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Original Research Article

Prevalence of cardiac complications in perinatally acquired human immunodeficiency virus infection in children in Southern India: an observational study

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ABSTRACT

Background: Human immunodeficiency virus (HIV) infection is a multisystemic illness that impacts most organ system, to investigate prevalence of cardiovascular abnormalities in children with perinatally acquired HIV infection.
Methods: This observational study was conducted in a tertiary care centre in Southern India. HIV-positive children between the ages of 18 months and 15 years were included. Cardiac abnormalities were defined as abnormalities identified on 2D echocardiography and/or electrocardiogram.
Results: The 73 children with HIV infection had their cardiac manifestations assessed. Median age of children was 8 years with 52% of female participants, 22 (30.13%) children had cardiac abnormalities, of which 5 (27.27%) were symptomatic. Overall, 21/22 (95.45%) children had abnormalities on their ECG, 16 (72.72%) had abnormalities on 2D echocardiography. Of these, we found that children with delayed diagnosis of HIV infection and with more advanced clinical and immunological staging in HIV are more prone to develop cardiac complications irrespective of antiretroviral therapy (ART).
Conclusions: HIV-related heart involvement is not uncommon, rather occur subclinical. A decreasing CD4 count and worsening clinical status are associated with increased risk. Hence its crucial to screen the children, diagnose at the earliest and timely manage the complications appropriately for prevention of early mortality.

Keywords: Perinatally acquired HIV, Cardiac abnormalities, Echocardiography, Electrocardiogram, ART

INTRODUCTION

HIV infection is on the rise and is expected to pose a growing global threat to public health. As per global estimate 2020, number of children living with HIV (CLHIV) was 1.94 million.[1] In India, a country with 1.3 billion people, children up to 18 years constitute 41% of the total population. Nevertheless, India lacks reliable estimates of the pediatric HIV burden as the national AIDS control program (NACP) publishes estimates of pediatric HIV infections based on the proportion of pediatric HIV infections to adult infections.[2,3] Mother-to-child transmission (MTCT) remains the main cause of HIV infection among children in India. Despite the availability of resources to prevent, identify and treat HIV in children, India's performance in this area is not optimal.

HIV infection is a multisystemic illness that impacts most organ systems. Individuals living with HIV may experience a variety of cardiovascular abnormalities,

some of which have been linked to poor outcomes. According to published research, heart involvement in HIV infection typically happens after a protracted viral infection and significant immunosuppression; as a result, it manifests later as a patient's longevity increases.[4] Heart symptoms in people with CLHIV can range from asymptomatic left ventricular dysfunction to dilated cardiomyopathy to congestive heart failure and can even be fatal.[5-7] In pediatric age group, cardiac abnormalities detected by echocardiography, even at the sub-clinical stage, constitute independent and poses substantial risk factors of early mortality. Given the opportunity, early detection facilitates early intervention.[8] These cardiac manifestations are not exclusively caused by the direct toxicity of the HIV on cardiac cells and other factors, such as immune reactions, nutritional deficiencies, opportunistic infections and ARV treatments are known to play a contributory role.[9] Ever since the introduction of highly active ARV therapies (HAART), which are not without any cardiac risk, some studies have been carried out, with varying results.[10] It is therefore pertinent to determine the prevalence of the cardiac abnormalities associated with HIV infection within the era of HAART.[11-13]

While a large body of research has been done on the relationship between HIV and the cardiac complications in adults, data in children is sparse. The prevention of early mortality largely relies on early detection and management. Therefore, this study intends to investigate the prevalence of the cardiac abnormalities in CLHIV since there is a dearth of research on the involvement of the heart in HIV infection in the pediatric subgroup of the Indian subcontinent population.

METHODS

This 12-month observational study was conducted at a tertiary care facility between September 2021 and September 2022 that treated pediatric HIV patients. Our study included all perinatally acquired HIV infected children between the ages of 18 months and 15 years who were either admitted to a pediatric unit or visited the high-risk HIV clinic in Karnataka institute of medical sciences, Hubli, Karnataka, India during the study period. If children were diagnosed at a later age, they were deemed perinatally acquired HIV infection if the mother was HIV positive. We excluded children with previous heart illness that could have been caused by other factors, such as congenital heart disease (CHD), rheumatic fever, children who were terminally ill, or children whose parents/guardian had not given their consent as well as those children whose duration of illness was unknown due to death of both parents. Ethical clearance was obtained from the institute ethical committee before commencement of the study. Informed consent was obtained from either of parent/guardian.

