

Original Research Article

Clinical spectrum of paediatric HIV infection in a tertiary care centre in South India

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ABSTRACT

Background: The global burden of paediatric HIV and acquired immune deficiency syndrome (AIDS) remains a challenge for healthcare workers around the world, particularly in developing countries. The objective of this study is to describe the spectrum of HIV infection in children including the mode of transmission, clinical manifestations and opportunistic infections associated with HIV infection.

Methods: Confirmed HIV seropositive children aged between 18 months to 19 years admitted to paediatric ward of JSS hospital, Mysore during two-year period were enrolled in this prospective observational study. Detailed history, socio-demographic characteristics and clinical manifestations were recorded in the predesigned performa. Nutritional assessment, complete physical, systemic and neurological examination was performed at the time of admission and was supplemented with ancillary investigations. Patients were correlated with modified WHO clinical case definition for AIDS and categorized as per revised CDC NABC classification of pediatric HIV infection.

Results: Forty HIV-infected children were enrolled: with mean age of 4.5 years. Vertical transmission was the predominant mode of HIV transmission (97.5%). Most of the children were severely symptomatic belonging to category-C of NABC classification. Common clinical manifestations noted were failure to thrive (45%), recurrent respiratory infections (42%), bacterial skin infection (36%), recurrent otitis (42.5%), papulo-pruritic dermatitis (22%), hepatosplenomegaly (85%), lymphadenopathy (45%) and HIV encephalopathy (52%). The common opportunistic infections observed were pulmonary tuberculosis (45%), recurrent diarrhoea (35%), oral candidiasis (30%). The rare presentations of HIV noted were chronic thrombocytopenia and a case of dilated cardiomyopathy.

Conclusions: Vertical transmission was the major route of HIV infection. HIV encephalopathy was more common among severely affected children. Tuberculosis was the commonest opportunistic infection.

Keywords: CDC NABC classification, Children, Failure to thrive, HIV infection

INTRODUCTION

The global impact of the Human Immunodeficiency Virus (HIV) epidemic has been so dramatic and devastating that it has been described as the "Epidemic of our century".¹ As on today, approximately 37 million people live with HIV infection world over. This includes approximately 2 million children with HIV infection.²

More than 90% of these patients with HIV infections are living in developing countries. In developed countries, pediatric AIDS constitute only 2% of all HIV infection. Whereas in Asia and Africa, it comprises 15-20% of all cases, due to greater affliction of women in the child bearing age group.³ Today India has approximately 2 million people living with HIV infection - the third

highest figure in the world after South Africa and Nigeria.⁴

Pediatric HIV infection occurs mainly through vertical transmission, with a prevalence of HIV around 0.5% in antenatal mothers. India has estimated 145,000 children <15 years of age who are infected by HIV/AIDS, and about 22,000 new infections occur every year. Children account for 7% of all the new HIV infections.⁵

"A child is not a miniature adult" this adage is appropriate for HIV/AIDS as it is anywhere else. The natural course, mode of transmission and clinical presentation of pediatric AIDS varies considerably from that of adults. Children tend to have a more bacterial and less opportunistic infection and tend to develop malignancies very rarely.⁶ One of the problems in establishing the diagnosis in developing countries has been the lack of adequate laboratory facilities and the fact that the clinical manifestation of HIV infection in children are often seen in uninfected children.⁷

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, Maharashtra, Karnataka, Tamil Nadu) account for 55% of all HIV infections in the country.

METHODS

Children and adolescents between the age group 18 months and 19 years treated at department of pediatrics, JSS Hospital, Mysore with confirmed HIV infection were enrolled in the study. This observational prospective study was conducted from March 2002 to February 2004. After taking written consent from either parent or attendant, clinically suspected cases beyond 18 months were subjected to HIV - ELISA. The HIV-1 and HIV-2 serology in all children was performed. The diagnosis of HIV infection was confirmed by two positive ELISA tests using two different HIV ELISA kits.

