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Profile of HIV infected children: A hospital based study at Eastern Nepal

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PEER REVIEW

Peer reviewer

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Comments

The article tries to elucidate common clinical features in HIV infected children in the region. It also highlights the late age of diagnosis. Risk factors among parents have been highlighted. Ineffective programme for prevention of mother to child transmission of HIV is also highlighted.

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ABSTRACT

Objective: To investigate the clinical, laboratory, epidemiological profiles and outcome in human immunodeficiency virus infected Nepalese children.

Methods: This was a hospital based prospective study. Human immunodeficiency virus-infected children presenting to pediatric immunology clinic at BP Koirala Institute of Health Sciences were enrolled and followed up.

Results: Median age at diagnosis among 39 enrolled children was 58 months. All children acquired infection vertically. Unsafe sex (74.4%) and intravenous drug use (25.6%) were the major risk behaviors in fathers. At presentation, 20.8% children were asymptomatic, 54.0% were malnourished, 41.0% were in WHO clinical stage 1, 17.9% were in stage 4, 74.4% were anemic, 17.9% had thrombocytopenia and median CD4 count was 543. Fever, lymphadenopathy, hepatosplenomegaly, skin eruptions and oral lesions were common presenting features (16.2%, 16.2%, 13.5%, 10.8%, and 8.1% respectively out of 74 features). Tuberculosis (16.0%), chronic otitis media (12.0%), scabies (10.7%), bacterial pneumonia (9.3%) and oropharyngeal candidiasis (6.7%) were common opportunistic infections. Antiretroviral treatment was started in 18 (46.2%) cases at median age of 67 months. Median change in CD4 count at follow up was significantly different between the groups receiving and not receiving antiretroviral treatment (+192 vs. -72; $P=0.045$).

Conclusions: Infection in children is vertical. Undernutrition, anemia, fever, lymphadenopathy, hepatosplenomegaly, skin eruptions, and ear discharge are common presenting features. Opportunistic infections are common and tuberculosis is the most common opportunistic infection followed by chronic ear infection, scabies, candidiasis and bacterial pneumonia. Timely antiretroviral treatment improves immune response.

KEYWORDS

HIV, Child, Signs and symptoms, Opportunistic infections, Treatment outcome

1. Introduction

Human immunodeficiency virus (HIV) infection in children is a family disease, with social, economic and medical aspects that make it one of the most challenging diseases of our time. At the end of 2010, an estimated 34 million people were living with HIV globally, including 3.4 million children

less than 15 years. The estimated number of children younger than 15 years living with HIV in Asia increased from 110 000 in 2001 to 180 000 in 2010. Number of children newly infected with HIV declined by 23.0% in Asia overall between 2001 and 2010, from an estimated 28 000 to 22 000. These figures probably indicate the slowing rate of HIV incidence in this region overall as well as the expansion of services

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to prevent mother to child transmission of HIV[1]. Nepal has high prevalence of HIV in South Asia. Current data indicate that HIV prevalence is around 0.39% in adult population (15–49 years). In Nepal, estimate hold that there are 3544 children living with HIV and about 435–650 newborns are infected with HIV every year without intervention[2].

In many developing countries of the world, number of paediatric HIV cases continues to rise due to increasing prevalence of HIV infection in women and ineffective measures for prevention of perinatal transmission[3]. Introduction of antiretroviral treatment (ART) has decreased mortality and progression to advanced human immunodeficiency virus (AIDS) in perinatally HIV-infected children, but information on modification of the rate of specific clinical events is limited[4]. Understanding the epidemiology of paediatric HIV infection and progression of disease may reveal opportunities to reduce and perhaps eliminate perinatal transmission in resource poor settings; and when prevention is not possible, identification of infected children will allow appropriate treatment to significantly improve their quality of life. Spectrum of clinical manifestations of HIV infection varies in infants and children in different areas of the world. Knowledge of clinical and epidemiological profile is crucial for clinicians to meet the diagnostic and management challenges presented by HIV infected children in resource poor setting[5]. Therefore we conducted this study to investigate clinical, laboratory and epidemiological profile in HIV-infected children in Nepalese context.

