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Did we overcome rheumatic heart disease or is it still a public disease burden?

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Abstract

Rheumatic heart disease (RHD), affecting approximately 32 million people all over the world is one of the major causes of cardiovascular morbidity and mortality especially in developing countries. In this ongoing pilot study, we aim to investigate the prevalence of both definitive and borderline RHD in Turkey as a developing country. A total of 386 healthy young individuals (45 female, 341 males) who applied to our Cardiology Clinic for being military personnel coming from different regions of Turkey in the year 2015, were recruited for our study. 2012 World Heart Federation (WHF) criteria for echocardiographic assessment and diagnosis of RHD were used. Study population was classified into one of the three groups as normal, borderline RHD and definitive RHD. The three groups were similar in terms of baseline characteristics and laboratory findings. Definitive and borderline RHD were found in 11 (2,9%) and 29 (7,5%) individuals, respectively. Abnormal thickening of the anterior mitral valve leaflet (AMVL) was found statistically significant between the normal and the RHD groups (3.1±0.6 vs 4.2±0.9, p<0.001). Even though the number of patients in our study is small, we found the incidence of borderline and the definitive RHD higher than we expected. Transthoracic echocardiography may be helpful in detecting RHD at the early-stages and preventing progression of the disease with secondary antibiotic prophylaxis.

Keywords: Rheumatic Heart Disease, Acute Rheumatic Fever, and Public Disease Burden

Introduction

Rheumatic heart disease (RHD), affecting approximately 32 million people all over the world is one of the major causes of cardiovascular morbidity and mortality especially in developing countries [1]. In most of the developed countries, RHD is no longer a social health problem. However, it is still endemic even in socioeconomically underdeveloped regions of developed countries like Australia [2,3]. Classically, RHD is sequelae of untreated group A beta-hemolytic streptococcal (GABHS) infections in individuals with genetic predisposition to RHD. Recurrent acute rheumatic fever (ARF) attacks are associated with severity of valvular injury [4,5]. However, many patients with RHD can present with advanced valvular disease findings without history of significant ARF attacks [6-8]. RHD is the only chronic sequelae of acute rheumatic fever that results in lifelong. However, it is a preventable disease with appropriate antibiotic therapy. Therefore, the detection of mild grade RHD and secondary penicillin prophylaxis is important for the prevention and progression of the disease in the asymptomatic population. Transthoracic echocardiography is an ideal imaging modality for RHD screening in asymptomatic individuals.

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In this pilot study, we aim to investigate the prevalence of both definitive and borderline RHD in Turkey as a developing country.

Material and Method

Our study was a prospective, cross-sectional and observational study. A total of 386 healthy young individuals (45 female, 341 males) who applied to the Department of Cardiology, Gulhane Training and Research Hospital, Ankara, Turkey for being military personnel coming from different regions of Turkey in the year 2015, were recruited for our study. According to the military regulations, all candidates have to be examined by routine echocardiography as a part of routine examination irrespective of the presence of any symptoms. To assess the presence of both definitive and borderline RHD, 2012 World Heart Federation (WHF) criteria for echocardiographic assessment and diagnosis of RHD was used [9]. Study population was classified into one of the three groups as normal, borderline RHD and definitive RHD according to the echocardiographic findings. All individuals in the study population had neither any symptoms nor history of cardiac diseases. After a 15-minute resting period, the patients were examined in the left lateral decubitus position with a Vivid S5 (GE Healthcare, Norway). Complete 2D, color, pulsed and continuous-wave Doppler examinations were performed according to the standard techniques. When a valve disease was diagnosed, a more

detailed examination was performed regarding the presence of echocardiographic criteria and morphological features of RHD. Echocardiographic criteria and morphological features of rheumatic heart disease, which were also used in our study population, were given in Table 1 and 2. Local Ethics Committee of our institute approved the protocol of study.

