Echocardiography Screening for Rheumatic Heart Disease in Ugandan Schoolchildren

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Background—Historically, sub-Saharan Africa has had the highest prevalence rates of clinically detected rheumatic heart disease (RHD). Echocardiography-based screening improves detection of RHD in endemic regions. The newest screening guidelines (2006 World Health Organization/National Institutes of Health) have been tested across India and the Pacific Islands, but application in sub-Saharan Africa has, thus far, been limited to Mozambique. We used these guidelines to determine RHD prevalence in a large cohort of Ugandan school children, to identify risk factors for occult disease, and to assess the value of laboratory testing.

Methods and Results—Auscultation and portable echocardiography were used to screen randomly selected schoolchildren, 5 to 16 years of age, in Kampala, Uganda. Disease likelihood was defined as definite, probable, or possible in accordance with the 2006 National Institutes of Health/World Health Organization guidelines. Ninety-seven percent of eligible students received screening (4869 of 5006). Among them, 130 children (2.7%) had abnormal screening echocardiograms. Of those 130, secondary evaluation showed 72 (55.4%) with possible, probable, or definite RHD; 18 (13.8%) with congenital heart disease; and 40 (30.8%) with no disease. Echocardiography detected 3 times as many cases of RHD as auscultation: 72 (1.5%) versus 23 (0.5%; \( P < 0.001 \)). Children with RHD were older (10.1 versus 9.3 years; \( P < 0.001 \)). Most cases (98%) involved only the mitral valve. Lower socioeconomic groups had more RHD (2.7% versus 1.4%; \( P = 0.036 \)) and more advanced disease (64% versus 26%; \( P < 0.001 \)). Antistreptolysin O titers were elevated in children with definite RHD.

Conclusions—This is one of the largest single-country childhood RHD prevalence studies and the first to be conducted in sub-Saharan Africa. Our data support inclusion of echocardiography in screening protocols, even in the most resource-constrained settings, and identify lower socioeconomic groups as most vulnerable. Longitudinal follow-up of children with echocardiographically diagnosed subclinical RHD is needed. (Circulation. 2012;125:3127-3132.)

Key Words: cardiology • echocardiography • pediatrics • rheumatic heart disease

Rheumatic heart disease (RHD) is the world’s most common acquired cardiovascular disease. It affects >15 million people, leaving hundreds of thousands with debilitating heart disease and 233 000 people dead each year. Historically, RHD disproportionately affects children living in poor, unsanitary, and overcrowded conditions. Practically eradicated in wealthy countries, RHD remains endemic in Asia, the Pacific Islands, and Africa—home to the largest number of victims. In sub-Saharan Africa, the hardest-hit area, >1 million children suffer from RHD; few receive the medical or surgical care needed to survive and lead normal lives.

Editorial see p 3060
Clinical Perspective on p 3132

If RHD is detected early, monthly penicillin injections (secondary prevention) are a cost-effective and clinically effective means of preventing more advanced cardiac disease. Recently, screening protocols that include primary echocardiography have been shown to have a higher sensitivity for the detection of subclinical RHD, with prevalence rates up to 10 times higher than clinical examination alone.

In recent studies using the consensus World Health Organization/National Institutes of Health (WHO/NIH) guidelines, echocardiographic screening has shown a high prevalence of subclinical RHD in India and the Pacific Islands. Although historical data identify sub-Saharan Africa as the area with the greatest prevalence of clinically detectable disease, the search for subclinical disease in this region has, thus far, been limited to Mozambique.

In the largest single-population study in Africa, we used clinical examination and echocardiography to screen almost 5000 Ugandan schoolchildren. We compared the yield of echocardiography screening and auscultation, evaluated the prevalence of RHD by sociodemographic criteria, and assessed the usefulness of laboratory data.
Table 1. Echocardiographic Diagnosis of Rheumatic Heart Disease According to the 2006 World Health Organization/National Institutes of Health Joint Criteria*14

<table>
<thead>
<tr>
<th>Classification</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>Definite</td>
<td>Has cardiac murmur* AND significant mitral regurgitation and/or significant aortic regurgitation AND a thickened mitral valve and/or elbow deformity of the anterior mitral leaflet</td>
</tr>
<tr>
<td>Probable</td>
<td>Comes from a population in which RHD is endemic AND has cardiac murmur* AND either significant mitral regurgitation and/or aortic regurgitation OR thickened mitral valve and/or elbow deformity of the anterior mitral leaflet</td>
</tr>
<tr>
<td>Possible</td>
<td>Comes from a population in which RHD in endemic, has no cardiac murmur, AND has thickened mitral valve and/or elbow deformity of mitral valve and/or significant mitral and/or aortic regurgitation</td>
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RHD indicates rheumatic heart disease.