2. Materials and methods

This was a prospective study carried out over a period of 3.5 years (May 1, 2009–October 31, 2012). All HIV positive children below 18 years of age presenting to paediatric immunology clinic of BP Koirala Institute of Health Sciences, Dharan, Nepal during the study period were enrolled, followed up and studied. Ethical clearance was taken from institutional ethical review board. Standard consent was taken from parents or care taker.

Demographic, clinical and laboratory details were recorded at presentation and updated in each visit. Details of opportunistic infections, treatment, compliance, complications and outcome were recorded during follow up visits. Nutritional status was classified according to World Health Organization (WHO) classification of protein energy malnutrition in under-five children and according to body mass index above the age of 5 years, using WHO growth

charts[6,7]. Weight for height or height for age or body mass index for age between -2 to -3 SD score was classified as moderate undernutrition and SD score below -3 was classified as severe undernutrition[6]. Anemia was defined as Hb <11.0 g/dL in children 6 months to 59 months of age or <11.5 g/dL in children 5–12 years or <12.0 g/dL in children 12 to 14 years of age as per WHO guideline for diagnosis of anemia[8].

Children on ART visited the clinic every month and children not on ART visited every 2–3 months, apart from emergency visits and admissions when required. Diagnosis of HIV was made by rapid diagnostic tests above 18 months of age and by two DNA PCR tests between 6 weeks to 18 months of age following WHO guideline for diagnosis of paediatric HIV as adopted by government of Nepal[2]. Clinical staging of HIV, use of ART and change of ART were based on the same guideline[2]. Diagnoses of opportunistic infections were largely based on history, symptoms, signs, clinical examination findings and supported by available laboratory test results. When tuberculosis bacilli could not be demonstrated despite strong clinical suspicion of disease, clinical judgment was used for diagnosis of tuberculosis. Such clinical diagnosis of tuberculosis was made depending upon history of contact, suggestive clinical features and indirect markers like Mantoux test or positive radiological findings. Mantoux test positivity was defined as induration size >5 mm as per WHO and national guidelines for HIV infected children[2]. Cotrimoxazole prophylaxis was started in all cases at diagnosis as per hospital policy. Absolute CD4 count was obtained using BD FACS Count 1.5, Becton, Dickinson and Company, BD Biosciences, USA. Though CD4 percent count is better for children, the machine used in our hospital provides only absolute count. CD4 count was obtained at presentation and every 6 months. Change in CD4 count for each case was calculated by subtracting CD4 count at presentation from CD4 count at latest follow up. Mann–Whitney *U* test was applied to test the change in median CD4 count between children receiving ART and children not receiving ART. The significance level was set at 5.0%. Data were recorded in predesigned record sheet, entered and screened for error in MS Excel and analyzed using SPSS 11.5 statistical software.

3. Results

3.1. Baseline characteristics

During the study period of 3.5 years, 39 HIV positive children were enrolled. There were 28 males and 11 females

with male to female ratio of 2.5:1. Most of the children were diagnosed late. Median age at diagnosis was 58 months with inter quartile range (IQR) of 36–90 months. All affected children received mixed breast feeding (mother's milk with other food). HIV test results were available in 33 mothers and 32 fathers, all of them were positive. Three (7.7%) children had lost both the parents, and 14 (35.9%) children had lost one of the parents at presentation.

Table 1 shows other baseline characteristics of children.

Table 1

Baseline characteristics of children.