Forty children with confirmed HIV infection were included in this study. Ethical approval was obtained from hospital ethical committee.

Detailed history and clinical examination was performed in all cases. The socio-demographic characteristics, risk factors, parental status, sibling status, natal history, developmental history, anthropometric measurements and clinical manifestations were noted in a predesigned performa.

The siblings and parents of all patients were also screened for HIV by ELISA tests after informed consent. The clinical findings were correlated with WHO modified definition for pediatric AIDS (1989) and children were classified into clinical categories using the revised CDC NABC classification of 1994.⁸ Clinical

diagnosis of the presenting illness was supplemented with ancillary investigations where possible. Protein energy malnutrition was graded as per IAP classification.

LIP was diagnosed on the basis of chronic cough and presence of reticulonodular opacities on the chest radiograph, with or without hilar adenopathy, persisting for more than 2 months and unresponsive to antimicrobial or antitubercular therapy.

PCP was diagnosed on findings of persistent cough and/or tachypnea with minimal findings on auscultation, hypoxemia on pulse oximetry, with x-ray evidence of bilateral diffuse infiltrates, response to co-trimoxazole and confirmed on bronchoalveolar or lung biopsy where possible. HIV Encephalopathy was diagnosed using CDC criteria: Neurologically normal at the baseline, subsequently developing any one of the following abnormalities like impairment of brain growth (microcephaly: head circumference falling less than two standard deviation from the mean for age and sex), decline of cognitive function and clinical motor dysfunction.⁹

The HIV-1 and HIV-2 serology in all children was performed using two different ELISA kits. UBI HIV $\frac{1}{2}$ EIA (Beijing United Biomedical Limited, China) and HIV-CheX (Xcytos Diagnostics Pvt. Ltd. Jyothi Industrial Estate, Bangalore) having a sensitivity of over 99.5% was used. An induration of 5 mm or more after 72 hours is taken as positive mantoux test.

Chest x-rays were taken for all cases. The investigations done as required are FNAC, sputum gastric lavage, stool microscopy and modified acid fast test, stool culture and sensitivity, blood culture and sensitivity, pus culture and sensitivity, CSF examination, CT scan, Echocardiography, CD4 count: CD4 lymphocyte subset testing was done using a flow cytometer (Becton Dickinson Fscan, USA) or using ELISA test (Capcellia CD4/8, Sanoli Diagnostics Pasteur, France). To describe nominal data simple percentages were used. Mean and standard deviations were used to describe normally distributed data from the subjects. The relationship between different continuous variables was determined by Spearman rank correlation test.

RESULTS

A total of 40 children with confirmed HIV test results were enrolled in the study. The age range was from 18 months to 10 years. In the above period a total of 414 HIV/AIDS cases were registered in our hospital AIDS cell. Pediatric HIV/AIDS constitute 7.24% of these cases. Out of the total 40 cases 24 (60%) were males and 16 (40%) were females.

The mean age of males was 4.8 years (SD 2.4 years) and in females mean age were 4.1 years (SD 2.2 years). Put together the mean age for both sexes was 4.4 with a

standard deviation of 2.3 years. The maximum cases are in the age group 1.5-3 years accounting for 40% cases followed by 27.5% in the age group of 4.5-6 years. It can be seen that 80% of the total cases were in the age below 6 years (Table 1).

Table 1: Distribution of age and sex of cases.

Age in years	Male (%)	Female (%)	Total (%)
1.5-3	8(20)	8(20)	16(40)
3-4.5	4(10)	1(2.5)	5(12.5)
4.5-6	6(15)	5(12.5)	11(27.5)
6-7.5	3 (7.5)	1(2.5)	4(10)
7.5-9	2 (5)	1(2.5)	3(7.5)
9-10.5	1 (2.5)	0(0)	1(2.5)
Total	24(60)	16(40)	40(100)

Thirty-nine (97.5%) of the 40 had acquired infection by perinatal transmission. In one child mode of transmission was unknown (2.5%).