*Consistent with any combination of mitral regurgitation or aortic regurgitation.

Methods

Setting and Survey

A cross-sectional population-based study was conducted in Ugandan primary schoolchildren between August and November 2010. Approval was obtained from the institutional review boards of the Children’s National Medical Center (Washington, DC), Makerere University (Kampala, Uganda), and the Ugandan Ministries of Health and Education. Letters inviting participation went to 21 randomly selected schools. Schools were assigned to a socioeconomic cohort, taking into account the location, tuition, and estimated average household income. Ten schools responded, and 6 were randomly selected schools. Schools were assigned to a socioeconomic cohort, taking into account the location, tuition, and estimated average household income. Ten schools responded, and 6 were selected to obtain a socioeconomic balance. Permission was obtained from the headmaster for pupil participation. Letters went home with all students providing parental notification about the study and their opt-out right.

A physician, research nurse, and research coordinator visited each school. All schoolchildren 5 to 16 years of age were included. Absentees were noted and revisits were arranged to maximize coverage. For each child, we obtained demographic information, recorded height and weight, conducted a clinical cardiac examination, and performed a screening echocardiogram (General Electric Vivid I, Milwaukee, WI; Philips Optigo, Andover, MA). Any child with mitral or aortic valve thickening or regurgitation or evidence of congenital heart disease was identified as an abnormal screening echocardiogram and referred to Mulago Hospital for follow-up echocardiography (Philips CX50 or General Electric Vivid 7) and clinical evaluation (history, physical examination, and laboratory values). Images were recorded for later analysis by 3 independent physicians blinded to all clinical data. Children were classified as having no, possible, probable, or definite RHD according to the WHO/NIH joint criteria (Table 1). Complete blood count, erythrocyte sedimentation rate, C-reactive protein, and antistreptolysin O (ASO) titers were obtained at follow-up visits. In cases when a child did not present for follow-up, diagnosis was made by school screening echocardiogram and clinical evaluation.

Children designated as having definite or probable RHD were prescribed penicillin prophylaxis every 4 weeks. Clinicians had the option to begin antibiotic prophylaxis in possible RHD patients according to the local standard of care. All positive cases were enrolled in a program for medical surveillance every 6 months, including clinical and echocardiographic review, initiation of antibiotic prophylaxis for advancing lesions, and attempted placement for surgical intervention when necessary.

Clinical and Echocardiographic Definitions

Cardiac auscultation was performed with the patient in the upright and left lateral decubitus positions. Children in whom the presence of a heart murmur consistent with any combination of mitral regurgitation or aortic regurgitation was seen and in whom RHD was confirmed echocardiographically were classified as having clinically detected RHD. Echocardiographic criteria were taken directly from the 2006 WHO/NIH expert consensus statement14 (Table 1). Only left-sided valves were examined for features of RHD; mild tricuspid regurgitation and mild pulmonary regurgitation were frequently noted but not regarded as indicating RHD. Significant mitral regurgitation was defined as a regurgitant jet at least 2 cm away from the coaptation point of valve leaflets, seen in 2 planes, mosaic in quality (high velocity), and persistent throughout systole. Significant aortic regurgitation was defined as a regurgitant jet at least 1 cm away from the coaptation point of the valve leaflets, seen in 2 planes, and mosaic in quality (high velocity).
cases of possible, probable, and definite RHD would be detected by citywide clinical screening compared with 5455 from echocardiographic screening. If expanded to the entire Ugandan population (an estimated 18 million children 5–16 years of age), 266 400 children would be detected by echocardiography, whereas only 88 200 would be found by clinical examination alone.

Discussion

In 2004, the WHO recommended that echocardiography be used to diagnose “silent but significant rheumatic carditis.” Since then, there has been much debate on which echocardiography protocol does the best job of diagnosing subclinical patients. In 2006, a working group put together by the NIH and WHO developed consensus guidelines for the echocardiographic diagnosis of possible, probable, and definite RHD. Only recently have the results of large-scale screenings using these guidelines begun to emerge. Although tested in India and the Pacific Islands, no data using these criteria are available for sub-Saharan Africa, the region of the world long thought to have the greatest prevalence. Our study attempts to fill that gap. In this, one of the largest single-population childhood RHD prevalence studies to date, we confirm a much higher rate of possible, probable, and definite RHD identified by echocardiography than by clinical examination alone—a 400% increase. Our data also provide further evidence that to maximize case detection, screening programs should focus on lower socioeconomic groups and a slightly older age cohort. Finally, this study highlights the shortcomings of the WHO/NIH criteria and the difficulty with their practical application.

