Title

Prevalence and follow-up of subclinical rheumatic heart disease amongst asymptomatic school children in a north-western district of India based on the World Heart Federation echocardiographic criteria

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Abstract

Background

Past active surveillance have reported prevalence of subclinical RHD amongst school children which are not comparable because of major differences in screening methods. The present study is based on the WHF criteria to assess the prevalence of subclinical carditis due to RHD and elucidate evolution of the disease when these children were placed on appropriate antibiotic prophylaxis and regular follow-up. This is the first large active surveillance study which has been conducted in a single district of India after the publication of WHF criteria and is reporting short-medium term follow-up data.

Methods

For active surveillance of RHD among urban and rural school children of Bikaner, a random inclusion strategy was adopted. The diagnostic labelling based on the echocardiographic criteria proposed by World Heart Federation was done by a group of experienced cardiologists. The follow up of the patients recruited in to the study was done to ascertain the early evolution of the disease in the presence of appropriate antibiotic prophylaxis.

Results

A high prevalence of subclinical RHD was noted in the study population. Pathological mitral and/or aortic valves regurgitation was the commonest lesion and significant proportion of cases improved on regular antibiotic prophylaxis. There was no case of fixity of leaflets/ stenosis.

Conclusion

The prevalence of subclinical RHD and these cases are reversible if appropriate antibiotic prophylaxis is instituted at an early stage.

Background

Acute rheumatic fever (ARF) with its most dreaded sequel, rheumatic heart disease (RHD) is truly an enigmatic entity. Its epidemiology continues to baffle us despite years of research.

The global burden of disease (GBD) study attempted epidemiological data modeling to arrive at figures of mortality and prevalence for India.This study estimated a decline of 18% (15.5 to 12.7 per 100,000) for ARF/RHD mortality during 1990-2015.(1,2) Thus, only a relatively small reduction in mortality in ARF/RHD has occurred over this period in India.

The diagnostic criteria (Jones' criteria) for ARF/RHD were not originally intended to be used for active epidemiological surveillance.(3) In the year 2002, the World Health Organization (WHO) recommended the continuation of the practice of active epidemiological surveillance of school children based upon the signs and symptoms included in the recommended diagnostic criteria for ARF/RHD. Accordingly, a second dataset has emanated from active epidemiological surveillance (school surveys) of ARF/RHD in many countries around the world.(4-9)

In the period from 1960-1990, active surveillance studies were based on clinical detection of ARF/RHD in asymptomatic school children using the Jones criteria.(10-12) The active surveillance studies conducted during 1990-2010 used echocardiography to confirm the diagnosis of cases detected by clinical screening. They reported a much lower prevalence of ARF/RHD ranging from 1.3 to 6.4 per 1000 compared to the 1960-1990 era.(7,13-15) From 2000 to 2010, another set of studies were conducted under the aegis of the Indian Council of Medical Research(ICMR) in the Jai Vigyan mission mode project and reported prevalences of ARF/RHD ranging from 0.1 to 1.2 per 1000.(16) Use of echocardiography as a confirmation tool had ensured effective weeding out of false positives cases of congenital heart disease and mitral valve prolapse etiology from the results and hence an even lower reported prevalence was seen

From 2010 onwards, echocardiography has been used as a universal screening tool to estimate the prevalence of RHD amongst asymptomatic school children in India and elsewhere. These studies have reported a very high prevalence of RHD especially subclinical RHD in the asymptomatic school children.(17,18,19)Based upon echocardiography studies conducted during last two decades, it is now clear that the carditis of ARF/RHD often begins insidiously and is subclinical in early stages. These studies have been the basis for two major developments:

(a) Inclusion of subclinical carditis as one of the major criteria in the latest update of the Jones criteria for the diagnosis of ARF/RHD.(20)

(b) Publication of the first set of echocardiographic criteria for the diagnosis of RHD by the World Heart Federation (WHF) in 2012 based on expert consensus.(21)

The present study is being conducted under the aegis of the Indian Council of Medical Research (ICMR) in the Bikaner district of India.The aim of this study is to establish the prevalence of subclinical RHD amongst asymptomatic school children based on the previously mentioned echocardiographic criteria (21) and also to assess the evolution of subclinical RHD when these cases are placed on appropriate antibiotic prophylaxis.

Although there has been one large study which carried out echocardiographic surveillance of approximately fifteen thousand school children, however, the study started enrolling the children before the publication of the WHF criteria (in 2008) and was carried out in multiple centers spread across several, relatively economically better off states of India.(19)

This is the first large study which started recruiting the children after the publication of the WHF criteria and has been conducted in a single district of a relatively backward state of India. Moreover, it is the first ever study which is reporting the follow-up of subclinical RHD cases after they been placed on appropriate antibiotic prophylaxis.

