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Clinical Features in Paediatrics HIV Infection and How They Correlate With Immunosuppression

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Abstract:
Background: *Clinical features of HIV infection in children are protean. Existing therapeutic and care decision making guidelines are predominantly based on CD4 counts and plasmaviral load that are not routine in our settings. The identification of surrogate markers (clinical symptoms and signs) that can correlate with immunosuppression, helps to optimize the need of CD4 counts and plasma viral loads.*
Materials And Methods: *All children who have come with paediatric HIV diagnosed and /or reporting paediatric centre of excellence at Osmania General Hospital, Niloufer Hospital and patients admitted at Niloufer Hospital, Hyderabad and were interviewed examined for symptoms, signs and all parameters were collected, analysed for how they are correlating with degrees of immune suppression.*
Results: *Of the total numbers observed (100)8 were asymptomatic, 32 belongs to stage2, 60 belong to stage3. No immunosuppression was found in 18 mild immunosuppression 24 advanced immunosuppression in 20, severe immunosuppression found in 38.*
Conclusion: *There is a wide spectrum of clinical manifestations CSOM, lymphadenopathy, persistent / recurrent fever, malnutrition and weight loss, chronic diarrhea, anemia being most common. Recurrent / persistent fever, chronic diarrhea,anemia were able to predict the immunosuppression as a surrogate marker. WHO clinical categories(stage1, 2, 3) are the best predictors of severity of immunosuppression(A,B, C, D,).*
Keywords*: AIDS: acquired immune deficiency syndrome, HIV: human immunodeficiency virus, NACO: national AIDS control organisation, WHO: world health organisation*

I. Introduction

HIV infection was first detected in 1981 in USA and 1986 in Chennai India. At the end of year 2009, 2.5 million children less than fifteen years are living in the world with HIV infection. HIV disease progress very rapidly in young children, especially in the first few months of life often leading to death. AIDS is the second most common infectious cause of deaths. In developing countries more than 90% of paediatric HIV infection due to perinatal transmission. Decision regarding initiation and changes in therapy is based on clinical condition, CD4 counts and plasma viral loads who have good correlation with disease progression. Both of these tests are relatively expensive and not easily available/affordable in developing countries. Development of surrogate markers in the form of clinical symptoms and signs and simple laboratory criteria can help in for early identification of cases and rational use of investigations. Hence in our situation cost is major issue in implementing management programmes, finding less expensive clinical/ basic laboratory surrogate markers can help to great extent in effective utilisation of health care services.

TABLE-1 REVISED CLASSIFICATION OF CD4 IMMUNOSUPPRESSION IN CHILDREN

CATEGORY	<11MONTHS (%)	12-35M (%)	36-59M (%)	>5YEARS
NORMAL(A)	>35	>30	>25	>500
MILD(B)	30-35	25-30	20-25	350-499
ADVANCED(C)	25-30	20-25	15-20	200-349
SEVERE (D)	<25% or <15OO cells	<20% or <750cells	<15% or <350cells	<15% or<200 cells/mm3

II. Aims And Objectives

Hypothesis:

There is a positive of resource constraint setting literature on paediatric HIV infection, clinical features and their association with CD4 counts, which is the gold standard for the severity of immunosuppression. In our settings the economics of health care is an important factor especially in the management of chronic and family disease such as paediatric HIV infection. Any identifiable features that could be able to correlate with immunosuppression would reduce the cost and enable continued comprehensive care.

Research questions:

Primary**:** are clinical features of HIV infected children in our settings similar to other Indian Western discriptions of features in a similar population?

Secondary: among clinical features (symptoms and signs) prevalent in HIV infected children which of these features are surrogate markers and correlate to the severity of immunosuppression as categorised as No, Mild, Advanced, Severe immunosuppression?

Primary objective: to document the profile of clinical symptoms and signs in paediatric HIV infection. It is descriptive and cross sectional in character. A detailed history, clinical examination findings documented and presented.

Secondary objective: to assess each of the above parameters (clinical symptoms and signs) as markers in the prediction of immunosuppression. Absolute of CD4+lympocyte count is taken as the gold standard in assessment of immunosuppression. Here the ability of each criteria to predict CD4+lymphocyte count is classified into No, Mild, Advanced, Severe immunosuppression categories shall be assessed using appropriate statistical methods. Thereby leads to early identification of children who were progressing to severe immunosuppression.