Characteristics	n ^a (%)
Age at diagnosis	
<18 months	1 (2.6)
18 months–5 years	21 (53.8)
5–10 years	14 (35.9)
>10 years	3 (7.7)
Mothers using ART ^b during antenatal period	0 (0.0)
Mothers receiving ART on presentation	11 (28.2)
Fathers receiving ART on presentation	5 (12.8)
Mothers' profession	
Homemaker	39 (100.0)
Fathers' profession	
Unemployed	11 (28.2)
Migrant worker	10 (25.6)
Driver	8 (20.5)
Businessman	5 (12.8)
Army man	2 (5.1)
Others	3 (7.7)
Modes of acquiring HIV ^c by children	
Mother to child transmission	39 (100.0)
Modes of acquiring HIV by mothers	
Through sexual contact with spouse	39 (100.0)
Modes of acquiring HIV by fathers	
Unsafe sex	29 (74.4)
Sharing of needle	10 (25.6)

^aNumber of cases, ^bAntiretroviral treatment, ^cHuman immunodeficiency virus.

3.2. Presenting features (symptoms and signs)

Among 39 cases, 8 (20.5%) cases were asymptomatic at presentation. Frequencies of symptoms and signs at presentation among 31 symptomatic cases are presented in Table 2. On assessment of nutritional status at presentation, no undernutrition, moderate undernutrition and severe undernutrition were present in 18 (46.2%), 12 (30.8%) and 9 (23.1%) children respectively. According to WHO classification system for clinical staging of HIV disease, 16 (41.0%) children presented in clinical stage 1, 13 (33.3%), 3 (7.7%) and 7 (17.9%) children presented in WHO clinical stages 2, 3 and 4 respectively.

Table 2

Frequency of presenting symptoms and signs among 31 symptomatic cases.

Presenting symptoms and signs	Frequency	Percent
Fever	12	16.2
Persistent generalized lymphadenopathy	12	16.2
Hepatosplenomegaly	10	13.5
Skin eruptions	8	10.8
Oral lesions	6	8.1
Cough	5	6.8
Ear discharge	5	6.8
Diarrhea	3	4.1
Hepatomegaly	3	4.1
Parotid enlargement	3	4.1
Altered sensorium	2	2.7
Warts	2	2.7
Clubbing	1	1.4
Dental caries	1	1.4
Regression of milestones	1	1.4
Total	74	100.0

Table 3 shows routine investigation findings at presentation.

Table 3

Abnormalities in routine investigation findings at presentation.

Investigation	Abnormality	Number of cases	Percent
HBsAg ^a	Positive	0	0.0
Hepatitis C antibody	Positive	0	0.0
LFT ^b	Raised enzymes	8	20.5
Urine routine	Albuminuria	2	5.1
Hemoglobin	Anemia ^c	29	74.4
Platelet count	<150000 cells/mm ³ (thrombocytopenia)	7	17.9
Leukocyte count	<4000 cells/mm ³ (leucopenia)	2	5.1
Mantoux test	Positive (>5 mm)	2	5.1

^aHepatitis B surface antigen, ^bLiver function test, ^cas per WHO cut off values [8].

Figure 1 shows distribution of CD4 count at presentation.

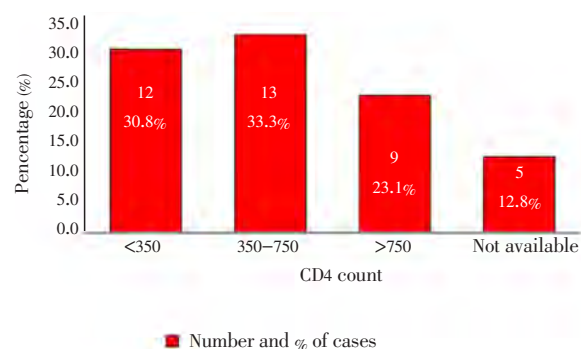


Figure 1. CD4 count at presentation.

3.3. Opportunistic infections

During the study period, 75 episodes of opportunistic infections were diagnosed. Table 4 shows frequencies of opportunistic infections diagnosed during the study period. Mycobacterium avium complex infection and fungal sepsis occurred in a child who had CD4 count 15, had treatment

failure and recovered with second line ART.

Table 4

Frequency of opportunistic infections.