Details about ART, the length of the disease, the WHO clinical stage, the CDC immunological stage, and a family history of HIV infection were recorded. To categorize patients in the appropriate immunological stage, their most recent CD4 values during the previous six months were taken into consideration. A thorough clinical evaluation was conducted, and indicators of cardiac involvement, such as abnormal heart rate and rhythm, cardiac murmur, and symptoms of heart failure, were sought after. Every child that was enrolled had a 12-lead electrocardiogram (ECG), a 2D echocardiogram, and a chest X-ray irrespective of symptoms.

The right atrial enlargement on a chest x-ray was identified by its prominent right border, the left ventricular enlargement by its apex displaced laterally and lower, the right ventricular enlargement by its high apex, and the left atrial enlargement by its double density cardiac shadow.[7] In the ECG, abnormalities related to rate, rhythm, axis, intervals, chamber dilatation, and conduction were examined. The 20th edition of Harriet Lane is used to determine normal ECG values.[14] A cardiologist verified and documented individual ECG. 2D echocardiography was performed by cardiologist and following parameters were looked for. Left ventricular end-diastolic dimension (LVDD), left ventricular end-systolic dimension (LVSD), inter ventricular septal thickness (IVS), left ventricular fractional shortening (LVFS), left ventricular ejection fraction (LVEF), pericardial effusion (PE) pulmonary hypertension, left ventricular hypertrophy (LVH), right ventricular hypertrophy (RVH) or any other structural lesion were looked for. By monitoring a tricuspid regurgitation jet and applying Bernoulli's equation, the pulmonary artery systolic pressure was estimated. To obtain systolic right ventricular pressure (SRVP), a fixed right atrial pressure value of 5 or 10 mm of Hg was added to the trans-tricuspid pressure gradient.[15] LV systolic dysfunction was defined as LVFS<28 percent. Ejection fraction below 55 percent was considered poor LVEF (Ref). The diagnosis of PE was made when the effusion was more than 4 mm.[16]

Determining the prevalence of cardiac disturbances in CLHIV as determined by 2D echocardiography and /or ECG was the primary objective of our study.

Sample size calculation

We used convenience sampling method for our study and enrolled all the perinatally acquired HIV infected children between the ages of 18 months and 15 years who were either admitted to our pediatric unit or visited the high-risk HIV clinic during the study period.

Statistical analysis

Analysis of the data was done using SPSS 25 and Microsoft excel. While proportions were used to represent categorical data, mean was used to represent continuous variables. The risk ratio was applied to

analyse the risk of the desired outcome. P<0.05 was considered as statistically significant

RESULTS

Table 1 illustrates the baseline characteristics of the study population. Present study enrolled 73 children with perinatally acquired HIV, who visited High risk clinic during the study period of 12 months. Age of children ranged between 18 months and 15 years, with median age of 8 years. Female children constituted 52% of study population, 33 (45.2%) children were classified as WHO clinical stage 3-4, whereas 41 (56.2%) children were classified as advanced CDC immunological stage. The median age of diagnosis was 4 years, and duration of ART ranged from 18 to 48 months with a median of 18 months. Of the enrolled participants, 12 were symptomatic, and 60% of overall participants were on ART.

Table 1: Baseline characteristics of study population, (n=73).

Characteristics	N (%)
Age of children (in years), median (IQR)	8 (4-11)
Range (in years)	1.5-15
Gender-female	38 (52.0%)
WHO clinical stage 3-4	33 (45.20%)
CDC stage advanced-severe	41 (56.2 %)
Duration of illness (in years)	8 (4-11)
Age at diagnosis (in years)	4 (2-7)
ART duration (in months)	18 (18-48)
Symptomatic	12 (16.4%)
ART	44 (60.3%)

SD: Standard deviation, IQR: Interquartile range, ART: antiretroviral therapy, CDC: Centre of disease classification, WHO: World health organization.

