistic Infections (n-44)

Opportunistic Infections	Number	Percentage	P-Value
Tuberculosis	30	68.2	P<0.05
Pnemocystitis Carinii Pneumonia	5	11.4	P<0.05
Esophageal Candidiasis	4	9.1	p>0.05
Cryptococcal meningitis	2	4.5	p>0.05
Recurrent Pneumonias	2	4.5	p>0.05
Cryptosporidial Infection	1	2.3	p>0.05
Total	**44**	**100**	**P<0.05**

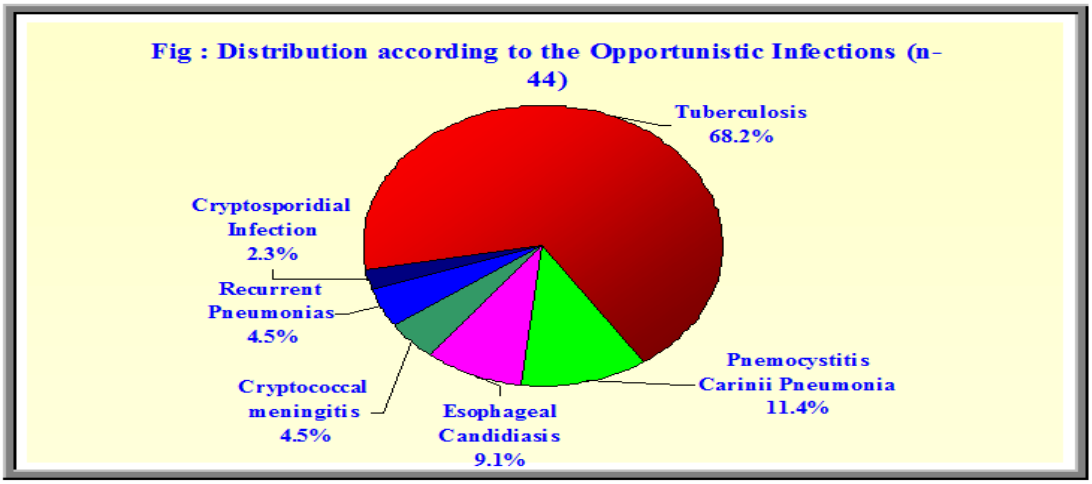

Figure 6: Percentage Variation of Oi's

Opportunistic infections were present in Table (4) It was observed that, 30(68.5%) cases were tuberculosis infection, 5(11.4%) suffering PCP, 4(9.1%), Esophageal Candidiasis, Cryptococcus Meningitis 2(4.3%) and recurrent pneumonias was 2(4.3%), 01 (2.3%) was Cryptosporidium. Overall prevalence of OI's among HIV infected children's were statistically significant p<0.05. As per the study lower base line CD4 count, Sever acute malnutrion (SAM), stunted growth and lesser BMI were considered for the predictors of OI's. Lower CD4 count at inception of HAART strongly associated with manifestation of OI's and different dermatological complications presented in Figure (6)

Table 5: Distribution of Tuberculosis Cases According to the Site of Presentation (N-30)

Tuberculosis	Number	Percentage	P-Value
Pulmonary TB	22	73.3	P<0.05
Disseminated TB	01	3.3	p>0.05
Miliary TB	02	6.7	p>0.05
Extra pulmonary TB: Abdominal TB	01	3.3	p>0.05
TB Lymphadenitis	04	13.3	P<0.05
Total	**30**	**100**	**P<0.05**

