Original Article

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Long-term Follow-up of Valvular Involvement in Children with Acute Rheumatic Fever Carditis: 15-year Results

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Abstract

Aim: Acute rheumatic fever (ARF) is a multisystemic inflammatory disease and remains an important health problem in low- and middle-income countries. The most important and potentially permanent adverse effect of the disease is cardiac involvement. This study aims to investigate the course of valvular lesions in ARF carditis and the factors that may affect their course during a long-term follow-up.

Methods: In this cross-sectional study, which is a type of observational study, the records of children diagnosed with ARF in our hospital between August 2003 and December 2018 were retrospectively reviewed. Valvular insufficiency was examined on echocardiography and compared with the previous findings. The changes in the valvular lesions and the factors that could affect them were evaluated. The results were analyzed statistically.

Results: The study included 90 patients with ARF who had been followed up for over a year. Of our patients, 37 (41%) were male and 53 (59%) were female. The mean age of our patients was 16.5±3.2 years. The mean age at diagnosis was 11 (4.2-18 years). The mean follow-up period was 67 (14-184) months. Carditis was present in 86 (95.6%) patients. Echocardiographically, mitral regurgitation (MR) was present in 83 (96.5%) patients and aortic regurgitation (AR) was present in 56 (65%) patients. 54 (62.7%) patients had both MR and AR. During the follow-up, MR persisted or progressed in 19 (22.9%) patients, regressed in 39 (47%) patients, and completely recovered in 25 (30.1%) patients. Aortic regurgitation persisted or progressed in 13 (23.2%) patients, regressed in 4 (7.1%) patients, and completely recovered in 39 (69.7%) patients.

Conclusion: The recovery rate of aortic valve lesions was found to be much higher than that of mitral valve lesions. Initially, The high rate of mild involvement in aortic valve lesions maybe effective in this context. Apart from this, the valve lesion types that have a negative course and the factors affecting them still need to be studied further. Benzathine penicillin prophylaxis remains the most effective method of preventing recurrence.

Keywords: Rheumatic fever, rheumatic heart disease, heart valve diseases

Introduction

Acute rheumatic fever (ARF) is a systemic autoimmune syndrome involving a combination of the joints, heart, brain, skin, and and subcutaneous tissues that develops following exposure to *Group A Streptococcus* [*Streptococcus pyogenes (GAS)*] pharyngitis or impetigo (1). It remains an important health problem in low- and middle-income countries. The most important and potentially permanent complication of the disease is cardiac involvement. The condition often occurs in valvular regurgitation of the left heart valves.

At disease onset, valvular insufficiency is the predominant finding, while in the chronic form, valve

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stenosis can also be seen. Some of the valvular lesions improve, while others progressively worsen over time and may even require surgical intervention (2).

The aim of this study was to investigate the course of valvular lesions and the factors that may affect it during a long-term follow-up.

Materials and Methods

Compliance with Ethical Standards

The study protocol was approved by the Uludag University Faculty of Medicine Clinical Research Ethics Committee (approval no.: 2023-9/16, date: 26.04.2023). Written consent was obtained from all participants, and the study complied with the Declaration of Helsinki.

Study Design

In this retrospective study the records of children diagnosed with ARF in our hospital between August 2003 and December 2018 were retrospectively reviewed. Patients with a follow-up period of less than 1 year were excluded from the study. Acute rheumatic fever diagnoses for all the patients were made in our hospital and we had records corresponding to their initial episode. All diagnoses were made according to the modified Jones criteria, and the revised criteria were used for patients diagnosed after 2015 (3,4). Demographic data and clinical, laboratory, and echocardiographic findings of our patients were all present and examined from the patient files. Clinical procedures performed on the patients all included detailed cardiovascular examinations, and benzathine penicillin prophylaxis regularity was thoroughly checked. Electrocardiography and echocardiography were performed for each patient at each follow-up. Echocardiographic reports were reviewed by the same physician, Muhammet Hamza Halil Toprak.

When evaluating valvular insufficiency, trivial insufficiencies that did not involve changes in the valve morphology (thickening, limitation of chordate movements) weren't considered pathological. Pansystolic mitral regurgitation (MR) and pandiastolic aortic regurgitation (AR) with a peak velocity greater than 3 m/ss were considered significant. Mitral regurgitation was classified into severity groups as mild, moderate, and severe based on the ratio of maximum insufficiency jet area to atrium area. Those with a rate of <20% were considered mild, those between 20% and 40% were considered moderate, and those >40% were considered severely insufficient. Aortic insufficiency was classified as mild, moderate, or severe based on the parasternal long axis insufficiency ratio, defined as the jet width divided by the left ventricular outflow tract width. Disabilities with a rate of <25% were considered mild, those between 25% and 45% were considered moderate, and those >45% were considered severe. At each follow-up, valvular insufficiency was examined on echocardiography and compared with the previous findings.

