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Rheumatic Mitral Stenosis: Long-Term Follow-Up of Adult Patients with Nonsevere Initial Disease

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Rheumatic mitral stenosis · Natural history · Echocardiography

Abstract
Introduction: There is no consensus regarding the natural history of rheumatic mitral stenosis (MS) among adults presenting with nonsevere disease. This study aims to describe the progression of stenosis among adult rheumatic MS patients, to identify predictive factors for progression, and to assess the incidence of complications. ***Methods:*** A retrospective cohort analysis was performed among patients with rheumatic MS treated at a single center. Eighty-five patients were included with mild to moderate MS, ≥30 years old on initial echocardiography. Demographics, medical history, echocardiographic reports over at least 10 years, and related complications were obtained from a computerized database. ***Results:*** Over a period of 13.1 ± 2.38 years, 75 patients (88%) had no significant progression in stenosis severity. The final echocardiographic assessment demonstrated 2 groups with a significant difference between them regarding the mitral valve area (1.58 ± 0.44 vs. 1.1 ± 0.26 cm^2, p = 0.001) and mean valvular pressure gradient (6.27 ± 2.52 vs. 8.5 ± 2.69 mm Hg, p = 0.01). Patients with indolent MS (group A) were compared to patients with progressive disease (group B), and a higher percent of Bedouin patients were found in group B (OR 8.036, p = 0.015). No significant differences were found in other parameters. Complications including atrial fibrillation, cerebral ischemic events, and impaired right ventricle function, although frequent, were not statistically different between the groups. ***Conclusions:*** An indolent natural progression of rheumatic MS was observed in our study. Despite this finding, it still has potentially deleterious effects. Bedouin patients have a higher risk for progressive disease.
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Introduction

Mitral stenosis (MS) is known as a disease of developing countries or populations with similar characteristics [1]. Distinguished from other valvular pathologies, MS originates almost exclusively from rheumatic heart disease [2], a late sequela of undertreated group A *Streptococcus* (GAS) infection. It is related to low hygiene and low accessibility of medical care services and antibiotics. The acute phase of rheumatic fever presents clinically 2–4 weeks after recovery from GAS pharyngitis and in 50–70%

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of the cases results in carditis [3] which involves mainly the mitral and/or the aortic valve. The acute phase injury is the basis of the development of the chronic valvulopathy. MS limits blood flow from the left atrium to the left ventricle, and over time, the most common clinical manifestation of MS is exertional dyspnea and exercise intolerance [4]. Some serious potential complications are associated with prolonged disease: while the stenosis progresses, pressure in the left atrium rises, resulting in left atrial enlargement and eventually atrial tachyarrhythmia: atrial fibrillation or flutter. These in turn can lead to thromboembolic events, most frequently to the cerebral circulation, resulting in cerebral ischemia and neurological damage. The elevated pressure in the left atrium can also result in pulmonary congestion and hypertension, which affect the right side of the heart, resulting in right ventricle dysfunction and tricuspid regurgitation. In turn, this may result in peripheral edema, ascites, and pleural effusions. The acceptable tool used to determine stenosis severity is the echocardiogram, based on European Association of Echocardiography/American Society of Echocardiography (EAE/ASE) definitions [5]. The severity of the stenosis is assessed by echocardiographic findings, with mitral valve area (MVA) as a main parameter and mean gradient and pulmonary artery pressure as supportive findings.

Compared to our study, previous studies regarding the natural history and stenosis progression were based on relatively short follow-up periods [6], relatively small populations [7], or addressed MS as a marginal issue [8]. Other studies just described echocardiography and X-ray changes [9, 10] and were performed >50 years ago, when echocardiography was not in use. In our study, we analyzed the stenosis progression using measurable values by echocardiographic assessments for a period of at least 10 years. Furthermore, we tried to define protective or aggravating factors by collecting information on demographics and medical comorbidities and collected data regarding the incidence of MS-related complications.

Materials and Methods

We conducted a retrospective population-based study, analyzing the echocardiographic reports of 143 patients with MS treated in the Cardiology Department of Soroka University Medical Center, located in southern Israel, who had at least 2 echocardiographic assessments, at least 10 years apart. Fifty-eight patients were excluded due to one or more of the following reasons:

1. Advanced stenosis severity in their first echocardiographic assessment: these patients already had severe disease, and data about the natural history and progression of their disease was unavailable.
2. Concurrent severe mitral regurgitation and/or aortic stenosis due to their influence on cardiac hemodynamics, which may disrupt the accuracy of valve and mean gradient echocardiographic assessment.
3. Senile calcific MS.

