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Decreased Prevalence of Rheumatic Heart Disease Confirmed Among HIV Positive Youth

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Abstract

Background: There is geographical overlap between areas endemic for rheumatic heart disease (RHD) and those endemic for human immunodeficiency virus (HIV). A recent pilot study demonstrated that children living with HIV might be at less risk for RHD development however, the sample size was too small to make definitive conclusions. Our objective was to determine the prevalence of RHD among HIV positive children in Uganda.

Methods: We conducted a prospective, cross-sectional study of HIV+ children (aged 5–15) receiving care at the Baylor Uganda HIV clinic, Kampala, Uganda. A focused echocardiogram and chart review was performed. A sample size of 988 children was needed to provide 80% power to detect a difference in population prevalence between HIV+ children and the general population, 2.97% (95% CI 2.70–3.24%), based on previous reports.

Results: Screening echocardiography of 993 HIV+ children found 15 individuals (1.5%, 95% CI 0.88% - 2.54%) with RHD. Of these 15, 2 were classified as definite RHD and 13 as borderline RHD. The majority of children had isolated mitral valve disease (93%). Children found to have RHD were older than without, 12 years vs 10 years; p=0.004. When separated based on geographic location, the prevalence of RHD among HIV-positive children from Kampala was 1.28% (95% CI 0.63% - 2.51%) compared to 2.1% (95% CI 0.89% - 4.89%) in those from outside Kampala.

Conclusions: Children living with HIV have a lower prevalence of RHD than the general pediatric population. Further studies are needed to explore this protective association.

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Keywords

Rheumatic heart disease; HIV; echocardiogram; cotrimoxazole; Uganda

Introduction

Rheumatic heart disease (RHD) is a chronic valvular heart disease that ultimately results from untreated or undertreated group A streptococcal infections, initially leading to acute rheumatic fever, an immune system overreaction, which can result in cardiac inflammation, scarring, and dysfunction[1]. RHD continues to cause significant morbidity and mortality in low-and-middle income nations. The 2015 Global Burden of Disease Study estimated 33.4 million prevalent cases with 319,400 deaths in 2015[2]. Specifically, among Ugandan school aged children, the estimated prevalence of RHD is approximately 3%, affecting 156,900 children[3–6]. The World Heart Federation has set a goal to achieve a 25% reduction in premature deaths from acute rheumatic fever and RHD among individuals aged less than 25 by the year 2025[7]. To achieve this goal, innovative approaches that are practical and cost-effective in low-resource settings are urgently needed.

Along with RHD, HIV is also highly prevalent in sub-Saharan Africa. HIV currently affects 0.5% of Ugandan children aged 0–14 years which corresponds to approximately 95,000 children[8]. The immune deficiency and dysfunction caused by HIV has been shown to impact susceptibility to other autoimmune diseases[9]. Thus, RHD and HIV, not only share a geographic overlap, but perhaps may also interact by altering the disease processes of each illness. A recent pilot echocardiographic screening study conducted in partnership between the Uganda Heart Institute and the Joint Clinical Research Center in Kampala, Uganda found a surprisingly low prevalence of latent RHD among HIV positive children. Screening of 488 HIV positive children revealed only 4 cases of latent RHD (2 borderline, 2 definite), for an overall prevalence of 0.82%[10]. This prevalence mirrors that seen in very-low risk populations (United States, high-income Australia[11,12]), where positive cases are thought to reflect the imperfect specificity of the echocardiographic criteria, not true disease. However, this data can only be considered hypothesis generating, as the sample-size was small, resulting in a 95% confidence interval (0.26–2.23%) that overlapped with the prevalence in the general Ugandan population[10].