Statistical Analysis

Statistical evaluation of the data was performed with Statistical Package for the Social Sciences 16 for Windows. Categorical data is divided into frequency and percentage (n, %). Continuous variable data were presented as mean ± standard deviation or median (min-max). The differences between categorical variable frequencies were investigated by the chi-square test. Normality analysis of the variables was performed with the Shapiro-Wilk test. Continuous variables that did not show normal distribution were compared with the Mann-Whitney U test. The significance level was set at α=0.05 ($p<0.05$).

Results

A total of 90 patients who were diagnosed with ARF in our hospital and had been followed up for more than a year were included in the study. Among the patients, 37 (41%) were male and 53 (59%) were female. The mean age of our patients was 16.5±3.2 years. The mean age at diagnosis was 11 (4.2-18) years. The diagnosis season was spring in 26 (28.9%) patients, summer in 23 (25.6%), autumn in 12 (13.3%), and winter in 29 (32.2%) patients. Only 6 (6.7%) patients had a family history of ARF.

The mean follow-up period was 67 (14-184) months. Carditis was present in 86 (95.6%) patients. The frequencies of other major findings are given in (Table 1). Echocardiographically, MR was present in 83 (96.5%) patients, and AR in 5656 (65%) patients. Fifty-four (62.7%) patients had both MR and AR. A total of 136 valve involvements was determined in 86 patients. The distribution and severity of valvular involvement at the time of diagnosis are given in (Figure 1). During the follow-up, MR persisted or progressed in 19 (22.9%) patients, regressed in 39 (47%) patients, and completely recovered in 25 (30.1%) patients. Aortic regurgitation persisted or progressed in 13 (23.2%) patients, regressed in 4 (7.1%), and completely recovered in 39 (69.7%). The progression of valvular lesions is given in (Figure 2).

The rate of complete recovery of aortic valve lesions was higher than that of mitral valve lesions, and the difference was statistically significant (69.7%, 30.1%, $p<0.01$).

Table 1. The frequencies of the major findings

Finding	n	%
Carditis	86	95.6
Arthritis	52	59.1
Corea	18	20.2
Subcutaneous nodules	1	1.1
Erithema marginatum	0	0

When the improvement and deterioration rates of mitral and aortic valve lesions were compared based on gender, no significant difference was detected for either of the valve lesions (p=0.68, p=0.12). When the improvement and deterioration rates of mitral and aortic valve lesions were compared based on age, no significant difference was detected for either of the valve lesions (p=0.89, p=0.98).

No significant difference was detected for either of the mitral and aortic valve lesions when the improvement and deterioration rates were compared according to age at the time of diagnosis (p=0.18, p=0.65).

Similarly, there was no statistically significant difference for the improvement and deterioration rates of mitral and aortic valve lesions based on the presence of chorea foreither of the lesion types (p=0.90, p=0.14).

Similarly, when the improvement and deterioration rates of mitral and aortic valve lesions were compared according to antistreptolysin O (ASO) levels at the time of diagnosis, no statistically significant difference could be detected for any of the valve lesions (p=0.90, p=0.14). The comparison of the factors affecting the course of aortic and mitral valve lesions ispresented in (Tables 2,3)

Recurrence was observed in 7 patients. Of these, 2 were seen in patients compliant with benzathine penicillin prophylaxis, and 5 were seen in patients who were non-compliant with benzathine penicillin prophylaxis. Two patients underwent surgical valve replacement due to cardiac failure. One patient underwent mitral valve replacement (MVR), and the other patient underwent simultaneous aortic and MVR.

Discussion

Acute rheumatic fever is a non-suppurative disease that occurs because of an autoimmune response to *GAS* pharyngitis. The disease mainly affects the heart, joints, and nervous system. It is more commonly encountered in children and young adults. Non-cardiac involvement of the disease is transient, while the most important permanent damage occurs as a result of cardiac involvement (5). For this reason, research on the understanding and treatment of heart lesions is important. Previously, the criteria for detecting carditis were based on physical examination for which the sensitivity was low (3). In recent years, with the widespread use of echocardiography to detecting carditis, it has been understood that cardiac involvement is actually