Data including demographics and clinical characteristics were attained from the computerized database of the Department of Cardiology at the Soroka University Medical Center. The study was approved by the Soroka University Medical Center Helsinki committee.

Echocardiographic data were collected from the patients first and last study reports and included: MVA, mean gradient over the mitral valve, left and right ventricles' size and function, systolic pulmonary artery pressure, and the existence of additional valvulopathies. We used the EAE/ASE definitions [5] to classify the severity grade of the MVA and the mean gradient for each patient. If there was a difference between the MVA grade and the mean gradient grade, we labeled the overall severity grade as a combination of both: for example, if according to the MVA there was mild stenosis and according to the mean gradient there was moderate stenosis, we labeled the overall severity as mild-moderate. We numbered the possible severity grades empirically from 1 to 5: 1 for mild, 2 for mild-moderate, 3 for moderate, 4 for moderate-severe, and 5 for severe. This scale was used for comparing stenosis severity in the first and last echocardiographic assessments. We analyzed stenosis progression by comparing initial and final stenosis severity. We defined the disease progression as indolent in patients whose stenosis severity increased by up to 1 point during the follow-up period (e.g., from 2 to 3 – mild-moderate in the first echocardiographic assessment to moderate in the last one) and as progressive for patients whose stenosis severity increased by 2 points and more. Accordingly, we divided the study population into 2 subgroups: group A – patients with indolent disease, and group B – patients with progressive disease. The division into subgroups enabled us to compare the demographics and complication rate between subgroups and to define protective or aggravating factors.

Differences between the 2 groups in sociodemographic characteristics, echocardiographic characteristics, and long-term clinical complications were assessed using t test or χ^2 test according to the variables' scale structures. The unique relative contribution of the independent sociodemographic variables (gender, ethnicity, and age at first echocardiographic assessment) to the explanation of disease progression was examined by a multiple logistic regression analysis. The variables were entered one by one into the model, and no interactions were found between them. ORs and 95% CI were computed, and a two-sided p value <0.05 was considered statistically significant. All tests were conducted using SPSS version 23 (IBM, Armonk, NY, USA).

Results

The study population included 85 patients after excluding patients as mentioned in the Materials and Methods section. Seventy-five (88%) of the patients were found to have indolent disease. The other 10 patients (12%) had progressive disease.

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Table 1. Demographic and clinical characteristics

	Group A (indolent disease, $n = 75$)	Group B (progressive disease, $n = 10$)	p value
Gender			
Male	17 (22.7)	3 (30)	0.694
Female	58 (77.3)	7 (70)	0.694
Ethnicity			
Jewish	70 (93.3)	6 (60)	**0.01**
Bedouin	5 (6.7)	4 (40)	**0.01**
Age at 1st echo, years, average ± SD	54.92±9.8	51.1±5.97	0.234
Follow-up duration, years, average ± SD	13.05±2.48	13.3±1.76	0.762
Hypertension	53 (70.7)	8 (80)	0.718
Diabetes mellitus	28 (37.3)	3 (30)	0.740
Dyslipidemia	57 (76)	9 (90)	0.439
Obesity (BMI >30)	35 (46.7)	4 (40)	0.748
Smoking	15 (20)	2 (20)	1

Values are given as absolute number (percentage) unless otherwise indicated. Bold values indicate statistical significance. BMI, body mass index; SD, standard deviation.

Table 2. Echocardiographic characteristics

	Group A (indolent disease, $n = 75$)	Group B (progressive disease, $n = 10$)	p value
MVA, cm^2			
1st echo	1.93±0.48	1.75±0.27	0.266
Last echo	1.58±0.44	1.1±0.27	**0.001**
Annual Δ	0.027±0.34	0.049±0.24	**0.05**
Mean gradient, mm Hg			
1st echo	5.77±2.08	5.1±1.64	0.334
Last echo	6.27±2.52	8.5±2.69	**0.01**
Annual Δ	0.038±0.19	0.25±0.12	**0.001**

Values are given as average ± SD, unless otherwise indicated. Bold values indicate statistical significance. MVA, mitral valve area; annual Δ, average annual difference in MVA/mean gradient values in consecutive years along the follow-up period.