It is important to understand if children living with HIV in RHD endemic regions have a different rate of RHD. Insight into potential disease modification between HIV and RHD could enhance the understanding of RHD pathogenesis as well as advance strategies for disease prevention. Hypotheses surrounding these findings include (1) children with HIV have better access to primary care, (2) children with HIV are protected from group A streptococcal infections through routine administration of cotrimoxazole prophylaxis, and (3) there is an RHD-protective immune modulation through the HIV infection. To answer these questions, a clinical site encompassing both a large HIV clinic with a robust patient population as well as a comprehensive cardiac center for treatment and follow up of children found to have RHD was necessary. Baylor Uganda and the Uganda Heart Institute both are located inside Mulago National Referral Hospital Complex in Kampala, Uganda, which

created an ideal research environment. Baylor Uganda serves as the national referral center for pediatric HIV care and treatment and as of June 2016 was treating 7,146 patients. Furthermore, the Uganda Heart Institute established a RHD registry in 2010 to ensure patients are given optimal and comprehensive clinical care within available resources including accurate diagnosis, routine follow-up, and invasive interventions where possible. As of 2015, over 800 patients have been enrolled and are being followed[13]. The primary aim of this study is to definitively determine the prevalence of RHD among HIV positive children in a large tertiary care clinic for HIV positive children in Uganda. The secondary aims were to determine if antibiotic use and immune system function impacted RHD prevalence in this population.

Materials and Methods

This is a prospective, cross-sectional study of HIV positive children (aged 5–15) receiving care at the Baylor College of Medicine Children's Foundation-Uganda (Baylor Uganda) HIV clinic located within Mulago National Referral Hospital Complex in Kampala, Uganda. The study was conducted between March 2017 and August 2017. Institutional review board approval was obtained from Children's National Health System, Baylor College of Medicine, Makerere University College of Health Sciences, and the Uganda National Council for Science and Technology.

Study Population

Baylor Uganda HIV clinic serves as a national referral center for pediatric HIV care and treatment. It provides HIV care and treatment services to HIV affected and infected children, adolescents and their families through a family centered approach. As of June 2016, there was in total 7,146 patients in treatment and of those, 3,287 children were between the ages of 5–15 years old. Specific clinic days are grouped by age, one group aged 0–10 years and the second group aged 11–17 years; for which study days were scheduled around. On recruitment days, all HIV positive children within the target age range were invited for study participation as they presented for routine outpatient follow-up.

Study Procedure

Enrolled children were assigned a study-specific ID number which was used on all written materials containing subject information as well as the subject identifier on the echocardiogram. A focused echocardiographic evaluation was performed by one of three pediatric cardiology fellows (I.H., J.N., E.N.). De-identified echocardiograms were then shared daily via a secure telemedicine connection with Children's National Health System in Washington, DC (LifeImage, Boston, MA), downloaded to a secure PACs system (Philips, Xcelera, Best, Holland), and interpreted remotely by board-certified cardiologists with expertise in RHD (A.B. and C.S.). Each ultrasound was given a diagnosis of definite RHD (A, B, C, or D), borderline RHD (A, B, or C), or normal according to the 2012 World Heart Federation guidelines for the echocardiographic diagnosis of RHD[14]. Results of echocardiograms were communicated with the child's primary physician at the Baylor Uganda HIV clinic, who communicated the results with the parent/guardian. Children found to have heart disease, either RHD or congenital/acquired heart disease, were linked to care at

the Uganda Heart Institute and those with RHD were invited for enrollment in the national RHD registry. The medical record was also reviewed to identify clinical information including: adherence rate to cotrimoxazole prophylaxis, adherence rate to antiretroviral therapy, and most recent laboratory values including CD4 count and viral load, when available.