We hypothesized that the follow-up of subclinical cases would enable us to identify the reversibility point of the disease which would probably be before the onset of the fixity of mitral valve leaflets which is traditionally considered early and specific marker of RHD.

Material & Methods

This cross sectional study was conducted in the Bikaner district of Rajasthan which is situated in the north -western part of India. Equal number of government and private schools were randomly selected from the rural and urban areas of the district. Three thousand children in the sixth to tenth standard classes corresponding to age-group of 10-15 years were randomly enrolled in the study after obtaining written, informed consent of the principal of the school and the parents/ guardians of the children. The study was conducted from November, 2015 to December,2018 after being approved by the ethics committee of Sardar Patel Medical College, Bikaner.
The sample size of three thousand was based on the total population of the district obtained from the population census. The randomization was done at three stages:

1) Random selection of equal number of schools from rural and urban areas of the district
2) Random selection of equal number of government run and private schools in both rural and urban areas
3) Random selection of equal number of children from five clusters aged 10-11 yrs, 11-12 yrs, 12-13 yrs.13-14 yrs. and 14-15 yrs
This multi-step randomization ensured equal representation of children from urban and rural areas as well as from poor and affluent backgrounds since children from private schools usually belong to a relatively affluent background. A pre-determined questionnaire was given to all children to assess their socioeconomic and demographic backgrounds.
All children were clinically examined by a cardiologist at the cardiology department of Prince Bijay Singh Memorial(PBM) hospital affiliated to Sardar Patel Medical College, Bikaner. A two dimensional trans-thoracic echocardiogram (2DTTE) was performed in all children using a Philips iE 33 ultrasound equipment (Philips Electronics India Ltd. Model no. iE33x MATRIX, part no. 8500-0082, SR no. B06B1).
The echocardiographic criteria proposed by the WHF for individuals aged ≤20years (21)were used for the diagnosis of ‘definite’ and ‘borderline’ RHD. as summarized below:
Definite RHD (either A, B, C, or D):
(A) Pathological mitral regurgitation (MR) which is characterized by the four criteria: 1.seen in two views, 2.in at least one view, jet length ≥2 cm,3.velocity ≥3 m/s for one complete envelope, 4.pan-systolic jet in at least one envelope And at least two morphological features of RHD of mitral valve(MV) which include anterior mitral valve leaflet thickening ≥3 mm.,chordal thickening, restricted leaflet motion, excessive leaflet tip motion during systole.
(B)Mitral stenosis(MS) mean gradient ≥4 mmHg after excluding congenital causes.
(C) Pathological aortic regurgitation(AR) which is characterized by the four criteria:1.seen in two views,2.in at least one view, jet length ≥1 cm,3.velocity ≥3 m/s in early diastole, pan-diastolic jet in at least one envelope and at least two morphological features of RHD of the aortic valve(AV) which include irregular or focal thickening, coaptation defect, restricted leaflet motion, prolapse.
(D).Borderline disease of both the AV and MV.
Borderline RHD (either A, B, or C):

(A) At least two morphological features of RHD of the MV without pathological MR or MS
(B) Pathological MR
(C) Pathological AR

The machine settings for color Doppler and pulsed wave Doppler were meticulously set as per the guidelines published by the WHF.(21)

A child was classified as having subclinical RHD if the diagnostic criteria of RHD (either borderline or definite) by echocardiography were present but were not detected clinically by the cardiologist during current or previous examination

All images/ videos were digitally preserved. All statistical analysis were done using epi-info software.

An informed, written consent was obtained from the parents/guardians of children diagnosed with RHD before starting antibiotic prophylaxis. A monthly injection of benzathine penicillin was begun if the child had no previous history of allergy to penicillin. Those who did not consent for injectable penicillin were placed on daily oral penicillin. In case of penicillin allergy, daily oral erythromycin. was given as an alternative. All children diagnosed with RHD, irrespective of their status of antibiotic prophylaxis were placed on annual follow-up wherein a repeat echocardiogram and clinical examination were performed annually. We report the results of the two-year follow-up.

Results

A total of 115 children out of 3000 screened were diagnosed with RHD as per the WHF criteria described above. This corresponds to an estimated prevalence of 38.3 cases with ARF/ RHD etiology per 1000 children.(Table I) Of 115 cases, 88 were diagnosed as 'definite RHD' and 27 as 'borderline RHD'.

All children had subclinical carditis/RHD since none were positive clinically. The distribution of the study variables included are given in Table I.