The clinical and investigational characteristics of children with diagnosis of cardiac involvement is presented in Table 2. In the current investigation, 22 (30.13%) children had cardiac abnormalities identified by ECG and/or echocardiography; of these, 6 (27.27%) had symptoms; palpitations was the most frequent symptom, followed by dyspnoea. Overall, 21 (95.45%) children had abnormalities on their ECG, 16 (72.72%) had abnormalities on 2D echocardiography, and 7 (31.81%) had abnormalities on their chest x-ray. On further exploration, we discovered that 7/22 children had abnormalities found using all three modalities (CXR, ECG, 2D echo); 15 children had evidence on both 2D echo and ECG; 8 had abnormalities found using ECG alone; and 1 had abnormalities found using 2D echo alone, and none with CXR alone.

Table 3 illustrates the factors theorized to impact the cardiovascular system in HIV infection. Of these, we found that children with delayed diagnosis of HIV infection were more prone to encounter cardiac involvement. Moreover, there was an elevated risk of cardiac involvement with more advanced clinical and immunological staging in HIV.

Table 2: Profile of children with cardiac complications, (n=22).

Characteristics	N (%)
ART	16 (72.72)
WHO stage 3-4	17 (77.27)
Duration of illness > 5 years,	17 (77.27)
Children diagnosed>5 years of age	13 (59.09)
CDC stage (advanced)	19 (86.36)
Symptomatic	6 (27.27)
Children with ECG findings	21 (95.45)
Sinus tachycardia	7 (31.81)
Ectopics	1 (4.5)
Rhythm abnormalities (RBBB/LBBB)	2 (9)
Features of LVH/RVH	3/3 (13.63)
Biventricular hypertrophy	5 (22.72)
Children with 2DEcho abnormalities	16 (72.72)
LVH only	5 (22.72)
RVH (± Pulm hypertension) only	6 (27.27)
Biventricular hypertrophy	3 (13.63)
Cardiomyopathy	2 (9)
Children with CXR abnormalities	7 (31.81)

ART: Antiretroviral therapy, WHO: World health organization, CDC: Centre of disease classification, ECG: Electrocardiogram, LVH: Left ventricular hypertrophy, RVH: Right ventricular hypertrophy, CXR: Chest X ray, N: number,

Table 3: Association of various factors with development of cardiac complications in CLHIV.

Variables	RR	95% CI	P value
Duration of illness (in years)	1.955	0.741-5.161	0.174
ART	2.109	0.868-5.126	0.113
Diagnosis >5 years of age	4.024	1.958-8.269	0.000
ART duration (in years)	0.759	0.335-1.720	0.527
WHO clinical staging (1-2 vs 3-4)	5.152	1.920-13.820	0.000
CDC staging (1-2 vs 3-4)	7.415	1.862-29.523	0.000

ART: Anti retroviral treatment, WHO: World health organization, CI: Confidence interval, RR: Relative risk, P<0.05 considered as significant

DISCUSSION

HIV infection has been acknowledged as a chronic rather than a terminal illness as life expectancy has improved, since the introduction of Highly Active Anti-retroviral therapy. Published studies show that 25 percent of children with perinatally acquired HIV infection die from the disease's consequences around the age of 10; infant

and younger child deaths, however, are uncommon. A recent study indicated that, during five years of illness, up to 28% of children with HIV experienced an impairment in heart function. Risk factors for cardiac problems include HIV encephalopathy, low CD4 count, past significant cardiac event, and rapid advancement of HIV infection.[11]

The present study found that 30.13% of children with HIV had cardiac abnormalities. The most common symptom was breathlessness and the most frequent clinical finding was persistent tachycardia. Sinus tachycardia was the most common ECG finding. On 2D echo, RVH and LVH were predominant cardiac abnormalities. Children who had advanced clinical and immunological staging as well as those with delayed diagnosis were frequently found to have these cardiac abnormalities.

Table 5 illustrates the variable magnitude of cardiac abnormalities observed in previous literature, which may be attributed to differences in the enrolled population.[17-18] Our study observed cardiac abnormalities in 30.13% of patients. In contrast to our study, which included children with all stages of HIV, a study by Okoromah indicated that cardiac abnormalities were present in 75.9% of children with AIDS (WHO stage 3-4).[18] Persistent tachycardia was reported to be the most prevalent clinical sign in previous research, which is in line with findings of this study.[21,22] Likewise, as in our study, rate and rhythm abnormalities were most prevalent ECG changes and were most often encountered in severe immunosuppressed children.