Table 1. 2012 World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease

Echocardiographic criteria for individuals aged ≤20 years
Definite RHD (either A, B, C, or D)
A. Pathological MR and at least two morphological features of RHD of the MV
B. MS mean gradient ≥4 mmHg
C. Pathological AR and at least two morphological features of RHD of the AV
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
Echocardiographic criteria for individuals aged >20 years
Definite RHD (either A, B, C, or D)
A. Pathological MR and at least two morphological features of RHD of the MV
B. MS mean gradient ≥4 mmHg
C. Pathological AR and at least two morphological features of RHD of the AV, only in individuals aged <35 years
D. Pathological AR and at least two morphological features of RHD of the MV

AR, aortic regurgitation; AV, aortic valve; MR, mitral regurgitation; MS, mitral stenosis; MV, mitral valve; RHD, rheumatic heart disease

Table 2. Echocardiographic criteria and morphological features of rheumatic heart disease

Echocardiographic criteria for pathological regurgitation	Morphological features of rheumatic heart disease
Pathological mitral regurgitation	**Features in the MV**
(All four Doppler echocardiographic criteria must be met)	• AMVL thickening ≥3 mm (age-specific)*
• Seen in two views	• Chordal thickening
• In at least one view, jet length ≥2 cm	• Restricted leaflet motion
• Velocity ≥3 m/s for one complete envelope	• Excessive leaflet tip motion during systole|
• Pan-systolic jet in at least one envelope	***Features in the AV***
Pathological aortic regurgitation	• Irregular or focal thickening
(All four Doppler echocardiographic criteria must be met)	• Coaptation defect
• Seen in two views	• Restricted leaflet motion
• In at least one view, jet length ≥1 cm	• Prolapse
• Velocity ≥3 m/s in early diastole	
• Pan-diastolic jet in at least one envelope	

AMVL, anterior mitral valve leaflet; AV, aortic valve; MV, mitral valve. *Abnormal thickening of the AMVL is age-specific and defined as follows: ≥3 mm for individuals aged <20 years; ≥4 mm for individuals aged 21–40 years; ≥5 mm for individuals aged >40 years

Statistical Analysis

The categorical variables were defined as percentages whereas the continuous variables were reported as the mean ± standard deviation (SD) and were compared using the Student t-test in case of normal distribution. The normality of the continuous variables was tested using the Kolmogorov-Smirnov test. Chi-square test was used to evaluate categorical variables. One-way ANOVA test was used for comparison between groups, and Tukey test was used for post-hoc analysis. Statistical significance was defined as $p < 0.05$. All statistical analyses and calculations were conducted using the SPSS 20.0 Statistical Package Program for Windows (SPSS, Chicago, IL, USA).

Results

A total of 386 healthy young (≤45 years old) individuals (45 female, 341 males; mean age 28.1±7.4) were included to our study. The three groups were similar in terms of baseline characteristics and laboratory findings (Table 3). Of these 386 subjects, 30 subjects (7,8%) were under the age of 20, 299 subjects (77,5%) were between 20-40 and 57 subjects (14,7%) were over 40 years old. Definitive and borderline RHD were found in 11 individuals (2,9%) and 29 individuals (7,5%), respectively. Of these 11 patients with definitive RHD, 1 patient (3,3%) was under the age of 20, 7 patients (7,5%) were between 20-40 and 3 patients (5,3%) were over 40 years old (Table 4). Only 8 patients (20,0%) with RHD had a murmur at cardiac auscultation, and only 9 patients (22,5%) had a history of previous frequent sore throat and tonsillitis. Nobody had clinical symptoms. In addition, abnormal thickening of the anterior mitral valve leaflet (AMVL) was found statistically significant between the normal and the RHD groups (3.1±0.6 vs 4.2±0.9, $p<0.001$). However, the thickness of the AMVL was not found statistically significant between the borderline and the definitive RHD groups (4.1±0.6 vs 4.2±0.6, $p=0.341$) (Table 5). The distribution of valve diseases among the study population is given in Table 6.