The demographic and clinical characteristics of the 2 subgroups are described in Table 1. We found that ethnicity is a statistically significant factor: Jewish patients had a more indolent course of valve stenosis progression compared to Bedouin patients ($p = 0.01$). None of the other study variables, neither clinical nor demographic, were found to have a significant protective or aggravating effect on the disease progression.

Patients' echocardiographic characteristics in each of the 2 subgroups are shown in Table 2. The final echocardiographic assessment MVA values were significantly higher in group A (patients with indolent disease) than in group B (patients with a progressive disease) (1.58 ± 0.44 vs. 1.1 ± 0.26 cm^2, respectively, $p = 0.001$). The final mean pressure gradient values were significantly lower in group A patients than in group B patients (6.27 ± 2.52 vs. 8.5 ± 2.69 mm Hg, respectively, $p = 0.01$).

We also found statistically significant differences between subgroups in the annual average of MVA decreasing rate and mean gradient increasing rate: the MVA annual decreasing rate among group A patients was 0.027 versus 0.049 cm^2 in group B patients ($p = 0.05$). The annual increase in the mean gradient among group A patients was 0.038 versus 0.25 mm Hg in group B patients ($p = 0.001$).

Results regarding major complications are presented in Table 3. There were no statistically significant differences in the major complication incidence rate between patients with indolent or progressive disease. The vast majority of the patients developed atrial fibrillation – 80% in both subgroups. Although not statistically significant, patients in group B showed a tendency to develop atrial fibrillation earlier, measured in years from the first echocardiographic assessment (5.5 ± 3.59 vs. 7.55 ± 5.12 years, $p = 0.347$). No statistical significance was found between the 2 groups regarding the incidence of cerebral ischemic events nor the time from the first echocardiographic assessment to stroke event.

Multivariate analysis results are shown in Table 4. Results indicate that Bedouin ethnicity is the single statistically significant variable predicting progression of the disease (OR 8.03, $p = 0.015$) while controlling for gender and age at the first echocardiographic assessment.

Discussion

Progression of rheumatic MS generally starts almost simultaneously with discovery: some patients will suffer a substantial and rapid progression with symptom onset during adolescence, and others will experience a more indolent nature of progression [1, 8, 11]. No consensus exists in the medical community and literature regarding the natural history of rheumatic MS among adults suffering from nonsevere disease in the initial echocardiographic assessment. The main purpose of this study

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Table 3. Long-term clinical complications

	Group A (indolent disease, $n = 75$)	Group B (progressive disease, $n = 10$)	p value
Atrial fibrillation	60 (80)	8 (80)	1
Years from 1st echo to atrial fibrillation, average ± SD	7.55±5.12	5.5±3.59	0.347
Cerebral ischemic events	25 (33.33)	1 (10)	0.166
Years from 1st echo to stroke, average ± SD	8.5±4.76	11±0	0.603
Multiple strokes (>1)	11 (14.67)	1 (10)	1
RV injury	15 (20)	3 (30)	0.435

Values are given as absolute number (percentage) unless otherwise indicated. SD, standard deviation; RV, right ventricle injury – dilation and/or hypokinesia.

was to assess whether MS is a progressive or indolent disease over time among such patients, and specifically among our unique population of Jewish and Bedouin patients.

Our results showed that over a period of 13.1 ± 2.38 years, the disease did not progress >1 degree of severity (based on the EAE/ASE classification) among the majority of our participants, indicating an indolent nature.

One of our secondary goals was to identify factors which have either aggravating or protective effects on the progression of the disease. Of 10 parameters studied, only ethnicity was found to have a protective/aggravating influence in Jewish/Bedouin patients, respectively. Previous studies [1, 11] suggested that patients in developed countries have a more indolent rate of stenosis progression compared to patients in developing countries. Although not attributed directly to ethnicity in these studies, we can use some of the explanations described in previous studies [12] to understand some of the reasons underlying these findings, as the characteristics of the Bedouin population in southern Israel are somewhat similar to those of developing countries:

- Socioeconomic and environmental factors such as low income and resulting overcrowding and poor hygiene: these factors can increase the spread of GAS strains and can be linked to higher rates of recurrence.
- Low awareness among these populations as to the significance of the first episode and the importance of compliance to treatment in initial and recurrent episodes.
- Healthcare factors such as low accessibility to medical care: many people in this population live in peripheral geographic areas and have less access to health services.

