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Prevalence of latent rheumatic heart disease among HIV-infected children in Kampala, Uganda

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Abstract

Rheumatic heart disease (RHD) remains highly prevalent in resource-constrained settings around the world, including countries with high rates of HIV/AIDS. Although both are immune-mediated diseases, it is unknown whether HIV modifies the risk or progression of RHD. We performed screening echocardiography to determine the prevalence of latent rheumatic heart disease in 488 HIV-infected children aged 5-18 in Kampala, Uganda. The overall prevalence of borderline/definite RHD was 0.82% (95% CI 0.26% to 2.23%) which is lower than the published prevalence rates of 1.5-4% among Ugandan children. There may be protective factors that decrease the risk of RHD in HIV-infected children.

Keywords

rheumatic heart disease; HIV/AIDS; echocardiogram; cotrimoxazole

Introduction

Rheumatic heart disease (RHD) is an endemic non-communicable disease that results from recurrent episodes of acute rheumatic fever (ARF), an auto-immune response to group A Streptococcus infection[1]. It remains a significant cause of morbidity and mortality worldwide, claiming more than 340,000 lives annually[2]. Now rare in developed nations, the incidence of ARF/RHD is more than 10-fold greater in resource-constrained countries[3].

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Secondary prevention of ARF with penicillin slows the progression of chronic RHD; yet patients in sub-Saharan African countries such as Uganda tend to present late in the course of disease with symptoms of advanced heart failure[4]. Few have access to palliative valve surgery. Screening asymptomatic children for latent RHD with echocardiography is therefore an attractive strategy to find cases at an earlier stage, though its clinical impact and cost-effectiveness are still debated[5,6].

Countries with the highest prevalence of RHD often have high rates of HIV/AIDS. Because of chronic immune activation and increased autoimmunity in patients with treated HIV[7,8], it is possible that concurrent HIV infection would modify the risk of ARF/RHD[9]. In this study, we used echocardiography to determine the prevalence of RHD in a cohort of HIV-infected children in Uganda compared to school-based screening studies conducted in the general population.

Methods

This is a cross sectional study of participants enrolled in two echocardiographic studies at the Joint Clinical Research Centre (JCRC) and the Uganda Heart Institute in Kampala, Uganda. The studies were approved by the Institutional Review Boards of University Hospitals Case Medical Center, Makerere University, and the Uganda National Council for Science and Technology.

For both studies, consecutive patients were recruited from the outpatient pediatric clinic. Children with advanced AIDS requiring hospitalization at the time of the study were excluded. The first study, conducted from June 2012 to January 2013, aimed to describe the prevalence of any cardiovascular abnormality on echocardiogram among HIV-infected children aged 1-18 years who had been on antiretroviral therapy (ART) for >6 months. These data were aggregated together with a screening study of children aged 5-20 years conducted in July and August 2013. The combined analyses were restricted to participants between the ages of 5-18 years. We collected clinical information by chart review. Mode of transmission could not be confirmed in most cases due to incomplete data; however, among 134 cases with available data, all were confirmed vertically transmitted or had a parent who was HIV+ suggesting vertical transmission. Data on cotrimoxazole use was also incomplete; but among 223 subjects with available data, 96% were prescribed cotrimoxazole prophylaxis.

All echocardiograms were performed by a cardiologist at the Uganda Heart Institute or a trained physician during established clinic visits at the JCRC. The echo protocol for RHD screening can be found in the online supplement (Supplemental Digital Content 1). Participants with an abnormal screening echocardiogram subsequently underwent a full clinical protocol at the JCRC or the Uganda Heart Institute. The final diagnosis of RHD was made based on this confirmatory scan according to 2012 World Heart Federation guidelines[5].

Characteristics of the study population are described as median (interquartile range) and frequency (%) according to RHD status. Continuous variables were compared using Mann

Whitney test, and Fischer's Exact tests were used to compare categorical variables. All statistical tests were two-sided with a significance level of $p<0.05$.