Opportunistic infections	Number of episodes	Percent
CSOM ^a	9	12.0
Scabies	8	10.7
Disseminated tuberculosis	7	9.3
Bacterial pneumonia	7	9.3
Oropharyngeal candidiasis	5	6.7
Viral warts	5	6.7
ASOM ^b	3	4.0
Muco-cutaneous Herpes	3	4.0
Pulmonary tuberculosis	3	4.0
Tinea corporis	3	4.0
Acute tonsillitis	2	2.7
Giardiasis	2	2.7
Pyoderma	2	2.7
Tubercular meningitis	2	2.7
Abscess	1	1.3
Acute gastroenteritis	1	1.3
Bacterial sepsis	1	1.3
Chickenpox	1	1.3
Chronic parotitis	1	1.3
Fungal sepsis	1	1.3
Herpes zoster	1	1.3
LIP ^c	1	1.3
Suppurative lymphadenitis	1	1.3
MAC infection	1	1.3
PCP ^d	1	1.3
UTI ^e	1	1.3
Viral hepatitis	1	1.3
Viral keratitis	1	1.3
Total	75	100

a–chronic suppurative otitis media, b–acute suppurative otitis media, c–lymphoid interstitial pneumonia, d–pneumocystis jiroveci pneumonia, e–urinary tract infection

3.4. Follow up and treatment

One case was lost to follow up and 1 case was transferred to another ART centre. Median duration of follow up was 22 (IQR, 16 to 29) months. ART was started in 18 (46.2%) cases. Median age at starting ART was 67 (IQR, 39 to 123) months. Anti-tubercular treatment was given to 11 (28.2%) cases. Treatment failure occurred in 2 (5.1%) cases and they were shifted to second line ART. Zidovudine caused anemia in 4 cases out of 18 treated cases. Zidovudine was changed to Stavudine in one case because of severe refractory anemia. None of the cases expired during study period.

3.5. Effect of ART on CD4 count

Absolute CD4 count could be obtained in 20 cases both at presentation and follow up. Median CD4 count was 543 cells/mm³ at presentation. Among them, 12 cases were receiving ART and 8 cases were not receiving ART. CD4 count was obtained every 6 months whenever possible. Final CD4 count that was considered for calculation of difference in

CD4 count was obtained at mean follow up duration of 25.9 (standard deviation 7.7) months. CD4 count showed overall rise in children treated with ART (median increase +192, IQR +15 to +527) and overall fall in children not treated with ART (median decline–72, IQR–199 to +88). Median change in CD4 count was significantly different between the groups of children receiving ART and those not receiving ART ($P= 0.045$ by Mann–Whitney U test).

4. Discussion

Paediatric HIV infection is worldwide public health challenge in its own right that disproportionately affects children in the poorest parts of the world^[9]. Mother to child transmission is the critical source of HIV infection to children in Nepal^[2]. All children in our study acquired HIV from mother. No mothers received ART during their pregnancy. In a similar Indian study, only 8.0% mothers of HIV infected children used ART during pregnancy^[5]. This shows that detection of HIV positive mothers and use of ART during pregnancy for prevention of mother to child transmission are inadequate in this region. Median age at diagnosis in our study was 58 months. Similar to our study findings, the median age of presentation in two Indian studies were 4 years and 6.24 years^[5,10]. This suggests that there is a delay in making diagnosis of paediatric HIV infection in this region.

Migrant worker, driver, businessman and army man were the major risk professions among employed fathers. In one study done in Nepal, Poudel et al. found high HIV prevalence among male migrant–returnees in Nepal where migration to India for work is common^[11]. The prevalent risk behaviours like unsafe sex among migrant workers and sharing of needle among intravenous drug users imply urgent need of the behavioural modification programme in this area to prevent the spread of HIV infection to general population and children. According to WHO recommendation for resource poor areas, those mothers known to be HIV–infected and whose infants are HIV uninfected or of unknown HIV status should exclusively breastfeed their infants for the first 6 months of life. They should introduce appropriate complementary foods thereafter, and continue breast feeding for the first 12 months of life^[12]. Being a resource poor country, Nepal also accepts this recommendation in its national guideline^[2]. None of the affected children received exclusive breast feeding for first 6 months in our study. Awareness regarding safe infant feeding practices need to be strengthened in this region.