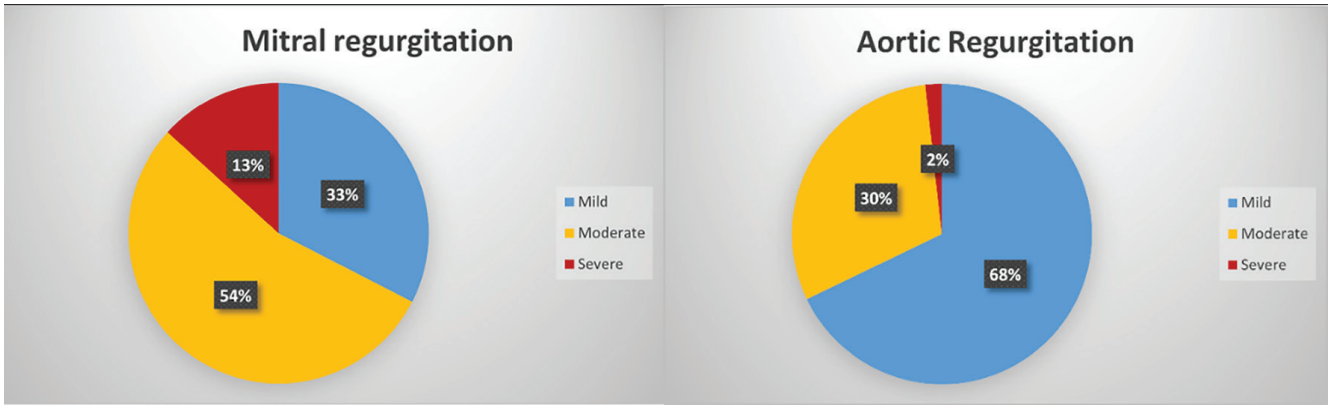


Figure 1. The distribution and severity of valvular involvement at the time of diagnosis

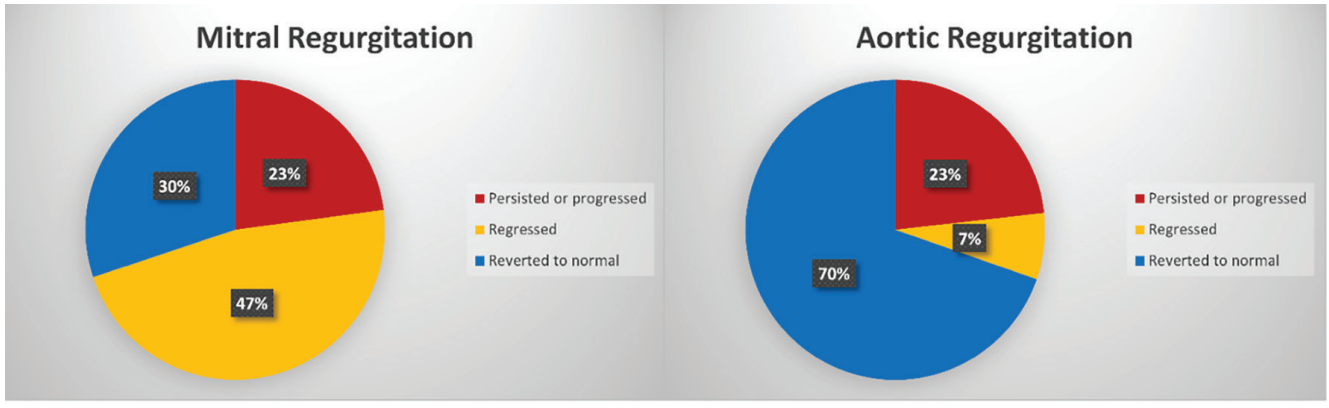


Figure 2. The progression of valvular lesions

Table 2. The comparision of the factors that affecting the course of mitral valve lesions				
Variable	**Cathegory**	**Persisted or progressed**	**Regressed**	**P-value**
Gender	Male	7	26	0.68
	Female	12	38	
Age		199.47±36.53	200.85±37.51	0.89
Age at diagnosis		141.41±23.20	129.32±35.16	0.18
ASO (IU/mL)		936	891	0.67
Corea	Positive	4	14	0.90
	Negative	14	50	
ASO: Antistreptolysin O				

Table 3. The comparision of the factors that affecting the course of aortic valve lesions				
Variable	**Cathegory**	**Persisted or progressed**	**Regressed**	**P-value**
Gender	Male	8	18	0.12
	Female	5	25	
Age		203.08±45.58	203.32±33.5	0.98
Age at diagnosis		130.41±30.5	135.58±35.7	0.65
ASO (IU/mL)		920.5	966	0.74
Corea	Positive	3	4	0.14
	Negative	10	39	
ASO: Antistreptolysin O				

more significant than previously believed. For this reason, echocardiographic findings have taken their place in the revised diagnostic criteria and are explained in detail in the literature (4).