Results

In total, 490 screening echocardiograms were performed among children aged 5-18 years of age; two were excluded because of incomplete data. Characteristics of the study cohort are described by RHD status in Table 1. Overall, median age (IQR) was 10 (7—13) years and 52.5% were female. Median CD4+ T-cell count was 801.5 (510—1201) cells/mm^3, and 96.1% were on ART. Of the 488 subjects who were included in the analysis, four were found to have latent RHD based on WHF criteria, giving a prevalence of latent RHD of 0.82% (95% CI 0.26% to 2.23%). Two subjects had borderline disease and 2 subjects had definite disease.

There were no statistically significant differences in age, gender, CD4, or ART use between children with and without latent RHD (Table 1; all $p>0.1$). Two of the four children with RHD were female, and the median age (IQR) was 12.5 (11.75—14) years. Median CD4+ T-cell count (IQR) of the children with RHD was 385 (264—708) cells/mm^3, compared to 803 (518—1200) among children without RHD. Power to detect statistically significant differences in these characteristics was limited by the small number of patients with RHD.

Discussion

In this echocardiographic screening study, we describe a low prevalence of RHD among HIV-infected children [0.82% (95% CI 0.26% to 2.23%)] compared to previously published studies of Ugandan school children. The first large screening study[10], conducted in 2010, found a prevalence of 1.4% RHD (0.2% definite and 1.2% borderline) among 4,869 Kampala school children aged 5-16 years. A 2-year follow-up echocardiogram, confirmed a prevalence of at least 1.2% in this original Kampala cohort[11]. A more recent study in Gulu (Northern Uganda; a population with less access to healthcare)[12] described a higher prevalence of 4% (1.1% definite and 2.9% borderline) among 4,773 children aged 5-17 years. These studies used the same protocol for RHD screening that was used in our study. For all of these previously published studies, HIV status was unknown, but presumed to be very low.

Interestingly, the overall prevalence of definite and borderline RHD in our study is similar to recently published studies from low-risk populations in Australia[13] and New Zealand[14]. The Australian study compared 1053 low-risk children aged 5-15 years from an urban, mostly non-Indigenous population to 4153 high-risk Indigenous children from remote island villages. The prevalence of RHD was 0.5% in the low risk population versus 2.1% in the high risk population. The New Zealand study described a similarly low prevalence of 0.5% (95%CI 0.1-1.8%) RHD in a population of 396 healthy 10-12 year olds from a high socioeconomic urban setting where no cases of rheumatic fever had been reported for >10 years. The authors suggest that 0.5% may be the false-positive rate when using the current WHF criteria. Applying a similar false positive rate to our HIV-infected Ugandan population would mean that the true prevalence of RHD is even lower than estimated.

Given the lower prevalence of RHD among this HIV-positive population, we propose several possible factors that may decrease their risk of developing RHD. For one, perinatally HIV-infected children have a much greater engagement in the health-care system from an early age compared to most children in Uganda. The JCRC offers close follow-up for HIV management with clinic appointments every few months that focus on adherence, other health problems, routine blood work, and frequent exposure to antibiotics if a child has a fever or sore throat. This enhanced access to health care may help protect these children from ARF and potential progression to chronic RHD.

Another possible explanation for these findings is that immunosuppression from HIV could be protective; a dampened immune system could decrease the tendency for some autoimmune diseases to manifest when the CD4+ T-cell count is low[15,16]. Our study population, however, had well-controlled disease and high CD4+ T-cell counts, and are thus more likely to have heightened immune activation and inflammation. Since most children with HIV are prescribed ART even in resource-limited settings, it is likely not possible to conduct an adequately powered study of RHD prevalence among children with poorly controlled HIV. To date, there have been no reports of RHD presenting as an immune reconstitution inflammatory syndrome (IRIS), but other autoimmune IRIS syndromes have been described[7]. It remains unknown whether residual immune activation that persists despite effective ART might alter the natural course of RHD.

