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Original Article

Paediatrics Section

Clinico-immunological Study of HIV Infected Children Attending ART Centre- A Prospective Longitudinal Study

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ABSTRACT

Introduction: Human Immunodeficiency Virus (HIV) infection is a growing concern in paediatric population and large number of children are registered and treated at Antiretroviral Treatment (ART) centres across the country. Children with HIV progress more rapidly, develop more bacterial infections, suffer from neurologic developmental problems and have higher mortality than adults. So the screening and counselling of HIV positive parents and their children must be done timely. This helps the physician for starting the treatment timely.

Aim: To determine the clinico-immunological profile of paediatric patients registered in ART, and to compare the immunological profile and clinical staging of paediatric patients receiving ART.

Materials and Methods: This prospective longitudinal study was conducted in the ART centre of Sarojini Naidu Medical College, Agra, Uttar Pradesh, India, from October 2017 to October 2018. Total 51 children, upto the age group of 18 years, suffering from HIV/Acquired immunodeficiency syndrome (AIDS) were enrolled in the study. Diagnosis of HIV was confirmed using Enzyme-Linked Immunosorbent Assay (ELISA) method (using two different antigens Comb HIV test, TRI-DOT) in children more than 18 months of age. In children less than 18 months age, diagnosis was confirmed using Deoxyribonucleic Acid (DNA) Polymerase Chain Reaction (PCR) (repeated twice with cessation of breast feeding for minimum of six weeks). Statistical analysis was done by using Statistical Package for the Social Sciences (SPSS) trial version 23.0 and simple frequency and Chi-square test was used for analysis.

Results: Majority of the children (20, 39.26%) were in the age group of 5-10 years, and male:female ratio was 2.4:1. Most common presenting complaint was cough (52.94%), followed by fever (47.05%), chronic diarrhoea (37.25%). Most common clinical signs seen were hepatosplenomegaly (41.17%), pneumonia (33.33%) and lymphadenopathy (31.37%). Initially the mean CD4 count was 370.31±231.5 cell/mm^3, and after starting ART mean CD4 count was 524.6±260.4 cell/mm^3. Significant improvement in CD4 count was observed in age group of 5-10 years (p-value=0.009), and 10-15 years (p-value=0.001) after six months of starting the ART. In the beginning, maximum (56.7%) children belonged to World Health Organisation (WHO) clinical staging III and after starting ART maximum 40% belonged to stage II.

Conclusion: The ART improves symptomatology and immunological status HIV infected children, so there is need to screen the children of HIV affected parents and identify the children suffering with HIV in order to initiate ART at the earliest indication in order to improve their general health, freedom from illness and better immunological status.

Keywords: Antigens comb HIV test, Antiretroviral treatment, CD4 count, Human immunodeficiency virus, TRI-DOT test

INTRODUCTION

The Human Immunodeficiency Virus (HIV) infection is a growing concern in paediatric population and large number of children are registered and treated at Antiretroviral Therapy (ART) centres across the country. Globally, an estimated 1.8 million children aged 0-14 were living with HIV at the end of 2019 and 150,000 children were newly infected. An estimated 100,000 children died of AIDS-related illnesses. Without access to testing and treatment, 50% of children with HIV will die by the age of 2 and 80% will not live to their fifth birthday [1]. In 2019, at the national level, there were an estimated 23.49 lac (17.98 lac-30.98 lac) People Living with HIV (PLHIV), with an adult (15-49 years) HIV prevalence of 0.22% (0.17- 0.29%). Children Living with HIV (CLHIV) comprised 3.4% of the total PLHIV estimates [2].