Of the thirty-nine mothers whose children acquired HIV vertically, none of them received anti-retro viral prophylaxis during their pregnancy and had breast fed their infants.

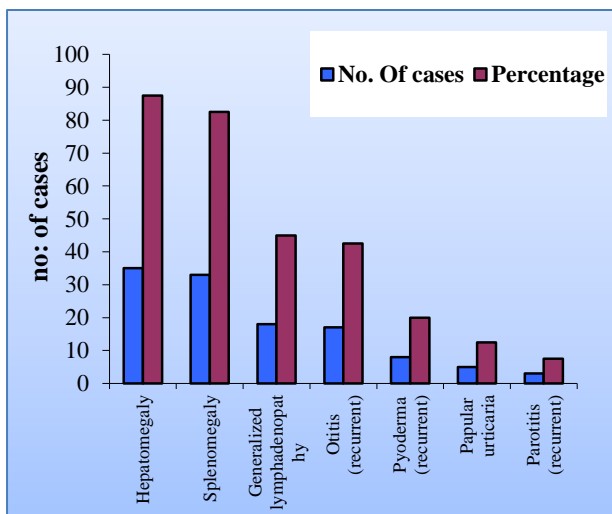


Figure 1: NABC category-A illnesses (n=40).

Majority of cases (70%) were diagnosed at age less than 5 years and 30% of cases between 5-10 years. The mean age of diagnosis in this series was 4.4 years. Of the total cases, 24 cases (60%) correlated with WHO modified definition for Paediatric AIDS (1989).

As per the clinical categories of children with HIV infection - CDC NABC classification two children (5%) were asymptomatic (Category-N) and 38 children (95%) were symptomatic. Maximum cases are in Category-C (severely symptomatic) constituting 62.5%, followed by Category-B (moderately symptomatic) 22.5% and category-A (mildly symptomatic) constitute 10% respectively.

Among the category-A symptoms the most common are hepatomegaly (87.5%) and splenomegaly (82.5%) (Figure 1). Generalized lymphadenopathy constitutes 45% followed by recurrent otitis media by 42.5%. In category-B failure to thrive and pulmonary tuberculosis are the most common manifestations constituting 45% each. Recurrent diarrhoea constitutes 35% followed by oral candidiasis by 30% (Figure 2).

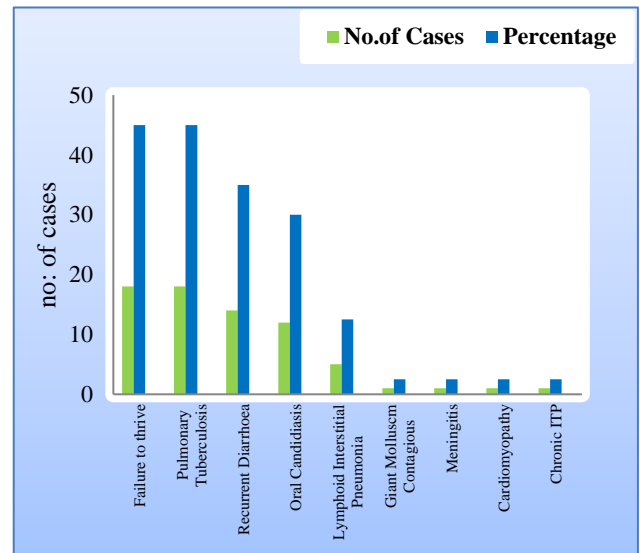


Figure 2: NABC category-B illnesses (n = 40).

HIV encephalopathy was the most common symptom among category-C manifestation accounting for 52.5% of cases. 17 cases had recurrent pneumonia (42.5%). LIP with bronchiectasis was noted in two cases (5%) whereas PCP was seen only in one case (2.5%). Extra pulmonary tuberculosis was seen in 2 cases (5%).

One had abdominal tuberculosis and other had tuberculoma (Figure 3).