Mitral regurgitation was the most common lesion (73%), followed by AR. Mitral stenosis was not detected in any child in our study.The highest prevalence was found in children belonging to low socioeconomic status and exposed to crowded areas at home or school.(Table II)

Parents of more than half (72 out of 115) of children with evidence of subclinical RHD consented for antibiotic prophylaxis and agreed to bring their child at the time of planned follow-up. The reasons for refusal to consent for participation were - fear of side effects of penicillin and beliefs that prophylaxis is unnecessary & potentially harmful since the child has no symptoms.

A total of 15 subjects developed mild reaction to penicillin or became intolerant to erythromycin. Prophylaxis was withdrawn for such cases as per the accepted ethics policy. Ultimately, 57 children out of the 115 children were placed on regular antibiotic prophylaxis and follow-up. Out of these 57 children, 14 subjects were on injection penicillin, 37 were on oral penicillin and 6 were on oral erythromycin prophylaxis at the end of two years' follow-up from the start of the study.

Since the enrollment process for the study spanned over 18 months, the duration of antibiotic prophylaxis was six months of 28 children, one year for 10 children and two years for 06 children at the time of two-year follow-up from the date when we started study. Twelve out of the 57 children placed on antibiotic prophylaxis did not come for repeat echocardiography as

they had either left the city or were unable to come due to paucity of time and other commitments. The parents of these children have agreed to come at a later date.

Twenty nine cases showed no change, fourteen cases showed improvement and two cases showed progression in their valve lesions on repeat echocardiogram. The two cases which showed progression had been on penicillin prophylaxis for six months and had been irregular in their monthly penicillin
injections. These changes in the grades of valve lesions as per the WHF criteria are depicted in greater detail in Table III.

Discussion

The present study used echocardiography for active surveillance and found a high prevalence of RHD (38.3/1000) based on WHF criteria. This prevalence is much higher than the same reported by another study conducted in India which was carried out from 2008 to 2014.(19) Since a part of the study was carried out before the publication of the WHF criteria, it is quite probable that only the cases recruited after 2012 would have been diagnosed as per WHF criteria. The active surveillance strategy for establishing the prevalence of RHD has gradually evolved from exclusive clinical screening to universal echocardiography over the preceding decades.(Fig.1)

Despite the adoption of universal echocardiography for active surveillance, the criteria for echocardiographic diagnosis of RHD have gradually evolved over the years. These changes have impacted the diagnostic labelling and thus the reported prevalence. The changes in the regurgitant jet length considered significant, morphological criteria and recommended gain settings in the diagnosis of subclinical carditis have potentially resulted in non-homogeneous reporting of subclinical cases over the years.The effects of these changes are appreciated by looking at the markedly different reported proportion of borderline and definite subclinical carditis cases enrolled in these studies conducted at different times in last two decades (18,19,23,24)

Secondly, the aforementioned study (18) was carried out in the rural and urban areas of Indian states namely Haryana, Gujarat, Manipur and Goa. These states have a relatively higher per capita income compared to Rajasthan where the present study was carried out. This may have contributed to the higher prevalence found in our study. Another similar study carried out in Eastern Nepal using the WHF criteria also reported a lower prevalence (10.2/1000).(22)

In our view, the variation in reported prevalence highlights the fact that the burden of RHD continues to be alarmingly high in the economically backward states of India and also, that similar studies need to be carried out in each state to ascertain the state-wise disease burden. The present study also showed a trend of higher prevalence of RHD amongst school children from rural schools compared to those from urban schools and belonging to poorer socioeconomic background. (Table II) These facts will be crucial in planning future allocation of resources to manage RHD in each state.

The prevalence of ‘definite’ RHD in the present study was found to be greater (29.3/1000) than the ‘borderline’ RHD (09/1000). This is in contrast to the previously mentioned studies (19,23) which reported a higher prevalence of ‘borderline’ RHD compared to the ‘definite’ RHD. Although, these differences are difficult to explain, yet they may indicate that the classification of RHD into ‘borderline’ and ‘definite’ RHD based on WHF criteria may not be very useful because of the following probable reasons:

1. The WHF criteria are qualitative with an element of subjectivity on part of the operator in classifying the disease as borderline or definite. In fact, we had compared our study results based on WHF criteria with an objective score and found discrepancy in the classification of cases. (23)
2. The classification appears redundant because most of the cases classified as 'definite' RHD in these three large studies are subclinical with no clinical case found in our study and reported prevalence of 0.36/1000 in the other study from India (19) and 2.4/1000 in the study from Nepal.(22)
3. There is no evidence in literature regarding any difference in the evolution of definite or borderline RHD which necessitates difference in the management of these cases.