Table 4: Prevalence of cardiac abnormalities in various studies.

Study	Incidence	M/C echo finding
Chelo et al[17]	89%	RV dysfunction (76%)
Lubega 2005[16]	51%	LV systolic dysfunction (17.4%)
Okoromah 2011[18]	75.9%	LV systolic dysfunction (33.7%)
Pushpalatha 2014[19]	42%	LV systolic dysfunction (19%)
Plein 2015[20]	18%	PE with wall motion abnormalities

The majority of CLHIV-related literature has described various spectrum of cardiac abnormalities. According to an Indian study, cardiac dysfunction was present in 76.9% of asymptomatic HIV-positive infants, with LVH and LV dilatation accounting for the majority of these cases (38.5%).[23] Likewise, few further studies reported that LV abnormalities as most common echo findings.[16,18,19] Conversely PE was shown to be the most frequent abnormality in research by Plein et al.[20] The most often identified anomalies in our investigation were RVH and LVH, with RVH being the most prevalent.

Most of the earlier studies have emphasized that severe immunosuppression and worse clinical stage is more frequently linked to cardiac abnormalities.[16,18,19,23] Our study supports the findings of the earlier studies. With respect to ART, earlier literature has demonstrated conflicting results. A study by Wamalva et al noticed increased risk of cardiac complications in ART exposed children, whereas, in support of another similar study, CHAART 2 study concluded that HAART use in HIV-infected children appears to be generally cardioprotective.[24,25]

As cardiac involvement in HIV is mostly subclinical, and tends to be more prevalent in children with advanced disease and long duration of illness without ART (late diagnosis), screening of these children with non-invasive tools like ECG and 2D echo will aid in prevention of early mortality and timely initiation of appropriate management.[26] This article highlights the significance of screening for cardiovascular complications in children diagnosed with HIV, as guidelines or recommendations do not currently exist. Such screening can mitigate cardiac morbidity and mortality and facilitate early intervention

One of the study's primary strengths was that it was one of the first to be undertaken out in Southern India and that it included children with both extremes of immunosuppression and exposure to ARV therapy. Nevertheless, there were some shortcomings to our study, including smaller sample size, smaller population under investigation with severe immunosuppression and unreliability about ART compliance, given that majority of children had lost their parents at the time of enrolment. To generalize the findings, more research with a larger sample size is recommended.

CONCLUSION

In conclusion, despite ARV therapy (HAART), cardiac involvement in HIV is not uncommon. A decreasing CD4 count and worsening clinical status are associated with increased risk. Additionally, this study found that a significant contributing factor to the development of these difficulties is the delay in diagnosing HIV infection in perinatally acquired infections and, consequently, the delay in starting treatment.

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REFERENCES

1. Luzuriaga K, Mofenson LM. Challenges in the Elimination of Pediatric HIV-1 Infection. Campion EW, editor. N Engl J Med. 2016;374(8):761-70.
2. HIV Estimations 2017 Report_1. 2017. Available at: https://naco.gov.in/sites/default/files/HIV%20Estima