III. Material And Methods

STUDY DESIGN:

PLACE OF STUDY: Niloufer Hospital and Osmania General Hospital, Hyderabad (Both are teaching hospitals, Osmania medical college).

PERIOD OF STUDY: March 2013 to April 2014.

SAMPLE SIZE: a total of 100 children were included in the study with age range from 0-15 years. The majority were aged between 5-10 years. There were 54 males and 46 females. 96% children acquired HIV infection through vertical transmission. Written consent was taken from the parents/guardian of children

DESIGN: Prospective cross sectional study

INCLUSION CRITERIA: All children attending ART clinic with paediatric HIV up to 15 years of age as determined below:

a) <18months: Virological tests (DNA PCR), as per recommendations OR an ELISA positive AND symptomatic as per the WHOclinical staging.

b) >18months: ELISA positive as recommended by WHO and NACO.

EXCLUSION CRITERIA:

a) Not consenting to detailed history, examinations as clinically indicated

b) For analytical component: All children whose parents are not willing for CD4/CD8 counts

c) All children who have presented with anemia and on zidovudine based ART regimen.

DATA COLLECTION:

A cross sectional study, in which subjects were interviewed, examined and investigated for symptoms, signs and all parameters were collected and were analyzed for how they are correlating with degrees of immunosuppression. Additionally the investigator was also responsible for counselling of parents of HIV infected children.

METHODS:

After written consent, clinical features (after detailed history and examinations) were documented on a proforma. The spectrum of clinical symptoms, signs were tabulated and described according to the frequency of occurrence. They were also compared to degrees of immunosuppression (immune categories). During analysis of data collected to identify surrogate clinical markers of immunosuppression, each feature was cross tabulated with 4 immune categories (No, mild, advanced, Severe) independently and with combinations of No and Mild Vs Advanced and Severe immunosuppression. A chi-square test was used to find statistical significance of the observed variations between groups. Probability value of <0.05 was considered significant. Those parameters, which showed significance were subjected to regression analysis and a correlation factor(r) > 0.5 was significant. The assistance of a statistical program SPSS was used for analysis.

LIMITATIONS AND ASSUMPTIONS:

i) For the secondary objective of the study, a longitudinal prospective will be better suited to study the clinical progression and correlation of clinical features with immunosuppression rather a cross sectional study.

ii) As the study was solely based on clinical features without laboratory investigations the conditions which requires laboratory tests to diagnose were not taken into the study.

iii) As the study was focused on clinical symptoms and signs only, the conditions in the WHO clinical stage 4 were not included in clinical staging.

IV. Results

A total of 100 children were included in the study with age range from 0 to 15 years. The majority were aged between 5-10years (41%). There were 54 males and 46 females.96% children acquired HIV infection through vertical transmission.

DESCRIPTIVE STUDY COMPONENT (please see descriptive graphs):

The study protocol requested the investigator to take detailed histories, physical examinations including anthropometry and counsel the parents regarding routine care. Children were classified according to WHO clinical categories based on documented clinical features. Among 100 subjects 8 were asymptomatic, 32 belonged to stage 2, 60 belonged to stage 3. These children were classified into immune categories based on CD4 counts according to WHO guide lines, as No immunosuppression, Mild immunosuppression, Advanced immunosuppression and Severe immunosuppression. The clinical features were documented and grouped into 4 immune categories. Among children in stage 1 all belong to No immunosuppression, among children in stage 2, 9 belong to No immunosuppression, 17 belong to mild, 5 advanced, 1 severe immunosuppression category. Among children in stage 3, most revealed CD4 counts indicating severe immunosuppression. Children were classified under various malnutrition categories according to Indian Academy of Paediatrics classification. The similar grading system of weight less than 80,70,60,50% of expected was used to grade children above 5 years of age for simplification of data presentation. Head circumference less than 2standard deviation was defined as "small head" and was documented in 8 children. Among all features most common manifestation was CSOM, found in 49 children. Fever lasting for more than 1month was found in 41 children. Clubbing is increasingly seen in HIV children also seen in 28 of observed children. Oral thrush was found in 14 children. Recurrent URTI (>6 episode per year) was seen in 26 children and recurrent LRTI especially pneumonia was seen in 26 children. Skin manifestations were found in 36 children. Among which papular urticaria was the most common lesion found in 34 children followed by pyoderma and abscess. Central nervous system abnormalities were found in 13 children, which included delayed mile stones (8children), seizures (5children). The spectrum of opportunistic infections observed in the study was tuberculosis, recurrent LRTIs. Diagnosis is clinical based on history and examination findings. Clinical features of cough, fever, crepitations with subcostal retractions defined Bronchopneumonia. This was seen in 26 children. Hepatosplenomegaly diagnosed clinically found in 20 children. Isolated hepatomegaly was seen more common than hepatosplenomegaly seen in 28 and isolated splenomegaly was rarely observed. Cardiac abnormalities clinically could not make out in the all children. Bleeding manifestations were observed in 12 children as characterized by epistaxis, muco cutaneous bleeds.