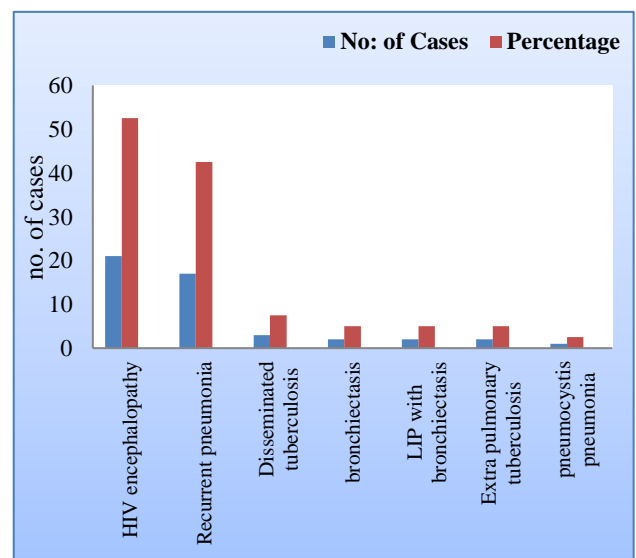


Figure 3: NABC category-C illnesses (n = 40).

Eight children (20%) were nutritionally normal in present study. Of these 2 cases were moderately symptomatic and 4 cases were severely symptomatic. Equal number of cases was seen among Grade II, Grade III and Grade IV malnutrition (9 cases each).

One case of kwashiorkor was seen with Grade IV malnutrition. Most common tubercular manifestation noted was pulmonary tuberculosis (78.3%). Three patients with severe infection presented with disseminated tuberculosis (13.1%) (Table 2).

Table 2: Different Tubercular manifestations (n=23).

Tubercular manifestation	No. of cases	Percent
Pulmonary Tuberculosis	18	78.3
Disseminated Tuberculosis	3	13.1
Abdominal Tuberculosis	1	4.34
Neuro-Tuberculosis	1	4.34

Recurrent pyodema (36.3%), papular urticaria (22.7%), and seborrheic dermatitis (13.6%) are the common skin manifestations in this study group. One child presented with extensive Tinea corporis involving the face, trunk and limbs.

Microcephaly was present in all except one case of HIV encephalopathy. Language is one domain that appeared to be highly vulnerable to the effect of CNS HIV infection (28.5%). Expressive language (5 cases) was significantly impaired compared to receptive language (1 case). Global developmental delay was present in two cases (9.5%). One child with motor delay had associated unilateral spasticity and hyper-reflexia.

The mean age of presentation of LIP was 5.6 years. All the patients with LIP presented with x-ray suggestive bilateral reticulonodular pattern. Tachypnea and clubbing was present in all patients (100%). Grade IV clubbing was noted in three cases. Hypoxia was detected by pulse oximeter, showing oxygen saturation less than 90% in 4 cases (80%). Associated features like generalized lymphadenopathy were noted in 2 cases (40%) and parotid enlargement was not detected in any of the cases. X-ray showed honey combing in two cases of LIP suggestive of associated Bronchiectasis (40%).

Tuberculosis (pulmonary and extra pulmonary) was the most common opportunistic infection constituting 62% of the cases. Pulmonary tuberculosis (18 cases) was the most common tubercular manifestation accounting about 78%. Recurrent pneumonia and CSOM were the second most opportunistic infections with equal number of cases (17 cases). Chronic diarrhoea constitute 37% and oral candidiasis constitute 32% of common opportunistic infections. One case of pneumocystis pneumonia was diagnosed in the study and it was histopathologically confirmed by postmortem percutaneous lung aspirate which showed P. carinii cysts in the alveolar space. Recurrent pyoderma was the most common opportunistic

skin infection (21.6%) and one case each of persistent herpes zoster, giant molluscum contagiosum and extensive tinea corporis was noted (Table 3).

Table 3: common opportunistic infections (n=37).