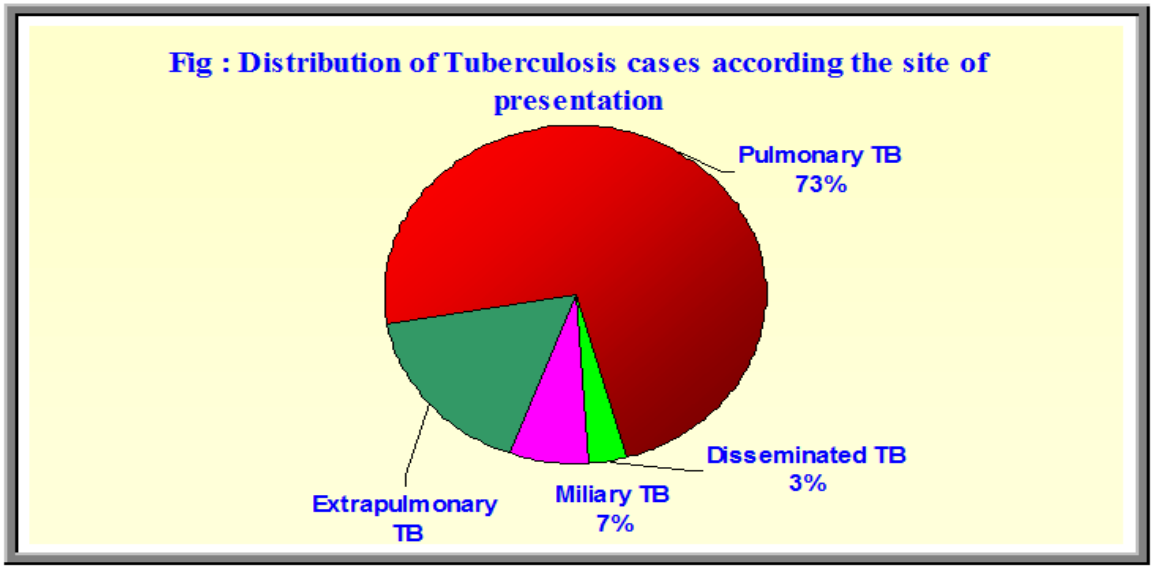

Figure 7: Different TB Manifestations

Majority of cases were PTB accounting for 22(73.3%). EPTB in 5(16.6%), Miliary TB in 2(6.1%) and Disseminated TB in 1(3.3%) Figure (7)

Table 6: Distribution of Cases of Opportunistic Infections According to Sex (n-44)

Opportunistic Infections	SEX		Total
	Male	Female	
Tuberculosis	**14 (46.7%)**	**16 (53.3%)**	**30**
Pnemocystitis Carinii Pneumonia	**3 (60%)**	**2 (40%)**	**5**
Esophageal Candidiasis	**3 (75%)**	**1(25%)**	**4**
Cryptococcal Meningitis	**1(50%)**	**1(50%)**	**2**
Recurrent Pneumonia	**1(50%)**	**1 (50%)**	**2**
Cryptosporidial Infection.	**1 (100%)**	**0 (0)**	**1**
Total	**23**	**21**	**44**

From the table(6) , it was found to be 46.7% males and 53.3% females were tuberculosis, 60% males and 40% females were infected PCP, and 7.5% males 2.5% female were infected esophageal candidacies.

Table 7: Table of Opportunistic Infection by Age Group (n-44)

Opportunistic Infections	Age group (Age)			Total
	2-5	5-10	10-15	
Tuberculosis	**17 (56.7%)**	**09 (30%)**	**04 (13.3%)**	30
Pnemocystitis Carinii Pneumonia	**05 (100%)**	**0.00**	**0.00**	05
Esophageal Candidiasis	**01 (25%)**	**03 (75%)**	**0.00**	04
Cryptococcal Meningitis	**0.00**	**02 (100%)**	**0.00**	02
Recurrent Pneumonia	**01 (50%)**	**01 (50%)**	**0.00**	02
Cryptosporidial Infection.	**0.00**	**01 (100%)**	**0.00**	01
Total	**24**	**16**	**04**	**44**

Present study documented that; the opportunistic infections were noticed age group between 2-5 years Table (7)

Table 8: CD4 Cell Counts of Children According to Age Wise Distribution (n-36)

1-5 yrs			6-12 yrs		
Immune Status	**CD4 counts**	**Cases**	**Immune Status**	**CD4 counts**	**Cases**
No Suppression	>1000/mm^3	2	**No Suppression**	>500/mm^3	4
Moderate Suppression	500-999/ mm^3	5	**Moderate Suppression**	200-499/mm^3	6
Severe Suppression	<500/ mm^3	6	**Severe Suppression**	<200/mm^3	13
Total		**13**	**Total**		**23**

Table (8) presented immunological suppression.Asper the study revealed that age group was classified between 1-5 years and 6-12 years. Immunological status was profounded by actual or observed CD4 count of HIV infected children .The study revealed that, age group between 1-5 years No suppression (>1000/mm3) was 2: Moderate 500-999 mm3 was 5: Sevre suppression < 500/mm3 was 6 and 6-12 years No Suppression >500mm3 was 4; Moderate Suppression 200-499/mm3 was 6 and severe suppression <200mm3 was 13. In HIV infected children severe suppression was significantly associated with different age group ($p<0.05$).

DISCUSSIONS

Present study revealed that, the opportunistic infections were most common manifestation in HIV infected