In fact, the present study is the first study of its kind in the entire world, wherein, we are reporting two years' follow-up of the subclinical cases diagnosed with RHD as per WHF criteria and placed on penicillin prophylaxis.During the course of our follow up of 2 years, no acute, clinical episodes of ARF/RHD were reported for these cases. Subclinical RHD improved in about 29% of children completing the follow up and progressed in mere 3.6% of participants completing the 2 years follow up.
We had previously also reported improvement at two years' follow-up in a small number of cases diagnosed as RHD based on World Herat Organization (WHO) criteria for pathological regurgitation and placed on penicillin prophylaxis.(24)

Based on our experience of studying subclinical cases, we feel that pathological MR and/or AR, irrespective of their severity, are probably the marker of early stages of ARF/RHD. This finding is noteworthy because it indicates that the reversibility point of the disease is prior to the onset of fixity of leaflets and stenosis. Pathological MR probably is the result of valvular edema leading to improper apposition of leaflets and thickening of leaflets which is the most common morphological abnormality found in the present study and other similar studies conducted the world over.(8,17)

We did not find a single case of mitral stenosis in the present study nor in our previous study (17). This is quite understandable because the presence of fixity and stenosis probably indicates a long-standing, chronic inflammation leading to scarring and restriction of valve leaflet mobility. The traditional school of thinking which considered fixity of valve leaflets, especially posterior mitral leaflet(PML);was probably based on the information obtained by performing echocardiography to confirm the diagnosis in clinically detected cases seen in doctors' consultation rooms/wards.

Although measurement of elevated anti-streptolysin O (ASO) titre and C-Reactive Protein(CRP) was not a part of the study protocol, it is quite likely that these values will help us ascertain whether we are dealing with an acute or chronic disease process.
Limitations:

The present study was carried out in the north western part of India which has not been much affected by economic upswings typically seen in the metropolitan areas and larger cities of India. Hence the results have limited value in terms of extrapolation to the entire country.

Second limitation is the high drop-out rate at follow-up and the variable duration of penicillin prophylaxis in the children undergoing repeat echocardiogram at the time of follow-up. The high drop out rate could not be circumvented as the parents did not give their consent because they were not convinced of the benefits versus risks of penicillin prophylaxis in asymptomatic children. However, we believe that once the guidelines are well established regarding the utility of prophylaxis in asymptomatic children, there will be greater acceptance amongst the parents.

Third limitation is that we did not measure the ASO titre or CRP in these cases to differentiate between acute or chronic disease process. These children are on regular follow-up and future echocardiograms and are likely to shed more light on the evolution of the lesions in children on penicillin prophylaxis.

Conclusions

The burden of subclinical RHD diagnosed is still very high in our area especially in the low income group. Health education and awareness camps should be started at school level. Measures like universal echocardiography screening should be done in all children age 10-15 years. All cases of subclinical RHD should undergo measurement of their serum ASO and CRP titres. They should be placed on appropriate antibiotic prophylaxis and regular laboratory and echocardiographic follow-up to document the evolution of the disease.

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Table I : Distribution of various study variables

Variables			
Prevalence of borderline RHD (overall)	9 per 1000		
Prevalence of definite RHD (overall)	29.3 per 1000		
Age-wise prevalence of definite RHD			
5-9 years	NA		
10-15 years	29.3 per 1000		
Boys	31.6 per 1000		
Girls	21.7 per 1000		
Prevalence of MVP	NA		
Prevalence of CHD	05 per 1000		

Table II: The distribution of cases as per socioeconomic and demographic parameters

	Variable	Prevalence (a)	Prevalence (b)	Odds ratio	95% CI
Location	Urban(a) vs Rural(b)	3.79	4.37	0.157	-1.69 to 4.64
School type	Govt(a) vs non-Govt(b)	5.36	3.03	9.96**	0.84 to4.02
Socioeconomic status	High(a) vs low(b) Middle(a) vs low(b)	1.91 3.66	4.79 4.79	11.05*** 1.47	1.29 to 4.28 -.77 to 2.77
Housing type	Katcha(a) vs Pucca(b)	4.2	3.81	0.047	-2.12 to 5.68
Family members	<=4(a) vs 5-9(b) <=4(a) vs >=10(b)	2.43 2.43	3.96 4.69	2.94 4.28*	-0.27 to 2.93 0.13 to 4.42

Table III : The number and proportion of children with changes in the echocardiographic features of subclinical RHD

Initial to at the time of follow up	Number	Percentage
Definite AR to absence of AR	3	5.4
Definite AR to borderline AR	1	1.8
Borderline AR to no AR	1	1.8
Definite MR to no MR	0	0
Definite MR to borderline MR	7	12.3
Borderline MR to no MR	1	1.8
Definite MR and definite AR to borderline MR and definite AR	1	1.8
Borderline MR to definite MR	1	1.8
Definite MR to definite MR and definite AR	1	1.8
No change in echocardiography status	29	51