tions%202017%20Report_1.pdf. Accessed on 12 January, 2024.
3. Age structure and marital status. Office of the Registrar General and Census Commissioner, India Ministry of Home Affairs, Government of India. Available at: https://censusindia.gov.in/census.website/. Accessed on 12 January, 2024.
4. Fisher SD, Lipshultz SE. Cardiovascular Abnormalities in HIV-Infected Individuals Braunwald's Heart Disease. 9th edition. 2007;1624-35.
5. Anita B, Kakrani GP, Hiremath MS. Cardiac Dysfunction Associated with HIV Infection. J Assoc Physicians India. 2003;51:1182.
6. Doddi S Aziz F. Human Immunodeficiency Virus–Associated Myocarditis. Internet J Intern Med. 2010;8(2):1528-8382.
7. Lipshultz SE, Easley KA, Orav EJ, Kaplan S, Starc TJ, Bricker JT, et al. Left Ventricular Structure and Function in Children Infected with Human Immunodeficiency Virus: The Prospective P 2 C 2 HIV Multicenter Study. Circulation. 1998;97(13):1246-56.
8. Lipshultz SE, Easley KA, Orav EJ, Kaplan S, Starc TJ, Bricker JT, et al. Cardiac Dysfunction and Mortality in HIV-Infected Children: The Prospective P 2 C 2 HIV Multicenter Study. Circulation. 2000;102(13):1542-8.
9. Khunnawat C, Mukerji S, Havlichek D, Touma R, Abela GS. Cardiovascular Manifestations in Human Immunodeficiency Virus-Infected Patients. Am J Cardiol. 2008;102(5):635-42
10. Lipshultz SE, Wilkinson JD, Thompson B, Cheng I, Briston DA, Shearer WT, et al. Cardiac Effects of Highly Active Antiretroviral Therapy in Perinatally HIV-Infected Children. J Am Coll Cardiol. 2017;70(18):2240-7.
11. Miller RF, Kaski JP, Hakim J, Matenga J, Nathoo K, Munyati S, et al. Cardiac Disease in Adolescents with Delayed Diagnosis of Vertically Acquired HIV Infection. Clin Infect Dis. 2013;56(4):576-82.
12. Okoromah CAN, Ojo OO, Ogunkunle OO. Cardiovascular Dysfunction in HIV-infected Children in a Sub-Saharan African Country: Comparative Cross-sectional Observational Study. J Trop Pediatr. 2024;58(1):3-11.
13. Pongprot Y, Sittiwangkul R, Silvilairat S, Sirisanthana V. Cardiac manifestations in HIV-infected Thai children. Ann Trop Paediatr. 2004;24(2):153-9.
14. Engorn B, Flerlage J. The Harriet Lane handbook. Twentieth Edition. Philadelphia: Saunders, An imprint of Elsevier Inc. 2015;143.
15. Gutgesell HP, Paquet M, Duff DF, McNamara DG. Evaluation of left ventricular size and function by echocardiography. Results in normal children. Circulation. 1977;56(3):457-62.
16. Lubega S, Zirembuzi GW, Lwabi P. Heart disease among children with HIV/AIDS attending the paediatric infectious disease clinic at Mulago Hospital. Afr Health Sci. 2005;5(3):219-26.
17. Chelo D, Wawo E, Siaha V, Anakeu A, Ateba Ndongo F, Koki Ndombo PO, et al. Cardiac anomalies in a group of HIV-infected children in a pediatric hospital: an echocardiographic study in Yaounde, Cameroon. Cardiovasc Diagn Ther. 2015;5(6):444-53.
18. Okoromah CN, Ojo OO, Ogunkunle OO. Cardiovascular dysfunction in HIV-infected children in a sub-Saharan African country: comparative cross-sectional observational study. J Trop Pediatr. 2012;58(1):3-11.
19. Pushpalatha S, Anitha K. A study of cardiac complications in HIV infected children. BMC Infect Dis. 2014;14(S3):O24.
20. Plein D, Van Camp G, Cosyns B, Alimenti A, Levy J, Vandenbossche JL. Cardiac and autonomic evaluation in a pediatric population with human immunodeficiency virus. Clin Cardiol. 1999;22(1):33-6.
21. Badal S, Gupta R, Kumar P, Sharma M, Chhajta DS. Cardiac manifestations in HIV infected children. Are they under diagnosed? HIV/AIDS Res Treat Open J. 2015;2(1):21-6.
22. Asnake S, Amsalu S. Clinical Manifestations of HIV/AIDS in Children in Northwest Ethiopia. Ethiop J Health Dev. 2005;19(1):24-8.
23. Shah I, Prabhu SS, V S, Shashikiran HS. Cardiac dysfunction in HIV infected children: a pilot study. Indian Pediatr. 2005;42(2):146-9.
24. Wamalwa DC, Obimbo EM, Farquhar C, Richardson BA, Mbori-Ngacha DA, Inwani I, et al. Predictors of mortality in HIV-1 infected children on antiretroviral therapy in Kenya: a prospective cohort. BMC Pediatr. 2010;10(1):33.
25. Idris NS, Cheung MMH, Grobbee DE, Burgner D, Kurniati N, Uiterwaal CSPM. Cardiac Effects of Antiretroviral-Naïve versus Antiretroviral-Exposed HIV Infection in Children. Ferrand RA, editor. PLOS One. 2016;11(1):e0146753.
26. Singh P, Hemal A, Agarwal S, Kumar D. Cardiac Manifestations in HIV Infected Children. Indian J Pediatr. 2015;82(3):230-4.

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