Acute rheumatic carditis is a chronic process that begins in childhood and young adulthood and usually continues into adulthood and is still one of the most important causes of acquired heart valve diseases in low- and middle-income countries (6). The worsening of valvular lesions and the factors affecting it are of scientific interest and represent the most important points to be explained in preventing disease sequelae. Our study aimed to monitor the change in valvular involvement over time and to investigate the factors that may affect it.

In the study conducted by Meira et al., (7) only 9 patients (6.2%) in the follow-up of 146 patients with carditis had normal echocardiography findings. In that study, the recovery rates of the aortic and mitral valves were not given separately. In our study, the rate of complete recovery of aortic valve lesions was higher than that of mitral valve lesions, and the difference was statistically significant (69.7%, 30.1%, p<0.01). It was initially thought that the high recovery rate in aortic valve lesions may be related to the high incidence of mild involvement.

Whether gender influences the healing of valvular lesions has been investigated in many studies, but no significant difference has been found (8,9). In our study, when the improvement and deterioration rates of mitral and aortic valve lesions were compared according to gender, there was no statistically significant difference for either of the valve lesions (p=0.68, p=0.12).

In the study conducted by Beaton et al. (8) on 60 patients with a follow-up period of 2 years, younger age was defined as a risk factor for the persistence of valvular lesions. In our study, which had a much longer follow-up period, there was no statistically significant difference between the valve lesions when the improvement and deterioration rates of mitral and aortic valve lesions were compared based on age (p=0.89, p=0.98).

In a prospective study conducted by Zühlke et al. (9) with a follow-up period of 5 years, no relationship was found between age at diagnosis and progression of valvular lesions. The results of our study were in line with their findings.

Contrary to the study (8), which showed that the recovery rate of valve insufficiency was lower in patients with higher ASO values at the time of initial diagnosis, our study showedshowed the baseline ASO values for both mitral and aortic valves did not affect the rate of improvement or deterioration (p=0.67, p=0.74). The follow-up period in that study was 2 years, while the mean follow-up period in our study was 67 months (approximately 5 and a half years).

Benzathine penicillin prophylaxis is recognized as the most effective treatment in preventing recurrences of ARF. It is known that the recurrence rate is higher in patients who do not comply with treatment (10-12). In our study, 5 out of 7 patients with recurrence did not comply with regular prophylaxis. There are studies showing that valvular lesions are aggravated and that patients with recurrence experience greater worsening (13). On the contrary, in our study, all 7 patients with recurrence were found to have decreased valve involvement. We could not find any reason to explain this.

Surgical valve replacement emerges as a treatment option for valve insufficiency in the presence of medically uncontrolled cardiac insufficiency. The underlying pathology may be acute chordae rupture or significant valve regurgitation that does not respond to steroid therapy (14). Two of our patients underwent surgical valve replacement. In one patient, MVR and aortic valve replacement were performed together, and in the other patient, only MVR was performed. Neither of these patients had recurrence.

Study Limitations

This study has several limitations. The study was conducted at a single center, and the relatively small number of patients included constitutes the main limitation. Despite these limitations, we believe that this study will make a significant contribution to the literature due to its long follow-up period.

Conclusion

Most of the valve lesions that occur due to ARF carditis either regress or completely resolve in the long term. Our study had a long follow-up period of 15 years, and the recovery rate of aortic valve lesions was found to be much higher than that of mitral valve lesions. The high rate of mild involvement in aortic valve lesions initially may be effective in this. Apart from this, the valve lesion types that have a negative course, and the factors affecting them, still need to be studied further. Benzathine penicillin prophylaxis remains the most effective method of preventing recurrence.

Ethics

Ethics Committee Approval: The study protocol was approved by the Uludag University Faculty of Medicine Clinical Research Ethics Committee (approval no.: 2023-9/16, date: 26.04.2023).

Informed Consent: Written consent was obtained from all participants, and the study complied with the Declaration of Helsinki.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.H.H.T., F.U., O.M.B., Concept: M.H.H.T., A.G., A.G., F.U., O.M.B., Design: M.H.H.T., A.G., A.G., F.U., O.M.B., Data Collection or Processing: M.H.H.T., A.G., A.G., F.U., O.M.B., Analysis or Interpretation: M.H.H.T., A.G., F.U., O.M.B., Literature Search: M.H.H.T., A.G., A.G., F.U., O.M.B., Writing: M.H.H.T., A.G., A.G., F.U., O.M.B.

Conflict of Interest: No conflicts of interest were declared by the authors.

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