When infected with HIV, children present with a

wide spectrum of clinical presentations. Predominant presentations include respiratory infections, malnutrition, diarrhea, and septicemia^[13]. Fever and persistent generalized lymphadenopathy were common symptom and sign at presentation in our study. Other common presenting symptoms and signs were hepatosplenomegaly, skin eruptions, oral lesions, cough and ear discharge. Presenting features in our study are almost similar and comparable to the findings of few other studies done in resource limited settings^[10,14]. Undernutrition is an important feature in HIV infected children in the developing world^[10,15]. On presentation, 54.0 % children in our study were undernourished. Majority of children presented in WHO clinical stage 1. Similar to our study, largest number of children presented in clinical stage 1 in study by Gomber *et al*^[10].

A study done in a part of Nepal bordering to India revealed the epidemic of HIV and hepatitis C among intravenous drug using populations^[16]. Our study area covers the same area of Nepal, but all children in our study were negative for hepatitis B and hepatitis C. Hematologic manifestations, particularly cytopenias, are common manifestations of HIV infection and AIDS^[17,18]. Anemia was the most common haematological abnormality at presentation in our study. CD4 cell count has great utility in clinical consideration of HIV disease^[19]. In our study, median CD4 count was 543 cells/mm³ in cases with available CD4 count. Severe immunosuppression with CD4 count less than 350 cells/mm³ was present in one third of cases at presentation. In an Indian study, median CD4 level in children at presentation was 298 cells/mm³^[5].

Tuberculosis represents the most common opportunistic infection seen in HIV infected children in the developing world^[3]. Tuberculosis was the most common opportunistic infection episode also in our study. But tuberculosis diagnosis in HIV is complicated by diminished sensitivity and specificity of clinical features and diagnostic tools like the tuberculin skin test and chest x-ray^[20]. Though tuberculosis was common in children of our study at presentation, Mantoux test was positive only in 2 cases. Since we used clinical judgment and indirect markers for diagnosis of tuberculosis, few cases might have been over diagnosed. Chronic suppurative otitis media, scabies, bacterial pneumonia, oropharyngeal candidiasis and viral warts were other common opportunistic infection episodes. Types and frequencies of opportunistic infections in our study are almost similar and comparable to those reported by other studies done in resource limited settings of Asia^[5,10,14]. *Pneumocystis jiroveci* pneumonia (PCP is considered to be the most common AIDS-defining condition

in children^[21]. Only one episode of PCP was diagnosed in our study. Rare occurrence of serious diseases like PCP, disseminated MAC, sepsis, and LIP in our study could be because all cases were given cotrimoxazole prophylaxis at diagnosis and almost half of the children were receiving ART. Pattern of opportunistic infections may be different in areas where ART is not easily accessible to needy children. In one Nepalese study including all age groups, oral candidiasis was the predominant opportunistic infection followed by streptococcal pneumonia, salmonellae infection, cryptosporidial infection and tuberculosis^[22]. Few opportunistic infections were probably under diagnosed in our study due to lack of sophisticated investigation facilities. This might be true in resource limited settings everywhere.

Early initiation of ART improves viral, immune, growth responses and survival in HIV infected children^[23, 24]. Sutcliffe *et al.* compiled data from multiple cohorts of infected children from resource limited settings and reported a median age at ART initiation of 5 years^[24]. Median age at initiation of ART was 67 months in children of our study. These figures reflect that there is delay in starting ART in resource limited settings. This could be because of inaccessibility to health care facility, late presentation and delay in diagnosis in these areas. CD4 count showed overall rise in children treated with ART and overall fall in children not treated with ART. Median change in CD4 count was significantly different between these two group (+192 *vs.* -72; *P*=0.045). In a similar study done in New Delhi, mean change in CD4 count in children was +317 among children on ART and -106 in children not on ART, over a follow up period of 6 months^[10]. These findings further support that initiation of ART improves immune response in HIV infected children and without ART there is progressive decline in immunity.