ANALYTICAL STUDY:

The secondary objective of the study is to evaluate the ability of each clinical symptom and sign as how it correlates with the degrees of immunosuppression. Each of the above feature described, results were cross tabulated with the 4 stages of immunosuppression, combinations of no and mild VS advanced and severe for analysis. Chi square was used to statistically significance of the observed variables. Probability of less than 0.05 was considered significant. Those parameters which showed significance was subjected to regression analysis and a r factor of more than 0.5 was taken as significant. Among all features 16 symptoms and signs were significant statistically. When these were again subjected to logistic regression the clinical symptoms and signs (recurrent fever, chronic diarrhea, anemia) have shown significant correlation with immunosuppression.

FREQUENCY GRAPHS:

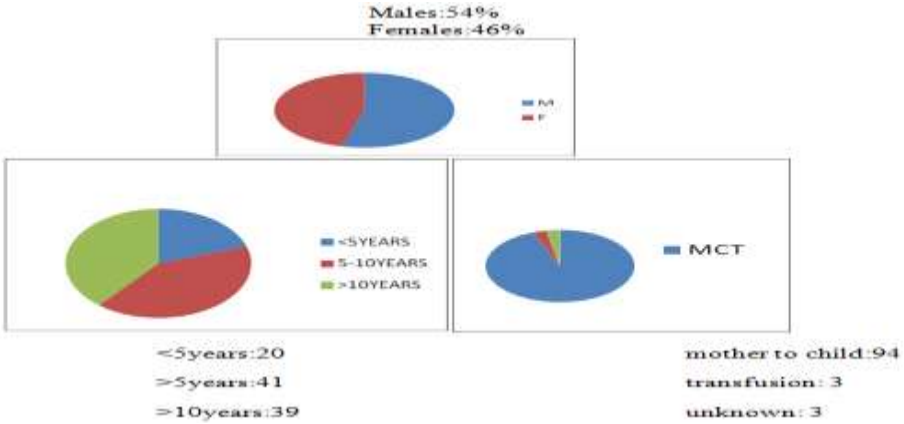


TABLE-2

AGE	FEQUENCY
<5years	20%
5-10years	41%
>10years	39%