Statistical Analysis

The intent of our analysis was to determine if there was a difference in prevalence of latent RHD between HIV positive children and the general pediatric population of Uganda. In total, as part of research and epidemiological studies[4–6], screening echocardiograms have been performed on 15,622 Ugandan children from three areas of the country (Kampala, Mbarara, Gulu). The pooled prevalence of latent RHD among these children is 2.97% (95% CI 2.70–3.24%). Prior pilot data in children with HIV suggested that the echocardiographic prevalence of RHD among HIV positive children in Uganda was 0.82% (95% CI 0.26–2.23%)[10]. Conservatively, we chose to double this prevalence to 1.6% and calculated a sample size of 988 children to provide 80% power to detect a difference in population prevalence, bracketing the 95% CI by 0.62 (0.98–2.2%), outside the 95% CI of the general population. RHD cases are reported as prevalence with 95% confidence intervals. Characteristics of the study population were described as median (IQR) and frequency (%) according to RHD status. Continuous variables were compared using the Mann-Whitney test and the Chi-Squared test or Fisher's exact test were used to compare categorical variables. All statistical tests are 2-sided with a significance level of $p<0.05$. All data were analyzed using MedCalc for Windows V.12.2 (MedCalc Software, Ostend, Belgium).

Results

In total, 993 screening echocardiograms were performed among children aged 5–15 years. Of the 993 children examined, 29 (2.9%) had abnormal echocardiograms. Of those 29 children, 15 were classified as having RHD with 2 classified as having definite and 13 classified as having borderline disease, resulting in an RHD prevalence rate of 15.1 cases per 1000 children (95% CI 0.88% - 2.54%). Of those with definite RHD, both cases were classified as WHF definite B (mitral regurgitation with at least 2 morphological mitral valve changes), and of the remaining 13 borderline cases, 2 were classified as WHF borderline A (>2 morphological mitral valve changes without pathological mitral regurgitation) and 11 were classified as WHF borderline B (isolated pathological mitral regurgitation with <2 morphological mitral valve changes). The majority of children with RHD had mitral valve disease (93%). The remaining 14 children with abnormal echocardiograms who did not have RHD were found to have either congenital heart disease or non-RHD acquired heart disease. No child with congenital heart disease was also diagnosed with RHD (Table 2).

The median age (IQR) of our cohort was 10 (7–12) years and 50.6% were female. Of the enrolled individuals, 71.7% lived within 25km of the Baylor Uganda HIV clinic (Table 1). Nearly all individuals were receiving both ART and cotrimoxazole prophylaxis at the time of the study. The most recent recorded CD4+ T-cell count and viral load was 1140 (IQR) 814.8–1508.5 cells/mm^3 and <20 (IQR) <20–100 copies/mL respectively. Specifically, RHD

positive children had a median CD4 count of 1090 (IQR) 720–1474 cells/mm^3 compared to 1142 (IQR) 817–1513 cells/m^3 in RHD negative children. 92.9% of children with RHD had a CD4 >500 cells/mm^3, and 91.8% patients without RHD had a CD4 level >500 cells/mm^3 at their last documented evaluation. With respect to viral load, RHD positive children had a median viral load of <20 (IQR) <20–484 copies/mL compared to <20 (IQR) <20–98 copies/mL in RHD negative children. 66.6% of patients with RHD had a viral load <20 copies/mL and 72.1% of patients without RHD had a viral load <20 copies/mL at their last recorded evaluation (Table 3).

Children found to have RHD were older than their RHD-negative peers 12 years vs 10 years; p=0.004; Table 1. In children with RHD, 40% lived greater than 25km from Baylor Uganda, compared to 28.9% in the non-RHD group. When separated, the prevalence of RHD among HIV-positive children from Kampala was 1.28% (95% CI 0.63% - 2.51%) compared to 2.1% (95% CI 0.89% - 4.89%) in those from outside Kampala. Otherwise there was no significant difference in gender, WHO HIV status, adherence to ART or cotrimoxazole, CD4 level, or viral load between the RHD and non-RHD individuals (Tables 2, 3). Additionally, there were no significant group differences in any of the measured echocardiographic parameters other than presence of mitral regurgitation (Table 2).

Discussion

This study confirms that children living with HIV have a lower prevalence of RHD than their HIV-negative peers. Compared to the overall pooled prevalence of latent RHD in Ugandan schoolchildren of 2.97% (95% CI 2.70–3.24%)[4–6], children from across Uganda living with HIV had an RHD prevalence of 1.5% (95% CI 0.88% - 2.54%).