children. Clinical features in HIV-infected children in our study had some similarities and few differences from the previous Indian studies (3–5, 7, 10, 12, 13). Compare demographic data and clinical features of our study with those of previously reported Indian studies. As in the previous series, mother to child transmission was the most common mode of transmission in our study (3–6, 11, 13). Multitransfused patients like those with thalassemia major, hemophilia, etc. can get the infection via transfusion of infected blood (2,3,5,10). Patients with thalassemia can acquire the infection despite the screening of donors due to the presence of the seronegative window period during which the antibodies are not detected but the donor is infectious (3, 5, 13). Also, some multi transfused patients can acquire HIV through blood transfusions received prior to the compulsory screening of donors (10). Compulsory screening of blood for HIV was started in India (including the study location) in 1989.Lodha et al. (13) have shown that despite mandatory screening, 30% of children in their series were infected through blood transfusions (some mothers had also acquired the infection due to blood transfusions) and considering the presence of 'window period' they recommend that blood products should be used only when absolutely indicated (13). Though Sen et al. (10) have described weight loss, prolonged pyrexia, generalized lymphadenopathy, epitasis, extensivepurpuric lesions and thrombocytopenia in these patients, most of our cases with thalassemia major were asymptomatic with regard to the HIV infection. The age of patients in the study by Sen et al. was 5.5 to 19.5 years, which was older than our patients with thalassemia major; this may explain the difference in the clinical manifestations (10). In the study by Dhurat et al. (4), six multitransfused HIV-positive patients were asymptomatic for a median period of about 3.5years (range, 1 to 5 years). This strengthens the idea that children who acquire HIV infection perinatally become symptomatic before those infected by other routes (4,5). It also suggests that blood/blood products should be used judiciously (4). HIV acquired via sexual abuse has been reported previously (4) but was not encountered by us.Daga et al. (12) reported the presence of known HIVinfection in one/both parents in 7 cases and poor compliance on the part of the fathers in 17 cases. This may be due to the social impact of the disease in India. In our study, a systematic attempt was made to study the HIV status of the parents and siblings after proper counseling. However, five fathers of affected children could not be tested because of denial. In fact, Daga et al. have hypothesized to suspect HIV infection in a child where the father does not visit the hospital or has infrequent visits (12). Of the 218 siblings of the 50 children, 108 were tested and 96 were detected to be HIV positive. This relatively high percentage of HIVpositivity in the siblings may be deceptive as 110 siblings were not tested. Twenty patients were either not immunized. In the present study, diarrhea was the presenting manifestation in 15 children, 35.7% (14 had bacterial diarrhea and 1 had giardiasis). Infections causing diarrhea in HIV infected children include rotavirus, *Shigellae*, *Campylobacter*, *E. coli*, cryptosporidiosis, isosporiasis, cytomegalovirus and atypical mycobacteria (5,9). However, we could not demonstrate any unusual organisms in our patients

We encountered tuberculosis in 30 cases (24.0%). Tuberculosis in various forms—pulmonary 22(17.60%)and extra pulmonary01(0.8%), TB disseminated 01(0.80%) , military TB(1.60%), TB Lymphadenopathy 04(3.20%) — has been reported commonly in HIV-infected children (4,5,7,12,13). One cannot depend on the Mantoux (tuberculin) test as it may be falsely negative in patients with HIV (12). Only four of eight children diagnosed to have tuberculosis had positive Mantoux test in the study by Daga et al.(12). Only three patients had positive Mantoux test in our study. As in other studies, lack of culture facilities has made it difficult for us to study the presence of a typicalmycobacteria and resistance pattern in HIV-infected children (5). Merchant et al. reported 84 cases (29.4%) with tuberculosis in a cohort of 285 cases; of whom 48 had pulmonary lesions, 21 had disseminated tuberculosis, 8 had tubercular lymphadenopathy and 7 had neurotuberculosis (5). Dhurat et al. have reported pulmonary tuberculosis in 16cases, 9 extra pulmonary (of whom 4 had pulmonary tuberculosis as well; extra pulmonary sites: abdominal-4, neurotuberculosis-2 and lymphadenopathy-3 cases)

(4). A similar spectrum of tubercular manifestations was seen in our study as well.

Dermatological manifestations were common in our study. As noted from the present series, most skin lesions are secondary to infections (9). Of the various non infectious conditions (seborrheic dermatitis, atopic dermatitis, eczema, psoriasis, drug eruptions, and skin lesions associated with nutritional deficiencies), we encountered Scabies, Pyoderma, Herpes Zoster, Multi dermatomal, Periporitis, Fungal infection of right toe, Molluscum Contagiosum and Seborrhea . Similarly, Dhurat et al., have reported seborrheic dermatitis (6 cases),chicken pox (4 cases; hemorrhagic in 2 cases) and herpes zoster (4).

CONCLUSIONS

Tuberculosis was the most common opportunistic infection in HIV infected children in the present study accounting for 30(68.2%). TB should be regarded as a sentinel illness for HIV infection and screening for the disease in all cases of HIV infected children and it should be recommended. Perinatal mode of transmission is the most common mode of acquiring HIV infection in children. More than 60% patients have severe protein-energy malnutrition. Gastrointestinal and respiratory system manifestations are common. Tuberculosis and candidiasis are the most common opportunistic infections in HIV-infected children. Knowledge of the clinical profile of HIVinfectedchildren is likely to help in better understanding of the disease and appropriate management. The commonest age of presentation was between 2 years to 5 years. Majority of the children belonged to 5-25th percentile for weight. The most common symptoms were fever, weight loss, and cough. Most of the children presented with failure to thrive, pallor, hepatomegaly, lymphadenopathy and splenomegaly. In the absence of early affordable antiretroviral therapy, prompt diagnosis and treatment of bacterial infections and Pnemocystitis Carinii Pneumonia prophylaxis with nutritional rehabilitation is the key to prolong life and ensuring optimal health on children with HIV infection.

RECOMMENDATIONS

Screening for all HIV positive children for tuberculosis is necessary as tuberculosis acts as a sentinel illness in these children. Nutritional Rehabilitation is also necessary as it plays a major role in preventing opportunistic infections. Early diagnosis of opportunistic infection is important in ensuring early treatment and optimal prophylaxis, thus improving the quality of life of HIV infected children. Early diagnosis of opportunistic infections also helps in planning steps to meet the management challenges presented by HIV infected children.

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