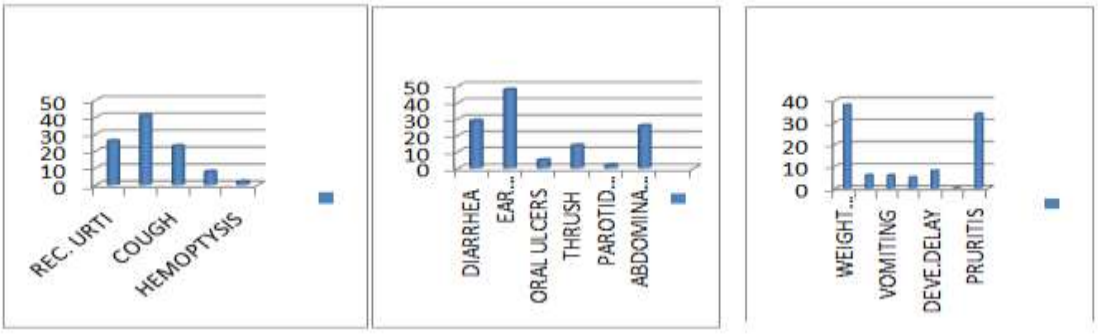
SEX	FREQUENCY
Male	54%
Female	46%

SYMPTOMS FREQUENCY: SIGNS FREQUENCY

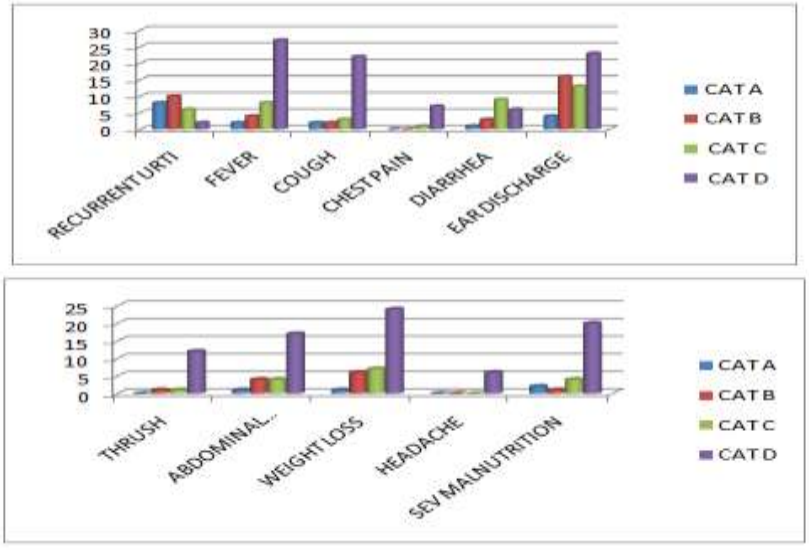
NAME OF SYMPTOM	FREQUENCY
Recurrent URTI	26%
Fever	41%
Cough	23%
Chest pain	8%
Hemoptysis	2%
Diarrhea	29%
Ear discharge	48%
Oral ulcers	5%
Thrush	14%
Parotid swelling	2%
Abdominal distension	26%
Weight loss	38%
Headache	6%
Vomiting	6%
Seizures	5%
Development delay	8%
Regression	
Pruritis	34%
Moderate malnutrition	27%
Severe malnutrition	27%

NAME OF THE SIGN	FREQUENCY
Pallor	27%
Icterus	-
Cyanosis	-
Clubbing	28%
Lymphadenopathy	45%
Edema	2%
CSOM	49%
Pneumonia	26%
Hepato splenomegaly	20%
Isolated hepatomegaly	28%
Isolated splenomegaly	2%
Bleeding manifestations	12%
Pyoderma	2%
Microcephaly	8%

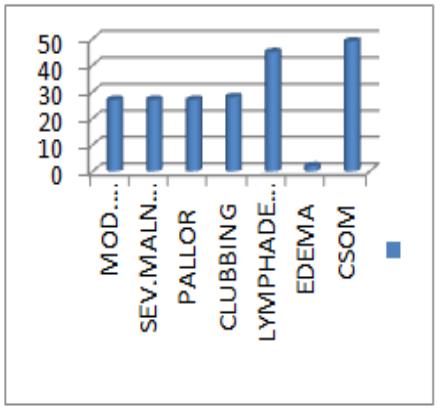
GRAPH SHOWING FREQUENCY OF SYMPTOMS

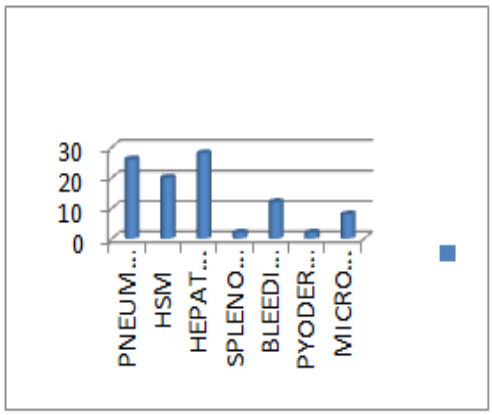


CROSS TABULATION OF SYMPTOMS



FREQUENCY OF SIGNS





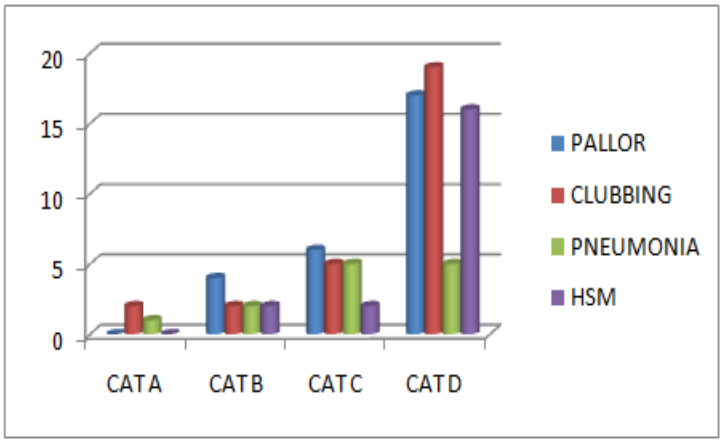


TABLE-3 CROSS TABLES:

SYMPTOMS	CATEGORY OF IMMUNE SUPPRESSION				P VALUE
	A(%)	B(%)	C(%)	D(%)	
Recurrent URTI	8	6	10	2	0.002
Fever	2	4	8	27	0.000
Cough	2	2	3	22	0.005
Chest pain	0	0	1	7	0.023
Diarrhea	1	3	9	16	0.003
Ear discharge	4	16	13	23	0.009

SYMPTOM	CATEGORY OF IMMNUE SUPPRESSION				P VALUE
	A%	B%	C%	D%	
Thrush	0	1	1	12	0.001
Abdominal distension	1	4	4	17	0.006
Weight loss	1	6	7	24	0.000
Headache	0	0	0	6	0.015
Vomiting	2	1	4	20	009
Severe malnutrition	0	4	6	17	0.000

SIGNS	CATEGORY OF IMMUNESUPPRESSION				P VALUE
	A	B	C	D	
Clubbing	2	2	5	19	0.001
Pneumonia	1	2	5	18	0.001
Heapatosplenomegaly	0	2	2	16	0.000

These symptoms and signs which showed significance were subjected to logistic regressional analysis.

LOGISTIC REGRESSION RESULTS

INFERENCE: Binary logistic regression was performed to predict the presence of greater immuno-suppression (C&D) keeping the following 13 variables which were significant in univariate analysis. The final model shows only three variables as significant predictors of greater immuno-suppression as shown in the table below.

TABLE-4 LOGISTIC REGRESSION RESULTS: VARIABLES IN THE EQUATION

		B	S.E.	Wald	df	Sig.	Exp(B)= Odds Ratio
Step 1[a]	FEVER(1)	2.212	.516	18.354	1	.000	9.130
	Constant	-.448	.267	2.817	1	.093	.639
Step 2[b]	FEVER(1)	2.593	.570	20.697	1	.000	13.369
	DIARREA(1)	2.458	.655	14.101	1	.000	11.681
	Constant	-1.196	.360	11.018	1	.001	.302
Step 3[c]	FEVER(1)	2.655	.603	19.407	1	.000	14.231
	DIARREA(1)	2.358	.687	11.771	1	.001	10.569
	PALLOR(1)	1.887	.699	7.293	1	.007	6.597
	Constant	-1.624	.425	14.575	1	.000	.197

a. Variable(s) entered on step 1: FEVER.

b. Variable(s) entered on step 2: DIARREA.

c. Variable(s) entered on step 3: PALLOR.

MODEL SUMMARY			
Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	113.041[a]	.206	.277
2	94.770[b]	.338	.455
3	86.205[b]	.393	.528
a. Estimation terminated at iteration number 4 because parameter estimates changed by less than .001.			
b. Estimation terminated at iteration number 5 because parameter estimates changed by less than .001.			

TABLE-5 Correlations

There is significant positive correlation between the two types of staging of disease and immunosuppression

			WHO CLINICAL STAGING	Imm_Suppression
Spearman's rho	WHO CLINICAL STAGING	Correlation Coefficient	1.000	.757**
		Sig. (2-tailed)	.	.000
		N	100	100
	Imm_Suppression	Correlation Coefficient	.757**	1.000
		Sig. (2-tailed)	.000	.
		N	100	100

**. Correlation is significant at the 0.01 level (2-tailed).

CHI-SQUARE TESTS			
	Value	Df	Asymp. Sig. (2-sided)
Pearson Chi-Square	82.415[a]	6	.000
Likelihood Ratio	82.686	6	.000
N of Valid Cases	100		

Out of all parameters which showed statistical significance, the parameters which can predict immunosuppression as a individual predictor of immune suppression are

-fever(more than 1 month)- r value

-diarhhea(more than 14 days)- r value

-unexplained anemia –r value

V. Discussion

The HIV pandemic entered the forth decade since its discovery and is rapidly growing. An estimated 2.5 million children less than 15 years are living with HIV globally[1]. This growing number of patients with pediatric HIV infection is a major burden on existing health facilities because of its associated morbidity and mortality. This comprehensive overview of clinical profile of pediatric HIV infection and an analytical attempt to alternate markers of severity of immunosuppression will enable the judicious utilization of health resources in our resource constraint settings.

