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Are minor echocardiographic changes associated with an increased risk of acute rheumatic fever or progression to rheumatic heart disease?

Marc Rémond [a,*,1], David Atkinson [b,1], Andrew White [c,1], Alex Brown [d,1], Jonathan Carapetis [e,1], Bo Remenyi [f,1], Kathryn Roberts [f,1], Graeme Maguire [g,1]

[a] James Cook University, Cairns, QLD, Australia
[b] Rural Clinical School of Western Australia, The University of Western Australia, Broome, WA, Australia
[c] James Cook University, Townsville, QLD, Australia
[d] South Australian Health and Medical Research Institute, Adelaide, SA, Australia
[e] Telethon Kids Institute, University of Western Australia, Perth, WA, Australia
[f] Menzies School of Health Research, Darwin, NT, Australia
[g] Baker IDI Heart and Diabetes Institute, Alice Springs, NT, Australia

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ABSTRACT

Background: The World Heart Federation criteria for the echocardiographic diagnosis of rheumatic heart disease (RHD) include a category "Borderline" RHD which may represent the earliest evidence of RHD. We aimed to determine the significance of minor heart valve abnormalities, including Borderline RHD, in predicting the future risk of acute rheumatic fever (ARF) or RHD.

Methods: A prospective cohort study of Aboriginal and Torres Strait Islander children aged 8 to 18 years was conducted. Cases comprised children with Borderline RHD or other minor non-specific valvular abnormalities (NSVAs) detected on prior echocardiography. Controls were children with a prior normal echocardiogram. Participants underwent a follow-up echocardiogram 2.5 to 5 years later to assess for progression of valvular changes and development of Definite RHD. Interval diagnoses of ARF were ascertained.

Results: There were 442 participants. Cases with Borderline RHD were at significantly greater risk of ARF (incidence rate ratio 8.8, 95% CI 1.4–53.8) and any echocardiographic progression of valve lesions (relative risk 8.19, 95% CI 2.43–27.53) than their Matched Controls. Cases with Borderline RHD were at increased risk of progression to Definite RHD (1 in 6 progressed) as were Cases with NSVAs (1 in 10 progressed).

Conclusions: Children with Borderline RHD had an increased risk of ARF, progression of valvular lesions, and development of Definite RHD. These findings provide support for considering secondary antibiotic prophylaxis or ongoing surveillance echocardiography in high-risk children with Borderline RHD.

1. Introduction

Prior to the introduction of echocardiography, diagnosis of rheumatic heart disease (RHD) was primarily based on auscultation. However, it has been shown that auscultation alone is neither sensitive [1] nor specific [2,3]. Increased availability of portable high-quality echocardiography to assess heart valve morphology and function has resulted in significant debate regarding the echocardiographic diagnosis of RHD. This debate has intensified owing to the publication of a number of RHD echocardiographic screening studies that have utilized differing diagnostic criteria [1,2,4,5]. To address this issue, in 2012 the World Heart Federation (WHF) published echocardiographic criteria for the diagnosis of RHD in the absence of a history of acute rheumatic fever (ARF) [6]. These WHF criteria include a category of "Borderline" RHD that encompasses minor heart valve abnormalities of uncertain clinical significance.

The importance of such minor abnormalities in a setting of high RHD risk was highlighted by a recent Australian RHD echocardiographic screening study (gECHO (getting Every Child's Heart Okay)) [7]. Of 3946 high-risk Aboriginal and/or Torres Strait Islander children, 0.9% met the WHF criteria for Definite RHD while 1.7% met criteria for Borderline RHD. Furthermore, mitral regurgitation (MR) was detected in 22.1%, aortic regurgitation (AR) in 4.4%, morphological abnormalities of the mitral valve (MV) in 2.9%, and abnormalities of the aortic valve (AV) in 0.9%.