Table 2. Demographic Characteristics

<table>
<thead>
<tr>
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<th>RHD Positive</th>
<th>RHD Negative</th>
<th>P</th>
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<tr>
<td>Mean age, y</td>
<td>10.1 (9.67–10.62)</td>
<td>9.38 (9.31–9.45)</td>
<td>0.002</td>
</tr>
<tr>
<td>Mean BMI, kg/m²</td>
<td>16.51 (15.95–17.07)</td>
<td>16.53 (16.45–16.61)</td>
<td>0.42</td>
</tr>
<tr>
<td>Male, %</td>
<td>40</td>
<td>48</td>
<td>0.16</td>
</tr>
<tr>
<td>Boarding, %</td>
<td>17.5</td>
<td>17</td>
<td>0.88</td>
</tr>
</tbody>
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RHD indicates rheumatic heart disease; BMI, body mass index. Numerical data are shown as means (95% confidence intervals).

Table 3. Socioeconomic Characteristics

<table>
<thead>
<tr>
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<th>Low SES</th>
<th>Middle SES</th>
<th>High SES</th>
<th>P</th>
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<tbody>
<tr>
<td>Total students, n</td>
<td>501</td>
<td>2560</td>
<td>1808</td>
<td></td>
</tr>
<tr>
<td>RHD positive, n (%)</td>
<td>14 (2.79)</td>
<td>32 (1.25)</td>
<td>26 (1.44)</td>
<td>0.036*</td>
</tr>
<tr>
<td>Probable/definite, n (%)</td>
<td>9 (64)</td>
<td>5 (16)</td>
<td>11 (42)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

SES indicates socioeconomic status; RHD, rheumatic heart disease.
*P values compare children in the low SES tertile with children in the middle and high SES tertiles.
Historically, sub-Saharan Africa has had the greatest prevalence of clinically detected RHD. Before 2000, cross-sectional surveys were undertaken in Kenya, the former Congo, Ethiopia, and Sudan using primary auscultation followed by echocardiography in suspicious cases. Clinical detection rates were low in otherwise healthy schoolchildren, ranging from 2.4 to 10.2 per 1000. In the last decade, echocardiography has proven to be more sensitive for RHD detection. Only 1 reported study used echocardiography-based screening and included sub-Saharan Africa, and it was performed before the availability of any published echocardiography-based guidelines. Between 2001 and 2002, Marijon et al found a much higher burden of disease (30.4 cases per 1000) in 2170 otherwise healthy schoolchildren in Mozambique. Our data from Uganda showed a lower burden of disease, with 15 cases per 1000, although still much higher than studies using auscultation alone.

Initial laboratory results were obtained on all children who presented for a follow-up examination at Mulago Hospital. A significant elevation of ASO titer was found in children categorized as definite RHD. An elevated ASO titer generally reflects exposure to streptococcus in the past 6 months. Thus, these results indicate a tendency toward repeat streptococcal exposures in children with the most severe disease. We believe that currently available laboratory tests are not likely to be helpful adjuncts to screening protocols. The development of biomarkers with better specificity and sensitivity for detecting RHD is an important area of future research.

RHD is a disease of cumulative exposure; a single negative screening does not guarantee a healthy outcome. It is also not practical, given limited resources and time, to screen every school-aged child annually. We show that children in schools with lower average socioeconomic representation were 200% more likely to have any category of RHD and 25% more likely to have possible or definite RHD. The ideal screening age that would optimize detection of children who will ultimately develop clinically significant RHD but are still in the subclinical phase is unclear. We speculate that the prime detection age of subclinical RHD is likely ~10 years as indicated by our findings. Beginning at 10 years of age, children were significantly more likely to have any category of RHD. The WHO/NIH criteria were developed with the goal of standardizing RHD detection by echocardiography in a high-risk population. They were intended for use in otherwise healthy subjects with no history of acute rheumatic fever. In an attempt to balance sensitivity (high disease catchments) and specificity (avoiding overdiagnosis), they included both clinical examination and echocardiographic data. They acknowledged the ambiguity of subclinical disease and attempted to account for it by offering 3 categories of disease: definite, probable, and possible.

After applying these guidelines, we believe that clinical examination is not a necessary component of echocardiographic screening protocols and may actually weaken them when used to classify disease. Clinical examination did not add any information that was not readily evident by echocardiography in any of the children in our cohort. Auscultation is, by nature, subjective. When scaling up screening protocols for country-wide RHD detection, it adds inevitable variability and inconsistency. One of the weaknesses of the 2006 WHO/NIH guidelines is that 2 patients who appear identical on echocardiograms can receive different diagnostic categories based solely on the presence (probable or definite) or absence (possible) of a murmur consistent with mitral or aortic regurgitation.