VI. Descriptive study:

The commonest mode of transmission of HIV infection is vertical transmission accounting for 96% of infected children. It was assumed on the basis of ELISA positive in the mother and absence of past history of blood transfusion to the child. The incidence of perinatal transmission ranged from 70.4%-87% in other Indian studies [2,3,4,5] .Though perinatal transmission was the commonest mode of presentation the majority of children were presented in the age group of 5–10 years. This apparent delay in presentation is due to poor degree of suspicion hence a delayed diagnosis and/or inadequate counseling of parents diagnosed to have HIV infection hence non testing of family members and offspring. The study population also included significant number of above 10years age group due to perinatal transmission. The survival of such population could indicate the intrinsic ability to protect the destruction of immune system by the virus. Stage 3 manifestations are the commonest presenting stage during initial diagnosis. Malnutrition was found in 54 children in that grade 1 and 2 were 27, grade 3 and 4 was seen in 27 children. The presence of malnutrition has varied, from 4.6% [2] to 100%[5]. Malnutrition in HIV is due to chronic diarrhea, recurrent / persistent infections, opportunistic infections or HIV infection per se. An underlying malnutrition related to socioeconomic status may explain some malnutrition especially when perpetuated by a chronic infection such as HIV usually in more than one family member. The dual threat of HIV and TB infection also leads to this problem. Among all the observed clinical features CSOM, generalized lymphadenopathy, persistent fever, malnutrition are the common ones. These observations are similar to other Indian studies[6]. Microcephaly is one criterion to define HIV encephalopathy and is the viral replication in the brain is usually a cause of this retarded growth of brain tissue. The presence of head circumference of less than 2standard deviation was found in 8 children. Most of these children are with advanced or severe immunosuppression. Delayed mile stones especially gross motor was the commonest neurological manifestation. Fever lasting for more than one month or recurrent fever (>3episodes) is one of the AIDS defining condition in resource poor countries (WHO guidelines). Severe immunosuppression leads to increased chance of persistent/recurrent secondary bacterial and viral infections. This in turn could manifest as a febrile illness that has a shown a significant association in the study. Cough of more than 14days duration along with fever can be attributed to opportunistic infections like tuberculosis and pneumocystis pneumonia. Cough was found in 23 children. Hemoptysis is seen in less number of children (8%) that indicates advanced pulmonary disease, rarely bleeding manifestation. Clubbing was seen in 28 cases, can be due to chronic respiratory infection like TB, pneumocystis, bronchiectasis rarely empyema in HIV. The occurrence of chronic/recurrent otitis media is a common manifestation (49%) and prevalence is similar to other studies [3].
There has been increased incidence of skin manifestations (36%) in that papular urticaria being most common, recurrent skin abscess was found in 2 cases when compared to other Indian studies[2,3,4,5] . The proportion of children with weight loss (38%) is very striking with most of the children in having severe immunosuppression. Persistent generalized lymphadenopathy was found in 45 children, this can be due to opportunistic infections and deposition of virus in the reticuloendothelial tissues leads to enlargement. Recurrent /persistent pneumonia was found in 26 children this can be due to opportunistic infection or other bacterial infection. Mycobacterium tuberculosis (26%) was the most common opportunistic infection including (pulmonary and extra pulmonary) suspected clinically based on clinical symptoms and signs, this is comparable to other Indian studies [2,5]. As the study didn't include laboratory investigations that is suspected on clinical basis like prolonged fever, chronic cough, chest pain, weight loss sometimes with lymphadenopathy. That was similar to other Indian studies. Bleeding manifestations were seen in 12 children that may be due to immune thrombocytopenic purpura. Hepatospelnomegaly was seen in 20 children and isolated hepatomegaly seen in 28 children. Isolated hepatomegaly is seen in 28, splenomegaly in 2% cases, overall 50% of cases with hepatosplenomegaly. This issimilar to other Indian studies [2,3,4,5] and also Italian register for HIV infection [6,7]. Actual incidence may be more than this as findings are observed clinically only.

