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Original Research Article

Opportunistic infections in HIV infected children and its correlation with CD4 count

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ABSTRACT

Background: HIV infected children usually have higher viral load, weaker immune system, variable latency period, fewer opportunistic infections and fewer medicines approved for management. Knowledge of the clinical profile in HIV infected children will help in better understanding of the disease and management. The present study was aimed to study the clinical presentation, opportunistic infections, WHO clinical stage, nutritional status and its correlation with CD4 count.
Methods: 50 children below 14 years of age and seropositive for HIV were included in this study and were categorized into WHO clinical stages. They were further classified based on CD4 count values in accordance with WHO classification of immunodeficiency.
Results: In the study 30% of children were in the age group of 4 to 7 years. The mean age of presentation was 7.12 years. 56% of children presented with WHO clinical stage III and 30% with stage IV at first visit. Vertical transmission was the predominant mode of transmission. Anaemia (48%), fever (42%) and cough (34%) were common symptoms. Pulmonary tuberculosis (28%) was the most common opportunistic infection seen at mean CD4 count of 267 ± 5.37.
Conclusions: The manifestations of HIV infection in children mimic a number of other illnesses. Anaemia, fever and cough were the common presenting clinical features. Tuberculosis is the most common opportunistic infection in HIV infected children. As WHO clinical stage and grade of PEM increases CD4 count decreases. CD4 count is a reliable marker of disease progression in HIV infected children.

Keywords: CD4 count, HIV, Opportunistic infection, PEM, WHO clinical stage

INTRODUCTION

Paediatric HIV is a major world health problem, which is progressing at an alarming rate. India has the 3rd largest number of people living with HIV/AIDS. Based on HIV sentinel surveillance 2008-09 it is estimated that 23.9 lakh people are infected with HIV in India out of which 4.4% are children.

Although children represent only 6% of all people infected with HIV/AIDS, out of this about 50% die within 2 yrs of onset, constituting about 18% out of the 3.2 million deaths due to HIV every year.[1] The predominant mode of transmission in children is vertical i.e., it is acquired through intrauterine, intrapartum or through breast feeding from a HIV infected mother.[2] Most of these children become symptomatic within 1-2 years of acquisition of HIV infection and majority if untreated die by 76-90 months of age.[3]

Children with HIV infection differ from HIV infected adult patients.[4] Soon after HIV was found to the cause of AIDS, it was shown that the virus binds to receptors on CD4 cells, enters the cells and uses them to create new

virus, destroying them in the process. This results in the depletion of CD4 cells and immunodeficiency.[5]

Clinical spectrum of presentation of HIV in children

The clinical presentation of HIV commonly seen in children is hepatosplenomegaly, generalized lymphadenopathy and failure to thrive. Common opportunistic infections are tuberculosis (TB), herpes zoster and simplex, recurrent pneumonia, chronic diarrhoea, and oral thrush. PCP pneumonia is common in infants.

Organ dysfunction due to HIV is seen in older children and includes HIV encephalopathy, HIV cardiomyopathy, haematological problems and proteinuria. Thus, untreated HIV in children is associated with high morbidity and mortality.[6,7]

Opportunistic infections (OIs) are the most common cause of death among children living with HIV/AIDS. These infections are called "opportunistic" because they take advantage of the weakened immune system and they can cause devastating illnesses. OIs are a sign of declining immune system. OIs in children are usually primary and have a more fulminant course in comparison to adults. OIs in HIV children are typically seen in children with severe depression of CD4 count or CD4%.[8]

Common OIs in HIV infected children are

Mycobacteria

- Tuberculosis
- Mycobacterium Avium complex (MAC)

Bacterial infection

- Invasive and recurrent Fungi
- Pneumocystis Carnii Pneumonia
- Candida, Cryptococcus, Histoplasmosis

Protozoa

- Toxoplasmosis
- Cryptosporidiosis

Viruses

- Cytomegalovirus
- Herpes simplex virus
- Varicella zoster virus
- Molluscum Contagiosum

With the increased availability of equipment to perform CD4 counts and the knowledge that CD4 cells were the primary target of HIV, the determination of CD4 count became the standard measure of immunodeficiency in HIV infected patients in resource rich countries. The relative ease of CD4 cell monitoring also led to its advocacy in treatment guidelines for determining when to start, stop or change ART and for deciding when to initiate prophylaxis for opportunistic infections. This is despite the fact that CD4 count does not always correlate with functional immunity; some patients with normal CD4 counts are susceptible to OIs and some patients with significantly depressed CD4 counts do not seem unduly susceptible to OIs. Hence this study attempts to correlate CD4 count with opportunistic infections. The objective of study was to study the clinical profile of opportunistic infections in HIV infected children under 14 years of age. To correlate opportunistic infections with CD4 count.