As we know that CD4 T-lymphocyte is the immune system cell that HIV infects and destroys, and the CD4 count roughly reflects the state of the immune system. This suggests CD4 count is reliable marker of clinical status. Children with HIV progress more rapidly, develop more bacterial infections, suffer from neurologic developmental problems and have higher mortality than adults. Common clinical manifestations in children include fever, persistent diarrhoea, oral thrush, recurrent pneumonia, chronic parotitis, generalised lymphadenopathy, delay in development with failure to thrive, and significant pruritic dermatosis[3]. Also, children with HIV infection suffer from opportunistic infections. The previous study [4,5] which was conducted on HIV positive children, to see the improvement after initiation of ART, it was found that, those children who were initiated on ART had a significant improvement in both clinical and immunological staging at the six months follow-up. So, this study aimed at comparing the association of clinico-immunological profile of HIV infected children before and after starting ART.

MATERIALS AND METHODS

This was prospective longitudinal study conducted in the ART centre of Sarojini Naidu Medical College, Agra, Uttar Pradesh, India, from October 2017 to October 2018. After the ethical approval from the Ethical Committee of the College, 51 children were included in the study. Their parents/guardians were briefed about the objectives of the study and informed /written consent obtained before enrolling their children in the study.

Diagnosis of HIV was confirmed by Enzyme-Linked Immunosorbent Assay (ELISA), performed in the Department of Microbiology, using two different antigens (Comb HIV, TRI-DOT) in children more than 18 month. In children <18 month, diagnosis was confirmed by positive Deoxyribonucleic Acid Polymerase Chain Reaction (DNA PCR) (repeated twice with cessation of breast feeding for minimum of six weeks).

Inclusion criteria: All the children under 18 years of age who were registered in the ART centre, and whose parents gave voluntary consent for interview and were ready for follow-up were included in the study.

Exclusion criteria: Children parents who did not give written consent to participate in the study were excluded from the study.

Study Procedure

After confirmation of the diagnosis and after obtaining informed/ written consent from the parents or the guardian, child was enrolled for study. Further following steps were taken for performing the study:

Step 1: A complete demographic profile of the children was taken (age, sex, occupation of parents, socio-economic class, presenting complaint/symptoms, developmental milestones, personal history and habits,immunisation status, maternal birth and feeding history, any treatment history).

Step 2: A complete physical examination of the children was done (anthropometry, general physical examination, and systemic examination).

Step 3: Then the children were subjected to baseline investigations available at the hospital including- complete blood count, serum creatinine/blood urea (renal function), serum bilirubin, Serum Glutamic Pyruvic Transaminase (SGPT)/serum Glutamic-Oxalacetic Transaminase (SGOT), chest X-ray, Mantoux test, urine routine/ examination and microscopic/examination, Erythrocyte Sedimentation Rate (ESR), blood sugar, Serum protein, Alkaline phosphate, Hepatitis C Antibody Test, Hepatitis B surface antigen).

Step 4: After the baseline investigation, for CD4 count of all the enrolled children, samples were tested by using Fluorescence Activated Cell Sorting (FACS) count (Bactec and Dickinson). After assessment on the basis of CD4 count and World Health Organisation (WHO) clinical staging children who were eligible for starting ART {according to National Aids Control Organisation (NACO) Guidelines} [3] were put on ART.

Step 5: Follow-up of patient:

- Follow-up of all the patients who put on ART was done every month, even in between a month period if patient was without any complaint and this follow-up was done for six months period. CD4 count of the patients was repeated after 6 months of follow-up (according to NACO Guidelines) [3].
- Patient was not eligible for ART was also followed-up every month for their clinical condition up to six months.
- Relevant investigation if needed (complete blood count, renal function, liver function etc.,) was carried out on the basis of clinicalassessment during the follow-up.

STATISTICAL ANALYSIS

Statistical analysis was done by using Statistical Package for the Social Sciences (SPSS) trial version 23.0 and simple frequency and Chi-square test was used for analysis. The p-value <0.05 was taken as significant cut-off value.

RESULTS

In the study, majority of children 20 (39.26%) were in the age group of 5-10 years and male:female ratio was 2.4:1. [Table/Fig-1] shows that maximum 27 (52.94%) of children presented with cough, followed by fever (47.05%) and chronic diarrhoea 19 (37.25%). One (1.9%) child was asymptomatic, and was brought to the ART centre. [Table/Fig-2] shows that most common clinical finding was hepatosplenomegaly (21,41.17%) followed by pneumonia (17,33.33%).