Table 3. Baseline demographic and laboratory findings of the study population

	Normal (n=346)	Borderline RHD (n=29)	Definite RHD (n=11)	P value
Age, (years)	29,73 ±11,36	26,75±11,62	28,09 ±12,5	0,549
Gender (Male) n,(%)	306 (%88,4)	25 (%86,2)	10 (%90,9)	0,367
Glucose, (mg/dL)	95,42 ± 8,75	96,65 ± 7,23	97,25 ± 3,48	0,724
Urea, (mg/dL)	25,32 ± 7,78	29,45 ± 6,89	31,08 ± 3,86	0,204
Creatinine, (mg/dL)	0,78 ± 0,12	0,86 ± 0,11	0,77 ± 0,26	0,123
Uric acid, (mg/dL)	5,02 ± 1,89	5,53 ± 2,12	4,48 ±1,29	0,448
HDL-C, (mg/dL)	43,02 ± 5,79	41,30 ± 7,34	39,90 ± 4,50	0,437
LDL-C, (mg/dL)	109,95 ± 29,50	110,22 ± 42,49	105,95 ± 38,40	0,117
Triglycerides, (mg/dL)	105,34 ± 36,35	117,45 ± 34,12	115,23 ± 46,29	0,389
Leukocytes, (103 µL)	5,12 ± 2,43	6,31 ± 1,26	5,75 ± 3,58	0,109
Neutrophil, (103 µL)	3,24 ± 1,12	3,67 ± 1,87	3,76 ± 1,21	0,203
Lymphocyte, (103 µL)	1,88 ± 0,72	2,64 ± 0,59	2,01 ± 0,57	0,198
Erythrocytes (103 µL)	5,21 ± 0,34	5,10 ± 0,67	5,14 ± 0,38	0,781
Hemoglobin (g/dL)	15,21 ± 1,24	14,41 ± 2,22	14,33 ± 1.33	0,309
Hematocrit (%)	45,86 ± 3,97	43,12 ± 5,31	43,54 ± 3,53	0,192
Platelet (103 /µL)	205,20 ± 49,12	235,67 ± 35,96	240,23 ± 62,23	0,089
ESR (mm/saat)	13,19 ± 5,54	11,96 ± 5,55	13,54 ± 8,98	0,441

HDL-C: High density lipoprotein cholesterol , LDL-C: Low density lipoprotein cholesterol, ESR: Erythrocyte sedimentation rate

Table 4. The number of the subgroups according to the age in the study population

	Normal	Borderline RHD	Definite RHD	Total (n)
≤ 20 Ages	24 (%80)	5 (%16.7)	1 (%3.3)	30
20-40 Ages	273 (%91.3)	19 (%6.4)	7 (%2.3)	299
>40 Ages	49 (%85.9)	5 (%8.8)	3 (%5.3)	57
Total (n, %)	346(%89.6)	29(%7.5)	11(%2.9)	386

Table 5. Thickness of the AMVL for Normal and RHD groups

	Normal (n=346)	Borderline RHD (n=29)	Definite RHD (n=11)	Comparison Group	Post hoc P value
Thickness of the AMVL	3.1 ± 0.6	4.1 ± 0.6	4.2 ± 0.6	Borderline vs. Normal	0.001
				Definite vs Normal	0.001
				Borderline vs Definite	0.341

Table 6. The distribution of valve diseases among the study population

		Normal (n=346)	Borderline RHD (n=29)	Definite RHD (n=11)
Mitral regurgitation	Mild	28 (8,0%)	17 (58,6%)	6 (54,5%)
	Moderate	-	5 (17,2%)	3 (27,2%)
	Severe	-	-	-
Mitral stenosis	Mild	-	2 (6,8%)	2 (18,1%)
	Moderate	-	-	1 (9,0%)
	Severe	-	-	-
Aortic regurgitation	Mild	10 (2,8%)	4 (13,7%)	3 (27,2%)
	Moderate	-	-	1 (9,0%)
	Severe	-	-	-
Aortic stenosis	Mild	-	-	-
	Moderate	-	-	-
	Severe	-	-	-