Table 1: Immunologic categories based on age specific CD4+ T-lymphocyte counts and percent of total lymphocytes.

Immunologic categories	Age of child					
	< 12 months		1-5 yrs		6-12 yrs	
	Cells/µl	(%)	Cells/µl	(%)	Cells/µl	(%)
No evidence of suppression	>1500	>25	>1000	>25	>500	>25
Evidence of moderate suppression	750-1499	15-24	500-999	15-24	200-499	15-24
Severe suppression	<750	<15	<500	<15	<200	<15

METHODS

Study design: Prospective observational study.

Inclusion criteria

All children seropositive for HIV/DBS positive/ whole blood PCR positive up to 14 years of age are included in the study.

Exclusion criteria

Patients with negative laboratory test for HIV are excluded from the study. All children seropositive for HIV will be included in the study. Written consent was taken from the parents before enrolling in the study. A detailed clinical evaluation (history and examination) and relevant laboratory investigations will be done for all

subjects as per the Proforma. Based on clinical presentations, the children were categorized into various WHO clinical stages. Weight for age was used to grade them (IAP classification) for protein energy malnutrition. They were further classified based on CD4 count values in accordance with WHO classification of immunodeficiency.

Investigations

Mandatory investigations

- ELISA (Tridot, Coombs and Capillus) test for HIV
- The CD4 count by flow cytometry
- DBS/ whole blood DNA PCR if child <18months of age
- Complete Haemogram

Optional investigations

- Sputum for AFB/gastric lavage for AFB
- Chest X-ray: Mantoux
- Blood culture and sensitivity
- CSF analysis and culture sensitivity
- Stool routine and culture sensitivity
- Ultrasonography abdomen/chest/cranium
- Fine needle aspiration cytology of lymph node
- CT scan and others.

Various samples e.g. blood, sputum, oral swab, stool, urine, CSF, lymph node aspirates were collected as per symptoms and clinical presentations. All the specimens were collected under universal aseptic precautions in suitable sterile containers.

RESULTS

Total no of children included in the study were 50. Among them 28 were males and 22 were females. Mean age of presentation is 7.12 years. Mean age of presentation in male children is 7.91±3.29. Mean age of presentation in female children is 5.18±2.95. The Mean age of presentation in male children was significantly higher than female children. In the study, female children had mean CD4 count 488±9.63, and male children had mean CD4 count 340±8.31.

Table 2: Age and WHO classification of immunodeficiency.

Age group	No evidence of suppression	Evidence of moderate suppression	Severe suppression	Total
0 - 5y	02 (18%)	05 (46%)	04 (36%)	11
5y - 7y	04 (27%)	04 (27%)	07 (46%)	15
7y - 10y	03 (27%)	03 (27%)	05 (46%)	11
10y - 13y	00	06 (46%)	07 (54)	13
Total	09 (18%)	18 (36%)	23 (46%)	50

Table 3: Frequency of various symptoms and signs in HIV infected children.

Symptoms and sign	%
Fever	42
Recurrent /Chronic diarrheoa	7
Cough	34
Weight loss	25
Skin lesions	23
Lymphadenopathy	17
Hepatomegaly	7
Hepatosplenomegaly	3
Anemia	48
Recurrent /persistent bacterial pneumonia	10
CNS involvement	9

Out of 50 children 54% of children are from rural area, 30% are from urban area, 16% are from urban slum. Vertical transmission was found to be the predominant mode of transmission in the study, which is 92%, based on maternal seropositivity. One case (2%) is transfusion associated and mode of transmission unknown in 8% cases.

Table 4: Opportunistic infections in HIV infected children.

Opportunistic infections	%
Pulmonary tuberculosis	26
Abdominal Tuberculosis	2
Tubercular meningitis	8
Oral candidiasis	10
Pneumocystis carinii pneumonia	8
Herpes Zoster	2

The study shows as the age advances the severity of immune suppression increases, highest immune suppression is seen in the age group of 10 to 13 yrs. The common presentations in the study are anemia (48%) followed by fever (42%) and Cough (34%). The most common opportunistic infection in the present study is pulmonary tuberculosis (28%) followed by oral candidiasis (12%).

Table 5: Correlation of CD4 count with opportunistic infections.

Opportunistic infections	Number (%)	Mean CD4 count± SD
Abdominal TB	01 (2%)	348
Pulmonary TB	13 (26%)	267±5.37
Oral candidiasis	05 (10%)	364.8±6.5
Tubercular meningitis	04 (8%)	319±3.36
Pneumocystis Jirovecii pneumonia	04 (8%)	261.25±10.8
Herpes zoster	01 (2%)	613
Total	28 (56%)	

Opportunistic infections were seen in 56% of children. Pulmonary TB is the most common opportunistic infection (26%) followed by oral candidiasis (10%) and Pneumocystis Jirovecii pneumonia was seen in 8% of children. Pulmonary TB is seen at mean CD4 count of 267±5.37, Oral candidiasis is seen at mean CD4 count of 364.8±6.5, Pneumocystis Jirovecii pneumonia is seen at mean CD4 count of 261.25±10.8, tubercular meningitis is seen at mean CD4 count of 319±3.36. The study showed 100% of children with Pneumocystis jirovecii pneumonia, 80% of children with pulmonary TB and 60% of children with oral candidiasis had evidence of severe immune suppression.