Opportunistic Infections	No. of cases	Percent
Tuberculosis (pulmonary and extra pulmonary)	23	62.1
Recurrent Pneumonia	17	46.0
Chronic Suppurative Otitis Media	17	46.0
Chronic Diarrhoea	14	37.0
Oral candidiasis	12	32.0
Recurrent Pyoderma	8	21.6
Pneumocystis pneumonia	1	2.7
Persistent Herpes Zoster	1	2.7
Giant Molluscum Contagiosum	1	2.7
Extensive Tinea Corporis	1	2.7

Mantoux tests were negative in all children. Chest x-rays were normal in 8 cases (20%). Patchy bronchopneumonia pattern was noted in 12 cases (30%). Diffuse infiltrate was seen in 7 cases (17.5%). Segmental or lobar lesions were present in 6 cases (15%). Bilateral reticulonodular pattern suggestive of LIP was present in 5 cases (12.5%). Out of these two cases had associated bronchiectasis. FNAC of enlarged lymph nodes were done in 5 cases. One case showed tuberculous granuloma and rest showed non-specific lymphadenitis. Aspiration cytology of liver, lung and lymph nodes were negative in cases of disseminated tuberculosis. Gastric lavage for AFB was done in four cases and the results were negative.

Modified Ziehl Neelson stain for *Cryptosporidium* was positive in one case. Of the 14 children with recurrent diarrhoea enteric pathogens were isolated in only 5 cases. These includes *Salmonella*, *Candida albicans*, *E. Coli* and *Giardia lamblia* and *Cryptosporidium*. Out of 17 cases with CSOM, pathogens were isolated from 4 cases, which includes *Pseudomonas aeruginosa* (2 cases), *Coagulase negative Staphylococci* and *Proteus mirabilis*. CD4 counts were done only in 8 children, as cost of the test was prohibitive for most of the families. Of the children in whom CD4 counts were done, 5 (62.5%) had evidence of severe immuno suppression. The lowest CD4 count noted was 148 cells/ μ L. The mean CD4 count level among 1-5 years age group was 374 cells/ μ L and 6-12 age group was 378 cells/ μ L.

DISCUSSION

Male to female ratio in the study was 1.5:1 and this is in accordance with the ratio observed by Verghese et al (1.3:1).¹⁰ The mean age at presentation was 4.4 years in this study and this correlates with the study done by Lodha et al (4.5 years).¹¹ The study done by Merchant et al showed 74.73% of patients were below the age of 5 years and this is in accordance with the 70% in the

present study.¹ Madhivanam et al study showed that 68.5% of children had both parents HIV sero positive and 22.8% had sero negative parents, where this study showed 82.5% of children had both parents sero positive and 2.5% had sero negative parents.¹² The obvious difference in these observations is due to the larger number of children who had been HIV infected by blood transfusion in Madhivanam et al., study.¹² Pediatric HIV represents primarily a vertically transmitted infection. In present study, vertical transmission was noted in 39 cases (97.5%) and transmission was unknown in one case (2.5%). Compared to the above studies the present study showed higher incidence of vertical transmission. The likely explanation for this is no patients with primary hematological or oncological diseases with HIV infection were included in this study. But the above-mentioned studies had included patients who acquired HIV infection by multiple blood transfusion to treat their primary diseases like thalassemia, hemophilia, Fanconi anemia, leukemia and exchange transfusion for hyperbilirubinemia.

Twenty percent of the children in the study have single parents and fifteen percent had lost both the parents due to AIDS related complications. This causes emotional and financial complications for these children. Majority of the children had lost their fathers (65% of the total deaths). These statistics clearly emphasize the 'family dimension' of the HIV pandemic. The increasing number of orphaned children of parents who have died from AIDS is an emerging crisis in many developing countries.

In the present study 60% of cases fulfilled the modified WHO clinical case definition. A study report by Daga et al showed that of 28 confirmed cases of HIV, only 6 (21%) fulfilled the WHO clinical case definition for AIDS in children.⁷ The higher sensitivity in this study can be explained by the inclusion of severe or repeated pneumonia as major criteria in the modified WHO clinical case definition whereas Daga et al., study was based on previous criteria.⁷ Moreover, this definition detects the presence of symptomatic AIDS and not HIV infection itself. In the Mumbai study a majority (35%) of cases were asymptomatic compared to 5% in present study. The mean age of diagnosis was 4.4 years in the present study, suggesting a delay in making an earlier diagnosis.