RHD has strong environmental etiology, and prevalence differs based on geographical location, even within the same country. Previous RHD screening studies in Uganda have occurred both in the capital city, Kampala, and a more remote, resource-poor area of the North, Gulu District. As might be expected, the prevalence in of RHD among all school children in Kampala is less than that of Gulu (1.5% vs. 4%)[4,6]. Importantly, the Baylor HIV clinic provides HIV consultation and care for children from across the country; over 30% of children studied were from outside the capital. Though underpowered to provide sufficient confidence intervals for causality, comparing our data with that of previous pooled RHD prevalence data[4–6], the prevalence of RHD among HIV positive children was less than their HIV negative peers both in Kampala (1.28% vs. 1.5%) and outside of the capital (2.1% vs. 4%). This similarly aligns with Okello's 2012 study that demonstrated that the risk of acquiring RHD increases with every kilometer from the nearest health center[15].

While this study was not powered to determine the etiological basis for the difference, there are several potential hypotheses worth exploring. Children enrolled at the Baylor Uganda HIV clinic have close follow up for HIV management with clinic appointments every few months focusing on medication adherence, psychosocial concerns, routine blood work, and treatment of concurrent illnesses. Moreover, walk in visits are accepted as well, particularly for treatment of febrile illness or pharyngitis with a course of antibiotics such as azithromycin or amoxicillin which are maintained in the clinic pharmacy. Although specific

inquiries about access to healthcare or socioeconomic status were not performed, children enrolled in the Baylor Uganda HIV clinic undoubtedly have improved access to health care when compared similar children not enrolled in the clinic.

A second explanation for these findings could be related to immunomodulation from the HIV infection potentially altering the autoimmune pathogenesis thought to lead to RHD. Patients with HIV and a low CD4 cell count have reduced risk of autoimmune infection[9,16], which increases as CD4 counts recover[17]. Specifically, both RHD and HIV appear to be associated with altered levels of circulating natural autoantibody to oxidation-associated determinants and thus, that there may be significant overlap between these two clinical conditions. This alteration in the natural autoantibody response in individuals with HIV has been speculated to directly impact the pathogenesis of RHD[18]. However, our study population had well-controlled disease making this mechanism less likely.

Finally, near universal use of cotrimoxazole prophylaxis in children infected with HIV may further reduce the risk of RHD. Cotrimoxazole is a broad spectrum antibiotic covering a range of bacterial and fungal pathogens. Although controversial, recent studies have shown group A streptococcal (GAS) infection appears to be susceptible to cotrimoxazole [19]. In this study, nearly all patients were receiving and adherent to cotrimoxazole prophylaxis, suggesting the possibility that childhood protection from GAS infection could be a driver of the lower RHD rates seen in this population. Further study is needed to fully understand this contribution.

Our study has several limitations. First, this study was not designed to determine causality, and although our results provide powerful insight into the potential disease interaction between HIV and RHD, our ideas on why HIV positive children have lower rates of RHD are speculative. Second, we were unable to capture data on socioeconomic status, known to be a driver of increased RHD prevalence[7,15]. We also had limited data on the age of HIV diagnosis and on the timing of cotrimoxazole and ART prescription, as many patients came to the Baylor Uganda HIV clinic as transfers with limited records. Finally, the most recent CD4 and viral loads were utilized for the analysis, not accounting for a history of poorly controlled disease that could have altered risk over time.

In conclusion, we present the largest RHD screening study of HIV-infected children. Our data confirms that the prevalence of RHD among HIV-positive Ugandan children is lower than the reported prevalence in a comparable population. There appears to be modulation of the RHD disease process within this population, though the exact etiology of this modulation remains to be determined. Further studies are needed to explore these hypotheses more extensively in regions where both RHD and HIV are highly prevalent.