Tubercular meningitis occurred with equal incidence (50%) with evidence of moderate suppression and severe suppression.

Hence it is concluded that opportunistic infections increase with increasing immunological category.

Table 6: Correlation of opportunistic infections with immunological category.

Opportunistic Infections	No evidence of suppression	Evidence of moderate suppression	Severe suppression	Total
Abdominal TB	0	1 (100%)	0	1
Pulmonary TB	0	3 (20%)	10 (80%)	13
Oral candidiasis	0	2 (40%)	3 (60%)	5
Tubercular meningitis	0	2 (50%)	2 (50%)	4
PCP	0	0	4 (100%)	4
Herpes Zoster	0	1 (100%)	0	1

The mean CD4 count in WHO clinical stage I is 1093±10.73. The mean CD4 count in WHO clinical stage II is 611±8.85. The mean CD4 count in WHO clinical stage III is 338.5±5.70. The mean CD4% in WHO clinical stage IV is 307 ±.09. Study showed children with WHO clinical stage 1 and II had no evidence of immune suppression in 100% of cases, children with stage III had evidence of moderate immune suppression in 46%, severe immune suppression in 50% of cases. Children with stage IV had evidence of moderate immune suppression in 29%, severe immune suppression in 71% of cases. The severity of immune suppression increases with increasing WHO clinical stages.

DISCUSSION

Out of 50 cases in the study, majority of children were in the age group of 4 to 7 years. The mean age of presentation was 7.12y. In the present study, 28 (56%) were males and 22 (44%) were females. Male to female ratio was 1:0.78. Similar male predominance was noted in other studies like Agarwal et al, shah et al and Sehgal et al.[9-11] It was observed that as age advances CD4 count decreases. As the age advances severity of immune suppression increases and hence the CD4 count decreases. Female mean CD4 count was 488 and for male it is 340, which is lower but the difference was statistically not significant. Similar result had been observed by Agarwal et al.[9] Out of 50 children majority of children were from rural area, followed by urban area and least from urban slum. Similar incidence had been found with study by Pol RR.[12] In the present study commonest mode of transmission was vertical transmission (92%). Many other studies also reported that vertical transmission was predominant route of transmission during first 14 years of life.[9,10,12] The study showed with the increasing WHO clinical stage there was decline of CD4 count, which is in accordance with study conducted by Agarwal et al.[9]

Study showed opportunistic infections in 56% of children. Pulmonary TB was the most common opportunistic infection (26%) followed by oral candidiasis (10%), Pneumocystis carinii pneumonia was seen in 8% of children. Pulmonary TB was seen at mean CD4 count of 267±5.37, Oral candidiasis was seen at mean CD4 count of 364.8±6.5, Pneumocystis carinii pneumonia was seen at mean CD4 count of 261.25±10.8, tubercular meningitis was seen at mean CD4 count of 319±3.36. Similar findings were observed in studies by Ramesh Pol R.[12] The study showed with the increasing WHO clinical stage there was decline of CD4 count. The

mean CD4 count in WHO clinical stage I is 1093±10.73. The mean CD4 count in WHO clinical stage II is 611±8.85. The mean CD4 count in WHO clinical stage III is 338.5±5.70. The mean CD4% in WHO clinical stage IV is 307 ±.09.

Study showed children with WHO clinical stage 1& II had no evidence of immune suppression cases, children with stage III had evidence of moderate immune suppression in 46%, severe immune suppression in 50% of cases. Children with stage IV had evidence of moderate immune suppression in 29%, severe immune suppression in 71% of cases. The severity of immune suppression increases with increasing WHO clinical stages.

CONCLUSION

There is high incidence of HIV cases in our study area because of the large number of migratory labour population residing in the area whose livelihood was maintained by daily earning duty. Tuberculosis and oral candidiasis are the most common opportunistic infections in HIV infected children. Children with lower mean CD4 counts are more likely to suffer from PCP and Pulmonary tuberculosis than other types of opportunistic infections. Perinatal transmission is the most common mode of acquiring HIV in Pediatric age group. As WHO clinical stage of HIV increases CD4 count decreases. CD4 count decreases as the grade of PEM increases. Besides ART, early diagnosis and prompt management of opportunistic infections is the cornerstone of HIV management

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