This study almost correlates with the study done by Tovo et al among HIV infected European children in category-A NABC manifestations like hepatomegaly, splenomegaly and lymphadenopathy.¹³ But category B and C manifestations - (moderate and severe symptoms) like pulmonary tuberculosis, recurrent pneumonia, recurrent diarrhoea and HIV encephalopathy had a higher incidence among in our study. Whereas compared to our children African children (Rwanda and Uganda), are severely symptomatic with a higher incidence of category-B and category-C symptoms.¹⁴

Compared to other Indian studies category-A symptoms like hepatomegaly, splenomegaly, and otitis media have a higher incidence in this study. Category-B symptoms were accordance with the other Indian studies. Category-B symptoms have higher incidence in the Lodha et al study, these include failure to thrive, recurrent pneumonia and recurrent diarrhoea.¹¹ Incidence of tuberculosis in this study is comparable with Lodha et al and Dhurat et al studies.¹⁵ Compared to other Indian studies category-C symptoms have a higher incidence in the present study except PCP. Compared with these studies HIV encephalopathies had a very high incidence in the present study. Impaired brain growth (microcephaly) was the major abnormality noted in our study. Early in the epidemic, HIV related encephalopathy was estimated to occur in as many as 50-90% of children with AIDS in the United States.¹⁶ More recent estimates of prevalence of HIV related CNS diseases are much lower, because of earlier and more effective antiretroviral treatment.¹⁷ Overall this study correlates well with the study done by Lodha et al.¹¹ Although conducted during the same period, in the same population the Mumbai studies (by Merchant et al and Dhurat et al) and south Indian studies [by Verghese et al (Vellore) and Madhivanam et al, (Chennai)] showed significant variations in the incidence of clinical manifestations.^{10,12,15}

In all these studies wide variation was particularly noted in respiratory conditions like pulmonary tuberculosis, recurrent/persistent pneumonia, LIP and PCP. This indirectly reflects the difficulty in making proper diagnosis of these conditions in HIV infected children. Most of these diseases had more or less similar clinical presentations, often have a negative tuberculin test, have poor response to antimicrobials or antitubercular therapy and almost similar radiological picture. So, diagnosis was often presumptive based on clinician's discretions. Pulmonary tuberculosis, a disease that is common in all population in India, was the most common opportunistic infection noted by us. Tuberculosis (both pulmonary and extra pulmonary) was the most common infection in this sample (57.5%). This was also the most common opportunistic infection in HIV infected adults followed up in our hospital. HIV associated tuberculosis is important not only because of its frequency but also one of the few HIV associated diseases that is transmissible to the non-HIV-infected segment of population. Early diagnosis and treatment of tuberculosis also have been shown to control HIV infection.

Lymphoid interstitial pneumonia, a form of chronic lung disease is a distinctive marker of pediatric HIV infection. 12.5% of children in this series had LIP. These children presented with chronic progressive cough, mild dyspnea, and were not associated with fever. All cases had clubbing; grade-IV clubbing was seen in three cases. Chest radiographs revealed reticulonodular densities. LIP affects children far more often than it has affected adults, perhaps reflecting the HIV specific lympho proliferative potential of the immature immune system. LIP is usually

associated with parotid enlargement, but it was not detected in any of our cases. LIP with bronchiectasis was an important feature noted in this study. Two cases of LIP had associated clinical and x-ray findings suggestive of bronchiectasis.

Only one case of PCP was detected in our study series, with confirmatory bronchoalveolar report. Merchant et al., study had shown a 4% incidence of PCP confirmed with bronchoalveolar lavage. In the Verghese et al study 8% were presumptively diagnosed to have PCP.¹⁰ The mean age of presentation of PCP is 5 month, with a high mortality in children below one year of age. Since our study group included children above 18 months and in addition, all infants born to HIV infected mothers and newly detected HIV infected children were on PCP prophylaxis, explains the low frequency in this study.