[Table/Fig-3] shows, the immunological profile of the 51 children. In 0-5 years age group, mean CD4 was 655.71 (cells/mm^3), in 5-10 years age group mean CD4 count was 371 and in >10-15 years age group mean CD4 count was 214.5 (cells/mm^3). In the one child of age group 15-18 years CD4 count was 57 (cells/mm^3).

Symptoms	Age 0-5 years (n=17)	Age >5-10 years (n=20)	Age >10-15 years (n=13)	Age >15-18 years (n=1)	Total
Cough	5	17	5	0	27 (52.94%)
Fever	4	12	7	1	24 (47.05%)
Chronic diarrhoea	6	11	2	0	19 (37.25%)
Skin infections	2	3	5	0	10 (19.60%)
Abdominal distension	1	2	0	0	3 (5.8%)
Abdominal pain	0	0	1	1	2 (3.9%)
Ear discharge	1	1	3	0	5 (9.8%)
Parotid enlargement	1	0	0	0	1 (1.9%)
None	0	1	0	0	1 (1.9%)

[Table/Fig-1]: Presenting complaints in HIV positive children vs age (At the time of registration in ART centre).
*Multiple responses

Signs*	Age 0-5 years (n=17)	Age >5-10 years (n=20)	Age >10-15 years (n=13)	Age >15-18 years (n= 1)	Total
Hepatosplenomegaly	4	10	6	1	21 (41.17%)
Pneumonia	5	6	6	0	17 (33.33%)
Lymphadenopathy	3	8	5	0	16 (31.37%)
Pallor	3	7	3	1	14 (27.45%)
Sign of vitamin A**	2	4	1	0	7 (13.72%)
Oral thrush	2	1	2	0	5 (9.80%)

[Table/Fig-2]: Clinical signs in HIV positive children according to age.
*Multiple responses, **Night blindness and bitot's spot

Age (years)	Pre ART CD4 count (cells/mm^3) (mean±SD)
0-5	655.71±389.27
>5-10	371±244
>10-15	214.5±128.55
>15-18	57

[Table/Fig-3]: Pre ART immunological profile of HIV positive children vs age (n=51).

Out of the 30 children who were put on ART, five were of 0-5 years of age, and their pre ART mean CD4 count was 753±464 (cells/mm^3). After six months the CD4 count came down to 626±353.07 (cells/mm^3), (p-value=0.1). Fifteen children were 5-10 years and their pre ART mean CD4 count was 450±335.29 (cells/mm^3) which became 636.66±382.18 (cells/mm^3), after six month post ART (p-value=0.009), that means there was significant increase in CD4 count after ART. Nine children were in age group of >10-15 years, their pre ART mean CD4 count was 221.22±126.95,which became 655.77±306.29 after 6 month post ART (p=0.001) shows significant improvement in CD4 count [Table/Fig-4].

Age (years)	Pre ART CD4 count (mean±SD)	Post ART CD4 count (6 months follow-up) (mean±SD)	p-value
0-5 (n=5)	753±464	626±353.07	0.1
>5-10 (n=15)	450±335.29	636.66±382.18	0.009
>10-15 (n=9)	221.22± 126.95	655.77±306.29	0.001
>15-18 (n=1)	57	180	-

[Table/Fig-4]: Comparison of mean CD4 count (cells/mm^3) at pre ART and post ART stage. CD4 count of children put on ART and followed-up to 6 month (n=30).

According to [Table/Fig-5], 3 (10%) who were initially in stage I before ART, after six months remained in same stage I. Two (6.7%) children were in stage II before ART, six month post ART both children regressed to stage I. On the other hand, 15 (56.7%) children were in stage III before ART, out of these children, one child regressed to stage I, whereas 12 children regressed to stage II and four children still remained in stage III. Eight (26.60%) children were in stage IV, out of which three regressed to stage III and five still remained in stage IV.