VII. Analytical Data:

The hallmark of HIV infection is the affection of the immune system leading to immunodeficiency that inturn leads to prolonged and unusual infections that are the major cause of morbidity and mortality. This worsening of immune system predicts the progression of disease. Absolute CD4 counts are the gold standard measure of immune status. Management decisions of HIV infected children are based on CD4 counts. This includes initiation of antiretroviral therapy, assessing response to treatment and prophylaxis for opportunistic infections. Decisions regarding immunization are also based on CD4 counts. Measurements of CD4 counts were relatively expensive and not widely available/accessible/feasible. In resource poor countries like India and sub-Saharan African countries the disease burden is high and finances matter. The presence of inexpensive surrogate routine markers (clinical symptoms and signs) for CD4 counts reflecting the immune status will go a long way in resourceful utilization of sparse resources.an analysis of clinical features as predictors of severity of immunesuppression was done to fulfill the studies second objective. The analysis compared each clinical feature compared each clinical feature with each immune category (no, mild, advanced, severe) individually and

combinations of immune categories (no, mild VS advanced, severe). The clinical categories (stage 1, 2, 3) were found to statistically significantly associated with immune categories (A, B, C, D individually and in combinations A and B Vs C and D). An increased number of study observations may have increased the strength of correlation. None of the asymptomatic children (stage 1) were severely immunosuppressed (stage C, D) and only child with stage 3 manifestations is immunocompetent (A, no immunosuppression). Children with clinical stage 1 manifestations were not immunosuppressed. Clinical stage 2 children are majority mildly immunosuppressed. Clinical stage 3 children having predominantly severely immunosuppressed. Among those clinical symptoms and signs some of the symptoms like recurrent URTI, persistent fever, chronic cough, chest pain, diarrhea, ear discharge, oral thrush, abdominal distension due to heaptosplenomegaly, isolated hepatomegaly, weight loss, headache, vomiting, severe malnutrition, pallor, clubbing, recurrent pneumonia can predict the immunosuppression. When these symptoms and signs have subjected to logistic regression analysis as individual predictor if immunosuppression only persistent, fever, chronic diarrhea and anemia were able to predict the immunosuppression.

Fever (prolonged fever- intermittent or continuous>1month) has been one of the AIDS defining clinical condition in pediatric HIV (WHO guidelines). Increased occurrence of fever was seen with worsening of immune status. This could be attributed to an increase in viral loads and possible secondary infections as children immune status worsens. This trend also seen in other Tovo et al[7] and the Italian registry[6].There was good correlation (r value14.2) between this individual symptom and immunosuppression category.

Chronic diarrhea: Occurs due to various reasons in HIV infected children. It might be due to viral, bacterial or protozoal causes. It leads to malnutrition, which further contributes to secondary infections. Worsening of immune status would logically increase the chance of infection with opportunistic infections and the incidence of diarrhea. The presence of diarrhea showed significant variation between groups of observations in those children with immunosuppression (A, B, C, D) individually or in combinations. This showed significant correlation with immunosuppression in isolation(r value 10.5).

Anemia:Anemia is the most common hematological manifestation of HIV infection, with the exception of CD4 lymphocytopenia. Cross sectional prevalence is 23-48% among children and adult studies have demonstrated that the occurrence of anemia is significantly correlated with stage of HIV disease especially if there is CD4 count less than 200 cells/mm3. This was observed clinically (eyes, palms, tongue,) and laboratorily as value<8mg/dl. Causes of anemia in HIV infection in children could be secondary to bone marrow infections, cytokine mediated suppression, direct HIV infection/effects, iatrogenic, nutritional, autoimmune, bleeds and GI losses. This showed significant correlation with immunosuppression in isolation(r value 6.5).

VIII. Conclusions

1) Perinatal transmission is the commonest mode of transmission of pediatric HIV infection. Transfusion related transmission though rare could still occur.
2) There is a wide spectrum of clinical manifestations with CSOM, persistent fever, and lymphadenopathy being most common.
3) Children with unexplained fever must raise the suspicion of HIV infection.
4) Malnutrition, weight loss, papular urticaria are next most common manifestations.
5) Recurrent fever, chronic diarrhea and anemia can predict the immunosuppression as a individual parameter.
6) Popular urticaria a non-specific reaction to environmental allergens and mosquito bites is seen in high proportion in HIV infected children.
7) Thrush, chronic diarrhea, bronchopneumonia/LRTIs and tuberculosis especially pulmonary are common infections.
8) WHO clinical stages remain the best predictors of immunosuppression. Stage 3 symptoms have increased chances of having advanced to severe immunosuppression.

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