Table 4. Progression of disease by multiple regression analysis

Variable	OR	95% CI	p value	Wald	SE
Age at 1st echo assessment, years	0.977	0.89–1.06	0.579	0.308	0.042
Gender, female	1.04	0.2–5.36	0.962	0.002	0.837
Ethnicity, Bedouin	**8.036**	1.49–43.19	**0.015**	5.899	0.858

Dependent value – progression of disease. Bold values indicate statistical significance.

A multivariable analysis was performed to assess whether the impact of ethnicity on disease progression rate remains statistically significant when adjusting for gender and age at the first echocardiographic assessment. Indeed, it remained statistically significant (OR 8.03). In other words, compared to a Jewish patient, a Bedouin patient has an 8 times greater risk to suffer from progressive disease. Cardiologists who treat Bedouin patients should take this into account and consider more frequent follow-up of patients while introducing educational interventions to increase awareness of the disease.

It is important to note that we found no statistically significant difference in the incidence rate of major complications between the 2 subgroups: precisely 80% suffered from atrial fibrillation in both subgroups, with an average time of appearance from the first echocardiographic assessment of 5.5 years in group B and 7.5 years in group A patients. As many as 26 out of 85 patients (30.6%) suffered cerebral ischemic events after the first echocardiographic assessment. Twelve patients (14.1%) experienced >1 event. The high rate of atrial fibrillation and stroke may be related to the rheumatic disease; how-

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ever, the high incidence of cardiovascular risk factors, such as hypertension and diabetes, could also contribute to this high complication rate.

Our study has certain strengths. For example, the average follow-up duration in our study of 13 years (range 10–19) is a strong point of this study as it provides more reliable information and a better understanding of the natural history and progression of the disease compared to previous studies with follow-up periods ranging from 28 to 40 months [6, 7]. Studies with longer follow-up-durations – ranging from 10 to 26 years [9, 10] – were performed in the 1960s and mainly assessed survival over time. Moreover, the mitral valve stenosis was described by means such as physical examination, as echocardiographic assessments were not in use at that time.

Our study also has some limitations. First, this is a retrospective analysis with all the potential drawbacks of such an analysis. Secondly, although the echocardiographic assessments were based on established criteria, small discrepancies in the precise measurements performed by the technicians at the time of examination cannot be excluded (although there would not necessarily be expected to be a difference between the subgroups in this aspect). In the south of Israel, many of the Bedouins live in circumstances with less than optimal sanitation and hygiene and with restricted access to medical care, whereas the Jewish population on the whole live in more acceptable housing with better access to medical facilities. This aspect of living conditions was not specifically investigated in the patients examined, and it may well be that the Bedouin patients involved were not different from the Jewish patients with regard to living conditions and access to medical care, in which case the difference seen may actually be an ethnic one and not related to hygiene or medical care. Specifically, in Israel, there is a very heterogeneous population mix, including Jews and Arabs with very differing socioeconomic status. In other countries with a large indigenous Bedouin population, there may be less variation in socioeconomic circumstances and thus less variation in the progress of MS. As a result, it could be that our findings are not necessarily generalizable to other countries with a more homogeneous population. Finally, the number of patients in the subgroups was relatively small, possibly affecting statistical comparison.

In conclusion, most of the young adult patients presenting with nonsevere rheumatic MS have an indolent natural progression. However, the general indolent progression of the valvular disease does not prevent significant clinical complications. Our findings also show that Bedouin patients are at a higher risk to suffer from a progressive disease. Therefore, we recommend that cardiologists who treat Bedouin patients should consider a higher frequency of follow-up visits and more effective primary prevention measures directed at this population.

Statement of Ethics

The study was approved by the Soroka University Medical Center Helsinki committee.

Disclosure Statement

No conflict of interest exists for any of the authors.

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Author Contributions

A.B. and E.M.-D. collected the data and helped with writing the manuscript. J.M.W. helped with the data analysis and writing the manuscript. S.C. performed the statistical analysis and contributed to writing the manuscript. R.I. proposed the idea of the study, supervised the data collection, and helped with writing the manuscript.

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