Prospective design and use of modern statistical tools are strengths of this study. This study describes authors' experience with HIV-infected children in a Nepalese hospital. Experience may be the same in other resource limited areas also. But, because of small number of HIV positive children and descriptive nature, findings of this study may not be generalized throughout all resource limited areas of the globe. Due to lack of advanced diagnostic facilities, clinicians working in resource limited areas have to rely on clinical features and indirect markers for diagnosis of many opportunistic infections. Therefore, few opportunistic infections might have been under diagnosed and few opportunistic infections might have been over diagnosed in this study. A more robust study with collection of clinical information prospectively from both HIV positive and HIV negative children in a case control manner besides

use of advanced diagnostic facilities for detection of opportunistic infections is further required to ascertain which clinical features and opportunistic infections are significantly associated with HIV infection in resource limited areas.

In resource limited area like Nepal, transmission through mother is the critical mode of HIV transmission to children and there is often delay in starting ART. HIV should be suspected when children present with unexplained under nutrition, anemia, prolonged fever, lymphadenopathy, hepatosplenomegaly, recurrent skin eruptions, oral lesions or chronic ear discharge. Opportunistic infections are common in HIV–infected children. To prevent further spread of HIV in general population and children, emphasis should be given to measures for early detection of infected pregnant mothers and children, timely initiation of ART in them, safe infant feeding practices and modification of prevalent adult risk behaviours like unsafe sex and sharing of needle.

Conflict of interest statement

Authors have no conflicts of interests to declare.

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Comments

Background

Every day more than 7000 children and young people around the world are infected with HIV, and most of these transmissions are occurring in developing countries. Countries like India and China are experiencing serious localized epidemics that are affecting millions of people including children. Limited data regarding clinical scenario of this disease, especially in children, is available from

Nepal, which is a small resource poor country located between China and India.

Research frontiers

Spectrum of clinical manifestations of HIV infection varies in infants and children in different areas of the world. Studies on pediatric HIV are being done to understand the epidemiology of paediatric HIV infection and progression of disease in resource poor areas where number of paediatric HIV cases continues to rise due to increasing prevalence of HIV infection in women and ineffective measures for prevention of perinatal transmission.

Related reports

Clinical epidemiological characteristics of pediatric HIV are almost similar in resource poor areas (Gomber *et al* (2011, India); Merchant RH *et al* (2001, India), Brown BJ *et al* (2011, Nigeria). But the epidemiological, clinical and outcome characteristics as well as problems related to pediatric HIV are somewhat different in affluent countries.

Innovations & breakthroughs

This is a descriptive designed study describing epidemiological, clinical and outcome pattern of HIV infection in children at resource limited area like Nepal. This study supports the existence of more or less similar situation of the disease clinico–epidemiological scenario in such areas. This study reveals some of the features unique to this area like very low prevalence of hepatitis B and C among HIV infected children, migrant workers as a reservoir of infection transmitting the disease to their wives and children *etc.* This study also shows improving trends in treatment and outcome in developing country like Nepal.

Applications

This study provides baseline clinico–epidemiological data regarding HIV infected children living in a resource constrained area. This study combined with similar other studies done in similar areas can provide up to date practical information to help health service providers to make evidence based decision on the management of HIV infected children. Such information will also be useful to formulate evidence based guideline for prevention and management of pediatric HIV infection appropriate to such areas.

Peer review

The article tries to elucidate common clinical features in HIV infected children in the region. It also highlights the

late age of diagnosis. Risk factors among parents have been highlighted. Ineffective programme for prevention of mother to child transmission of HIV is also highlighted.

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