Pre ART clinical stage	Post ART children in clinical stage			
	I	II	III	IV
I n=3 (10%)	3	0	0	0
II n=2 (6.7%)	2	0	0	0
III n=17(56.7%)	1	12	4	0
IV n=8 (26.6)	0	0	3	5
Total: 30 (100%)	6 (20%)	12 (40%)	7 (23.3%)	5 (16.7%)

[Table/Fig-5]: Comparison of World Health Organisation (WHO) clinical staging at pre and post ART.

DISCUSSION

As we all know that, HIV disease progresses very rapidly in most young children, especially in the first few months of life, often leading to death. Without care and treatment, about one third of infants living with HIV will die in their first year of life and almost half of the children with HIV will die the second year of life. Globally, the number of children younger than 15 years living with HIV infection has increased from 1.6 million in 2001 to 2.5 million in 2009. In 2009 alone, globally, 370,000 children under the age of 15 years were newly infected. It was estimated that currently about 115,000 children are living with HIV in our country [3].

In this study, 39.26% children were in the age group of 5-10 years and male:female ratio was 2.4:1. The most common complaint was cough (52.94%), followed by fever (47.05%). The finding of this study was consistent with observations made in others studies [6-9]. Similar to others [6-9] in the present study the most common clinical sign was hepatosplenomegaly (41.17%), followed by pneumonia (33.33%). In this study, the baseline mean CD4 count of 50 children was 324.38±190.46 cells/mm^3 maximum was in 0-5 years (655±389.270 and least was in 15-18 years (57±0.0 cells/mm^3). It indicates degree of immuno-suppression increased as the age of children increased. Similarly, Gomber S et al., studied the profile of HIV infected children from Delhi and their response to ART in 100 children who were brought for follow-up till six months [4]. In their study they found that baseline mean CD4 count was 961.6±535.1 cells/mm^3 in 1-5 years and lowest (422±226.3 cells/mm^3) in above 13 years. This study also shows similar correlation with degree of immune-suppression and age.

In present study, we compare the pre ART CD 4 count of eligible children (n=30) with post ART CD4 count and we have found that the post ART mean CD4 count of these children increased to 524.6±260.4 cells/mm^3 from baseline pre ART CD4 (370.31±231.5 cells/mm^3) count. This significant increase in CD4 count was seen in 5-10 years (p-value <0.009), and 10-15 years age group (p-value <0.001) respectively. Similarly Natu SA and Daga SR, in their study found that after initiation of ART in 25 children older than 18 months, their mean CD4 counts was increased from 488/cmm to 765/cmm (p-value <0.001) [10]. Memirie ST also found that the mean percentage of CD4 T-cells rose from 9.5% at baseline to 18.7 % at 6 months (p-value <0.001) in 50 subjects [11]. Parakh A et al., conducted a study and they also found that the median CD4 increased from 6.0 % at baseline to 15.5% at six months [12]. Therefore, our study is consistent with above studies.

In the present study, at the beginning maximum (56.7%) children belonged to WHO clinical staging III and after starting ART maximum (40.0%) improved to stage II. Gomber S et al., in their study on 100 children, found that on initiating ART there was significant improvement in both clinical and immunological staging at the 6 months follow-up [4]. A study conducted by Verma SK et al.,on 50 children found that, initially 26 children were in clinical stage III which improved to clinical stage II and at first follow-up maximum increase in CD4 count was also seen in this stage (from 221.19±80.88 (cells/mm^3) to 351.11±124.65 (cells/mm^3)) [5].

Limitation(s)

Since NACO guidelines were followed for the selection of study subjects, the sample size was small (n=30). Due to constraint of resources, only one follow-up of study subjects was done for estimation of CD4 count.

CONCLUSION(S)

There is improvement in the immunological status of the children who are taking ART recommended by the NACO. So, the children of HIV affected parents screened timely and identify the children suffering with HIV to initiate ART as early as possible to improve their general health, freedom from illness and better immunological status.

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