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Table 1 -

Demographic Data

	Overall n=993	RHD n=15 (1.5%)	No RHD n=978 (98.5%)	p-value
Demographic Data n=987*				
Age (years) (n=987)	10 (7–12)	12 (11–13)	10 (7–12)	0.004
Gender (n=984)				
Male	487 (49.4%)	11 (73.3%)	476 (49.1%)	
Female	497 (50.6%)	4 (26.7%)	493 (50.9%)	
WHO HIV Stage (n=982)				0.255
I/II	308 (31.4%)	2 (13.3%)	306 (31.2%)	0.16
III/IV	674 (68.6%)	13 (86.7%)	661 (68.4%)	
<25km from Baylor Uganda HIV Clinic (n=979)	702 (71.7%)	9 (60.0 %)	693 (71.1%)	0.502

* 6 subjects with missing demographic data (not available in EMR)

Table 2 -

Echocardiographic Data

	Overall n=993	RHD n=15 (1.5%)	No RHD n=978 (98.5%)	p-value
Echocardiographic Data n=993				
Fractional shortening (n=974)	36 (32.7–40)	34 (31.6–36.5)	36 (32.8–40)	0.053
Ejection fraction (n=984)	64 (60.7–68)	63.9 (61–67.7)	64 (60.7–68)	0.733
MV E (n=962) (RHD n=11)	97 (87–109.7)	90 (83.3–98)	97 (87–110)	0.155
MV A (n=959) (RHD n=11)	57 (49–66.3)	51 (47–60.5)	57 (49–66.3)	0.231
MV E/A (n=959) (RHD n=11)	1.7 (1.4–2)	1.65 (1.5–2.1)	1.7 (1.4–2)	0.903
Lateral Wall TDI E' (n=793) (RHD n=11)	17 (15–19)	16 (13–17.8)	17 (15–19)	0.265
MV E/E' (n=784) (RHD=10)	6 (5–7)	6 (5–7)	6 (5–7)	0.655
Mitral Regurgitation				<0.0001
None	850 (85.6%)	1 (6.7%)	849 (86.8%)	
Trivial	123 (12.4%)	5 (33.3%)	118 (12.0%	
Mild	17 (1.7%)	8 (53.3%)	9 (1.0%)	
Moderate	3 (0.3%)	1 (6.7%)	2 (0.2%)	
Aortic Regurgitation (n=987)	6 (0.6%)	1 (6.7%)	5 (0.5%)	0.171
Tricuspid Regurgitation (n=988) (RHD=14)	130 (13.1%)	1 (7.1%)	129 (13.2%)	0.785
Pericardial Effusion (n=975)	3 (0.3%)	0	3 (0.3%)	0.033
Non-RHD Cardiovascular Disease Identified (n=14)	14 (1.4%)	0	14 (1.4%)	
Mitral Valve Prolapse		0	7	
Dilated Cardiomyopathy		0	3	
Atrial Septal Defect		0	2	
Dilated Ascending Aorta		0	1	
Myxomatous Posterior Leaflet		0	1	

Table 3 -

Clinical Data

	Overall n=993	RHD n=15 (1.5%)	No RHD n=978 (98.5%)	p-value
Clinical Data n=987*				
Receiving ART (n=986)	983 (99.7%)	15 (100.0%)	968 (99.7%)	0.032
Adherence to ART >80%** (n=962)	878 (91.3%)	13 (87.7%)	865 (91.3%)	0.861
Receiving cotrimoxazole (n=984)	974 (99.0%)	14 (93.3%)	960 (99.9%)	0.367
Adherence to cotrimoxazole >80%** (n=844) (RHD n=13)	721 (84.1%)	11 (84.6%)	710 (84.1%)	0.755
Most recent CD4 (cells/mm3) (n=917) (RHD n=14)	1140 (814.8–1508.5)	1090.5 (720–1474)	1142 (816.8–1513)	0.558
Most recent viral load (copies/mL)*** (n=880) (RHD n=14)	0 (0–100)	0 (0–484)	0 (0–98)	0.672

* 6 subjects with missing demographic data (not available in EMR)

** Year average from most recent recorded clinic data

*** If viral load assay was either “not detected” or <20 copies/mL, reported as 0