In addition, although the WHO/NIH joint guidelines proved helpful in the overall disease classification and epidemiology of a population, we found some difficulty in consistently applying them clinically for the diagnosis and treatment of the individual patient. Prescription of secondary prophylaxis for patients who are found to have definite and probable RHD is obvious. These children have traditional, clinically detectable RHD, and studies have shown the protective effect of penicillin in preventing advanced valvular disease. So how do we treat patients who fall into the “possible RHD” category? The guidelines leave this decision to the discretion of the treating physician. Under the WHO/NIH approach, a patient with echocardiographic findings of RHD in the absence of clinical examination findings can reach only the category of possible RHD. This is true even if a patient has both morphological valve changes and significant valvular regurgitation. Our cohort included 4 such patients. They were prescribed secondary prophylaxis. Children with isolated significant mitral regurgitation without morphological valve abnormalities were not given secondary prophylaxis. Thus, the WHO/NIH “possible” designation is imprecise, failing to capture different treatment courses within that diagnostic group.

This difficulty stems from the continued uncertainty of the significance of subclinical carditis. Certainly, echocardiographic detection of morphologically abnormal valves or...
significant valvular regurgitation does not guarantee later progression to advanced valvular disease, nor has the clinical effectiveness or cost-effectiveness of secondary prophylaxis in this population been studied. Absent evidence-based treatment protocols for subclinical disease, however, the correct treatment course for these children remains unclear. Risks on both sides force clinicians to exercise caution when labeling children with RHD. Overdiagnosis carries the cost of potential lifelong antibiotic prophylaxis, the discomfort of injections, and the social stigma of chronic disease. Underdiagnosis, or even delayed diagnosis, diminishes the ability to detect clinically silent disease, to provide secondary prophylaxis, and to prevent more advanced disease. This ultimately decreases the value of RHD screening.

Studying the natural history of children diagnosed with subclinical RHD holds the most promise. These children presumably have the most to gain from early detection and secondary prophylaxis, but there are currently few data to support this assumption. In a very small Chilean study, 10 children with known acute rheumatic fever and the absence of auscultatory findings were found by echocardiography to have subclinical valvular changes. Six of these children were followed up prospectively for 5 years, and 3 continued to have valvular changes.22 More recently, follow-up data from a cohort of 100 echocardiographically diagnosed Indian schoolchildren with subclinical disease showed that at an average of 15 months from the time of diagnosis, 68% showed no progression of disease, 4% showed worsening of disease, and 28% showed regression of disease.15 No data on the effectiveness of secondary prophylaxis in this population have been reported. While more data are being collected, we emphasize that every child with suspicious findings should continue to have both clinical and imaging follow-up to monitor for disease progression.

In February 2012, the World Heart Federation published the first evidence-based criteria for echocardiographic detection of RHD. These guidelines resolve many of our concerns. They remove clinical examination from the diagnosis. They divide disease into definite and borderline and provide subcategories within each for different combinations of disease (isolated valvular regurgitation, isolated morphological change, etc.). Large-scale screening and follow-up studies using these new guidelines in the developing world will be very important to develop more precise screening protocols and treatment recommendations.

Currently, secondary prophylaxis is the best available weapon in the fight against RHD. Despite the limitations of the WHO 2006 guidelines, they are the most comprehensive that add echocardiography to clinical assessment. The inclusion of echocardiography without the exclusion of physician examination is an expected step in the evolution of RHD screening guidelines, especially in the developing world where the cost of echocardiography remains a potential obstacle to widespread screening. The advent of portable echocardiography makes it feasible to conduct screening outreach programs that identify disease at an early stage. Ongoing trends in miniaturization and portability may provide cost savings, but comparable screening accuracy is not guaranteed. More formal longitudinal comparative economic analyses are needed that would include the costs of a large-scale screening program, follow-up evaluations, increased use of penicillin, and savings from decreased burden of RHD. We anticipate, even with these added variables, that echocardiographic screening will prove to be a valuable investment in public health, even in the most resource-constrained communities.

Our data add to the growing body of support for widespread echocardiographic screening in the developing world. They show that prevalence rates of subclinical disease in sub-Saharan Africa are high, on par with those in other developing nations.15 Most important, our data inform choices about diagnosis, age, and socioeconomic status that should influence the design of future screening programs. As echocardiographic screening protocols continue to develop, we stress the need for validated definitions of echocardiography-diagnosed subclinical RHD. This will take time and can be accomplished only by well-constructed longitudinal follow-up studies. The next phase of this project includes a longitudinal component and should produce publishable results.

Conclusions

The 2006 WHO/NIH joint criteria showed RHD prevalence in Kampala, Uganda, that was comparable to the rate recently found in India (2%).15 Targeting screening efforts at 10-year-old children in lower socioeconomic cohorts may maximize subclinical detection. In light of the high prevalence of subclinical RHD in the developing world, including sub-Saharan Africa, international efforts should make long-term follow-up of subclinical rheumatic carditis a top priority in the fight against noncommunicable disease and medical equity in these regions.

Disclosures

None.

References