The clinical significance of a diagnosis of Borderline RHD or other non-diagnostic valvular abnormalities in individuals without a history of ARF remains unclear and has been identified as a priority for investigation [6,8]. If these abnormalities represent the earliest changes of RHD then offering such individuals regular secondary prophylaxis may

* Corresponding author.
E-mail address: marc.remond@my.jcu.edu.au (M. Rémond).
[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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prevent disease progression. In contrast, if they are simply a variant of normal echocardiographic findings then unwarranted treatment should be avoided.

The Rheumatic Fever Follow-Up Study (RhFFUS) aimed to clarify the significance of minor echocardiographic changes by determining if they were associated with an increased risk of ARF or progressive heart damage consistent with the development of Definite RHD.

2. Methods

The methodology of the RhFFUS study has been described previously [9]. Briefly, RhFFUS was a prospective cohort study of Aboriginal and/or Torres Strait Islander children aged 8 to 18 years residing in 32 remote Australian communities. Participants comprised a subset of children who had received an echocardiogram during the earlier gECHO study between September 2008 and November 2011 [7]. They were enrolled in RhFFUS between 2.5 and 5 years after their baseline gECHO echocardiogram.

Cases were children with non-specific changes of the MV or AV detected during gECHO. Cases were subdivided into two categories: those with Borderline RHD on the WHF criteria and those with minor non-specific valvular abnormalities (NSVAs) not meeting the Borderline RHD definition (see Box 1). Criteria for Cases were more sensitive than the WHF criteria for Borderline RHD as there remains uncertainty regarding the interpretation and significance of minor echocardiographic abnormalities. Controls (two per Case) were selected who were age, gender, community and ethnicity-matched to Cases and had a prior normal gECHO echocardiogram.

2.1. ARF outcome

For each participant, interval diagnoses of ARF between their baseline gECHO and subsequent RhFFUS echocardiograms were assessed from jurisdictional ARF/RHD notification databases. Participants with an episode of ARF before gECHO were excluded.

The use of secondary antibiotic prophylaxis was a potential confounder of ARF risk. Data relating to dates of injections of long-acting benzathine penicillin (LAB) for participants prescribed prophylaxis were obtained from jurisdictional ARF/RHD databases. Based on timing of these injections, and on the assumption that a single dose provides 28 days of protection against Group A streptococcal (GAS) infection and possible ARF, we calculated the "days-at-risk" of ARF for each participant during the period between their baseline gECHO and subsequent RhFFUS echocardiograms.

Box 1
Criteria used to classify participants recruited to RhFFUS. *Criteria for morphological features of RHD of MV and AV, and pathological AR and MR as described by WHF criteria [6].

CASES

Echocardiogram from gECHO that did not fulfill WHF criteria for Definite RHD [6] but which met one of the following:

1. ***Borderline RHD under WHF criteria*** [6]
   - A. At least two morphological features of RHD of the MV* without pathological mitral regurgitation* (MR) or mitral stenosis; or
   - B. Pathological MR with no or one morphological feature of RHD of the MV; or
   - C. Pathological aortic regurgitation* (AR) with no or one morphological feature of RHD of the AV*.

2. ***Non-specific valvular abnormalities (NSVAs)***
   - One morphological feature of RHD of the MV and/or one or more morphological feature of RHD of the AV without pathological MR or AR; or
   - Multiple MR jets and/or multiple AR jets (in at least two views) that do not fulfill WHF criteria for pathological MR or AR; or
   - MR ≥ 2 cm or AR ≥ 1 cm (that does not fulfill WHF criteria for pathological regurgitation) with no morphological features of RHD of the MV or AV.

CONTROLS

Normal screening echocardiogram from gECHO defined as:

- No morphological features of RHD of the AV or MV; and
- No MR ≥ 1 cm; and
- No AR; and
- No other acquired or congenital valvular heart disease.

2.2. Progression of valve lesions outcome

Progression of valvular abnormalities was assessed prospectively using transthoracic echocardiography and standardized operating and reporting procedures [9]. A Vivid *i*/*e* portable cardiac ultrasound machine (GE Healthcare, Freiburg, Germany) was used with a standardized machine setup [7,9]. All echocardiograms were performed by accredited echocardiographers who were blinded to participant status as Case or Control.