The risk of RHD may also be reduced by the pleiotropic effects of cotrimoxazole (trimethoprim/sulfamethoxazole) prophylaxis. Nearly all children with HIV infection in Uganda receive cotrimoxazole to protect against opportunistic infections and recurrent bacterial infections. It is a broad-spectrum antibiotic covering a range of bacterial and fungal pathogens, including some activity against malaria and Mycobacterium tuberculosis. Although conventional teaching is that group A Streptococcus is not susceptible to cotrimoxazole, a recent study in Australia found that S. pyogenes is susceptible to cotrimoxazole in vitro if cultured in media with low thymidine[17]. It is possible that cotrimoxazole may provide some protection against group A Streptococcus in vivo, but clinical studies to support this claim are still in progress.

Continued use of prophylactic cotrimoxazole once CD4+ T-cell counts recover decreases mortality in HIV-positive children and adults, especially in developing nations[18,19]. The ARROW trial, conducted in Zimbabwe and Uganda, found that children and adolescents who continued cotrimoxazole had less malaria, pneumonia, septicemia, diarrhea, and meningitis, when compared to those individuals who stopped cotrimoxazole after two years[18]. Children who continued cotrimoxazole also had higher hemoglobin, improved CD4+ T-cell count, and improved weight-for-age Z scores. Finally, cotrimoxazole may potentially decrease immune activation and inflammation by altering the gut microbiome and reducing microbial translocation[20]. These pleiotropic effects are cited as the rationale for an ongoing trial of cotrimoxazole to reduce mortality in high-risk HIV-uninfected children with malnutrition[20]. Whether cotrimoxazole might reduce the risk of acute rheumatic fever and chronic RHD in HIV-uninfected populations is an intriguing hypothesis that could be tested in endemic settings such as Uganda.

Although this is the first and largest RHD-screening study of HIV-infected children to date, our study did not include an HIV-uninfected control group. We were limited to comparing our findings with previously published studies that utilized different sampling methods; however, our study included many of the same co-investigators and shared the same echo screening protocol of these prior Ugandan studies. Our study was also limited by the number of children with HIV infection who were available to screen, resulting in a wider 95% confidence interval of our point estimate. Although we did not formally test for statistical differences in prevelance compared to other published Uganda studies for the reasons mentioned above, the strikingly lower estimate is nonetheless compelling and merits future study in larger sample sizes recruited across multiple institutions in Uganda or sub-Saharan Africa. Our study was limited by a paucity of sociodemographic or clinical information on all study participants. Because of the smaller sample size, we also had limited power to detect differences in these clinical and demographic factors between children with and without latent RHD. Finally, exclusion of hospitalized children may have introduced selection bias in our study, but hospitalization is uncommon among children with HIV on ART and thus unlikely to significantly affect our results.

In conclusion, the prevalence of latent RHD among HIV-positive children in Kampala was lower than the reported prevalence in a comparable school-aged population. Children in this study may be exposed to protective factors that decrease their risk of developing RHD, such as extensive engagement in the health-care system or use of cotrimoxazole prophylaxis. It remains unknown whether acquired HIV in adolescence or young adulthood might adversely affect the progression of pre-existing RHD due to chronic immune activation. Further epidemiologic and mechanistic studies are needed to explore this hypothesis in a region where both HIV and RHD are highly prevalent and morbid.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Characteristics of HIV-infected subjects with latent RHD by echocardiography compared to those without RHD.

	Overall n=488	Latent RHD n=4	No RHD n=484	P-value*
Age (years)	10 (7.0—13)	12.5 (11.8—14)	10 (7.0—13)	0.11
Sex				1.0
Male	232 (47.5%)	2 (50%)	230 (47.5%)	
Female	256 (52.5%)	2 (50%)	254 (52.5%)	
Current CD4 (cells/mm3)	801.5 (510—1201)	385 (264—708)	803 (518—1200)	0.18
ART use	469 (96.1%)	4 (100%)	465 (96.1%)	1.0

Data presented as median (Interquartile Range) or frequency (%).

* Latent RHD vs. No RHD