Discussion

Even though the number of patients in our study is small, we found the incidence of borderline and the definitive RHD higher than we expected. Although the pathophysiology of RHD has been elucidated, the prevention of the development or progression of the disease has not been achieved precisely at present. ARF is an autoimmune process in which antibodies against streptococcal antigens are targeted to cardiac, synovial and neuronal tissues. ARF can manifest with arthritis, carditis, erythema marginatum and Sydenham chorea [10]. While most of the systemic involvement can limit itself, especially recurrent attacks can lead to irreversible valvular thickening and fibrosis. It has previously been shown that poor living conditions, poor educational level and inadequate access to health care are related to the severity of RHD. [11] Transthoracic echocardiography is an inexpensive, easily accessible method of imaging that can be used to detect early stage RHD. Since there is no consensus on the criteria to be used in RHD screening, a guideline was published by the World Heart Federation in 2012 and the "borderline" and "definite" RHD criteria were defined [9]. Borderline RHD forms a heterogeneous group and is not considered to be entirely benign. Approximately one in four of these patients develop moderate-to-severe valve disease [11]. Markers related to disease progression are uncertain. In many cases, secondary antibiotic prophylaxis is not initiated in cases of borderline RHD [13]. However, there are some studies evaluating the feasibility of prophylaxis in borderline RHD cases with the presence of concomitant moderate-severe valve insufficiency [11]. Valvular damage and disease progression are more pronounced in definite RHD patients. In a study, 20 patients with definite RHD diagnoses were followed for 7.5 years without antibiotic prophylaxis, and 70% had persistent disease or progression, and 20% of them required valvular surgery [11]. It is known that timely surgical or percutaneous interventions in patients with severe rheumatic heart disease improve prognosis [14,15]. However, these patients who have undergone valve replacement use lifetime anticoagulants and are at higher risk of bleeding complications and infective endocarditis than the normal population.

Primary prevention should target hygiene and improvement in living conditions to prevent GABHS infecitons. These environmental changes require a significant infrastructure investment in the whole country [16]. The correct diagnosis and timely delivery of proper antibiotic treatment for streptococcal throat infection will also prevent the immunological process which leads to ARF. Streptococcal rapid diagnostic tests, the presence of microbiology laboratories, experienced health personnel, and proper penicillin therapy are important steps in this process. Clinical judgment and treatment of patients with penicillin without throat culture is likely to reduce the frequency of RHD [17]. Secondary prophylaxis with intramuscular benzathine penicillin is a low-cost treatment with proven efficacy in the prevention of recurrent streptococcal throat infections and valvular injury and in the prevention of community health [18,19]. The effect of secondary prophylaxis on heart failure development or mortality is related to the onset of the prophylaxis at an early stage of the disease [20]. Secondary prophylaxis has been shown to have no effect on heart failure and mortality in Sub-Saharan African countries and in Northern Australia where echocardiographic screening has not been adequately performed and patients have been presented with advanced RHD [21]. These findings demonstrate the importance of echocardiographic screening for the early recognition of the disease and the immediate onset of secondary antibiotic prophylaxis [21,22]. Studies on RHD and ARF in our country have reported different results regarding the frequency of these diseases [23-25]. This is not surprising considering the heterogeneous nature of our country in terms of socioeconomic level. In a study conducted by Olguntürk et al. in 1990s, 4086 school age individuals in Ankara were evaluated regarding the ARF and RHD. The prevalence rates of ARA and RKH were reported as 3.7 and 0.73, respectively [26].

There may be several important reasons for the difference in the frequency of RHD in our country. The fact that the criteria used in the definition of RHD are different from each other can be an important reason for the difference. It is also important that patient populations are completely different. The presence of military candidates from our country's rural areas in our study population could be one of the factors that could explain the difference. If we consider the heterogeneity in the socioeconomic level of our country, even in different districts of the same province, we can say that larger studies are needed in this regard. We think that individuals aged $\leq$ 20 years may be considered for routine echocardiography screening, as this age group benefits the most from early detection and secondary prevention of RHD. However multicenter prospective studies with larger cohort are needed to support our suggestion.

Our study has important limitations. The low number of samples and the single centered nature of the study can be counted as the most important limitations. The diagnosis of patients was made by transthoracic echocardiography and was not confirmed by transesophageal echocardiography. Since our study population was military personnel, the vast majority of the population was male. Since there is not enough data about the female individuals, our findings can not be extrapolated female individuals.

Conclusion

Even though the number of patients in our study is small, we found the incidence of borderline and the definitive RHD more than we expected. Transthoracic echocardiography may be helpful in detecting RHD at the early-stages, and preventing progression of the disease with secondary antibiotic prophylaxis. Improving living conditions and care for hygiene will also reduce GABHS spread. There is a need to raise awareness of primary and secondary prevention measures in order to reduce cardiovascular morbidity and mortality associated with RHD. We believe that multicenter prospective studies with larger cohorts related to this issue will help health policies in terms of community health.

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