Progression of valve lesions was determined by a specialist pediatric cardiologist (BR). For each participant, baseline gECHO and subsequent RhFFUS echocardiograms were read individually (and categorized as Normal, NSVA, Borderline RHD [6] or Definite RHD [6]) and then compared to assess for valvular changes. The reader was blinded to the initial gECHO report for the baseline echocardiogram and to the status of participants as Cases or Controls. Reporting was based on a standardized reporting template [9].

"Progression of any valve lesion" was defined as the echocardiographically significant:

- development of any significant morphological or functional abnormality [6] in a Control; or
- development of a new morphological or functional abnormality [6] in a Case; or
- progression of severity of a functional valve lesion (regurgitation/stenosis) based on standard severity criteria [10–12] (i.e. mild to moderate, or moderate to severe).

An additional outcome measure was a diagnosis of Definite RHD [6].

Inter-observer reliability could be assessed as each participant's baseline echocardiogram was read twice (initially during gECHO and subsequently during RhFFUS).

2.3. Sample size calculations

Sample size estimations were based on projected rates of ARF based on the annual incidence of ARF in people with known RHD (2.5%) and the background annual incidence of ARF in 5 to 14 year old Aboriginal and Torres Strait Islander children in the NT (0.27%) (personal communication Northern Territory ARF/RHD register) over a five year period. Based on an assumed alpha of 0.05 and beta of 0.1 (power of 90%) detecting a difference of one or more episodes of ARF in 12.5% of Cases and 1.35% of Controls over five years of follow-up, and using a ratio of Cases to Controls of 1:2, would require a sample size of 83 Cases and 165 Controls or a total number of 248 reviews.

There were no clear data to inform the powering of progression of non-specific echocardiographic changes. Nonetheless, if it is assumed that at most 5% of Controls will develop morphological and functional valvular changes on echocardiography compared with 20% of those with preexisting non-specific changes then it would require the follow-up of 77 Cases and 154 Controls to detect such a difference with the tolerances above.

2.4. Statistical analysis

Statistical analysis was performed using Stata™ version 12.1 (StataCorp, Texas, USA) and SPSS version 20 (IBM Corp., Armonk, NY). Efficacy of matching of Cases and Controls was determined using χ^2 analysis for categorical measures and the Mann–Whitney U tests for non-parametric numerical measures. Bivariate analysis of outcome measures was undertaken comparing all Cases to all Controls, Borderline RHD Cases to their Matched Controls, and NSVA Cases to their Matched Controls. A p-value less than 0.05 was taken to indicate statistical significance. All tests were two-sided.

ARF incidence rates (IRs) were calculated both for "total time" between baseline gECHO and follow-up RhFFUS echocardiograms and for the "days-at-risk" between these dates. Incidence rate ratios (IRRs) were calculated for matched groups and an IRR with a 95% confidence interval (CI) not including one was taken to be statistically significant.

Risk of progression of valve lesions, and progression to Definite RHD, was calculated for matched groups. Absolute risk difference and relative risk (RR) between groups were determined with 95% CIs. Where the 95% CI of a RR did not include one, statistical significance was inferred.

Logistic regression models were developed to identify independent factors associated with progression of valve lesions and progression to Definite RHD. These models incorporated all factors associated with each outcome on bivariate analysis with a p-value <0.1. These factors comprised: age, gender, days between echocardiograms, receiving secondary antibiotic prophylaxis, and status as Borderline RHD of the MV (Borderline RHD category A or B) [6] or Borderline RHD of the AV (Borderline RHD category C) [6] or NSVA.

Inter-rater reliability was assessed using the linearly weighted Kappa statistic.

2.5. Ethics

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by Human Research Ethics Committees in all jurisdictions where recruitment was undertaken [9]. Written informed consent was obtained from all participants or their guardians.