Respiratory tract infection is a common pediatric illness but is more persistent and refractory to treatment in HIV infected children. 42.5% of our children presented with recurrent pneumonia. A study done by Lodha et al showed a higher incidence of recurrent/persistent LRTI (86.4%) and a low incidence is reported by Merchant et al (8.4%).¹¹ As in other studies from India and other tropical countries, bacterial pneumonia occurred more frequently than PCP and LIP. This reflects the greater importance of bacterial infection in tropical countries as well as limited diagnostic options for the diagnosis of PCP and LIP. Chronic suppurative otitis media was seen in 42.5% of our children. Mainly gram-negative pathogens were isolated from these patients.

A distinguishing clinical finding in this study, not seen in such a large number in other studies in India was HIV encephalopathy. 52.5% of present study group had HIV encephalopathy. Microcephaly suggestive of impaired brain growth was the major abnormality noted in present study, which was not taken into consideration in other studies. Head circumference falling below 5th centile without an alternate explanation was seen in 20 cases.⁹ Development delay was noted in 10 cases in which global developmental delay was seen in 2 cases. The high incidence of encephalopathy in this series of children is comparable with 'Italian Register for HIV infection in Children' published in Lancet 1994, accounting 58% of cases.¹⁷

Oropharyngeal candidiasis was the most common form of fungal infection seen in 30% of our children. This infection is another indication of impaired T-cell function in these children. Other oral lesions like gingivitis and caries were found in many of our patients.

Recurrent diarrhoea with weight loss is one of the major and most serious clinical manifestations of AIDS. In present study population 14 children had recurrent diarrhoea. Fungal pathogens were isolated in 2 cases, which include candida albicans and cryptosporidium. Skin disease can be an early HIV associated

manifestation. Papulo pruritic eruptions, thought to be, due to hypersensitivity reaction to environmental factors or allergens such as insect saliva or mosquito bites was seen in exposed part of the body was found in five patients. These conditions have been described as one of the initial manifestations of HIV infection in Haitian adults and children.¹⁰

Infants who acquire HIV perinatally have birth weight and height percentiles comparable to uninfected ones but may develop postnatal growth retardation. Chronic diarrhea, opportunistic infections or HIV infections per se may be responsible for protein energy malnutrition. This was one of the common clinical features of immunodeficiency noted by us (80%). Grade III and grade IV PEM was noted in 18 cases (45%). Therefore, nutritional interventions should be instituted early in the care plan of these children.

The rare initial presentations of HIV noted in this study were a case of thrombocytopenia with bleeding manifestations in a 2½ year old boy later diagnosed as HIV related chronic thrombocytopenia and a 4½ year old child whose parents were known cases of HIV presented with symptoms and signs suggestive of congestive cardiac failure. On investigation chest x-ray revealed gross cardiomegaly and echocardiography was suggestive of dilated cardiomyopathy. Dilated cardiomyopathy in HIV infection may be related to a direct action of HIV on myocardial tissue or an autoimmune process induced by HIV alone or conjunction with co-infecting viruses.¹⁹

CONCLUSION

The clinical manifestations of HIV infection are protean and can mimic a number of other illnesses. A high index of suspicion would therefore help in early and appropriate diagnosis. The common clinical manifestations were malnutrition, chronic diarrhoea, recurrent respiratory tract infection, tuberculosis and hepatosplenomegaly. The higher incidence of HIV encephalopathy in this series highlights the need for developmental and neurological assessment of the HIV infected child at regular intervals. Microcephaly was present in majority of cases with HIV encephalopathy, hence head circumference measurement can be used as a simple screening method to suspect HIV encephalopathy. Vertical transmission is the major cause for pediatric HIV infection. PMTCT is the most cost-effective intervention that can prevent mother to child HIV transmission.

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