

Clinical features and mid- and long-term outcomes of pediatric patients with subclinical carditis

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A study to examine mid- and long-term outcomes in patients with subclinical carditis was conducted. Data obtained at the time of diagnosis and during the follow-up of 158 patients diagnosed with subclinical carditis were retrieved and analyzed. Most patients had isolated mitral insufficiency. Frequency of morphological changes in the mitral valve was significantly lower in patients with at least one additional Jones criterion both at baseline (10.3% vs. 48.8%, $p < 0.01$) and at the end of the follow-up (27.8% versus 43.5%, $p = 0.11$). Mean jet size for mitral (12.0 ± 8.8 versus 18.2 ± 5.5 mm, $p < 0.01$) and aortic (4.1 ± 4.0 versus 14.0 ± 5.8 mm, $p = 0.008$) insufficiency were decreased compared to baseline. Improvement in mitral insufficiency was more frequent among patients with more than five years of follow-up (82.6% versus 60.0%, $p = 0.039$). Subclinical carditis due to acute rheumatic fever is not a benign and temporary condition. These patients should be given secondary prophylaxis.

Key words: subclinical carditis, acute rheumatic fever, follow-up, mitral insufficiency, aortic insufficiency.

Rheumatic carditis is still the most important cause of acquired heart disease among children and young adults in developing countries. The severity of the first cardiac episode and recurrences are major determinants of the prognosis and natural course of the disease¹. Some researchers have proposed the term “subclinical carditis” for patients with rheumatic arthritis and chorea exhibiting no pathological cardiac sounds at auscultation but showing signs of pathological mitral and/or aortic valve insufficiency with Doppler echocardiography²⁻⁴. Subsequent studies have provided supporting evidence for “subclinical carditis” as a diagnostic category; however, the role of these findings in the diagnosis of acute rheumatic fever has been a subject of debate. At present, some researchers consider subclinical carditis a major diagnostic criterion for acute rheumatic fever diagnosis⁵⁻¹¹, while others view it among the minor criteria¹²⁻¹⁵. Based on the results of a study conducted by our team, we consider subclinical carditis as a major criterion for the diagnosis of acute rheumatic fever⁹.

In our center, we encounter patients with no pathological cardiac murmur who have no systemic, congenital, or infectious cardiac disease but present with arthritis due to rheumatic fever, Sydenham’s chorea or reactive arthritis and demonstrate pathological mitral and aortic insufficiency with Doppler examination (conventional and color). Patients evaluated echocardiographically for other reasons, such as chest pain, innocent murmur or syncope, who demonstrate pathological mitral and/or aortic insufficiency and have additional historical and clinical findings compatible with a previous attack of rheumatic fever are also frequently encountered. According to our treatment policy, these groups of patients receive secondary prophylaxis due to presumed subclinical carditis.

In this study, we aimed to examine the mid- and long-term outcomes in patients with subclinical carditis -in addition to rheumatic arthritis, arthralgia or chorea- and in patients with presumed previous attack of subclinical carditis.

Material and Methods

Patients

Patients evaluated at the pediatric cardiology department of Hacettepe University between June 2000 and January 2010 and diagnosed with current or previous subclinical carditis were included in this study. Patients were divided into two groups: Those with signs and symptoms consistent with acute rheumatic fever such as chorea, arthritis and arthralgia but with no overt cardiac involvement other than echocardiographic findings, and those who were echocardiographically evaluated for other reasons such as chest pain, syncope and innocent murmur and were incidentally found to have echocardiographic evidence of subclinical carditis. Patients diagnosed with clinical carditis were not included in the study. A total of 158 patients, 109 found incidentally and 49 with at least one Jones criterion, were diagnosed as subclinical carditis. Available demographic data, complaints during evaluation at the outpatient clinic, and physical examination and laboratory findings were retrieved from medical records.

Echocardiographic Evaluation

General Electric Vingmed System Five Performance® (Vingmed Sound, Horten, Norway) echocardiography device with 3.5 or 2.5 MHz transducer was used in this study. To obtain optimal imaging, echocardiographic evaluation was performed with the patient in the left lateral decubitus or supine position. The following views were obtained: parasternal long axis, parasternal short axis, apical four-chamber, subcostal frontal and caval, and suprasternal. Cardiac valves and chambers were evaluated. In addition, continuous wave (CW) Doppler echocardiography was done to evaluate mitral and aortic insufficiency.

Criteria set out by the World Health Organization (WHO) were used to differentiate between physiological and pathological mitral and aortic insufficiency¹⁶. Thus, pathological insufficiency was defined as follows: (1) color jet size >1 cm; (2) color jet visible in at least two positions; (3) Doppler flow velocity of jet with mosaic character ≥ 2.5 m/sec; and (4) holosystolic Doppler signal in mitral insufficiency and holodiastolic signal in aortic insufficiency. A

diagnosis of subclinical carditis was made when a patient had no murmur or only a soft 1-2/6 innocent systolic murmur of short duration in combination with pathological mitral and/or aortic insufficiency on echocardiography and historical and/or clinical findings compatible with rheumatic fever. Prolapse of the cardiac valves, increase in thickness of mitral and aortic leaflets and the presence of rheumatic nodules giving the valve a beaded appearance were considered as morphologic changes. Subclinical carditis patients with or without additional acute rheumatic fever criteria (i.e. patients with current and previous subclinical carditis, respectively) were compared with regard to changes in valvar characteristics during follow-up.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) version 17.0 for Windows was used for the data analysis. For comparison of categorical variables, chi-square test was used. Wilcoxon signed-rank test was used for continuous variables to examine the differences from baseline. A p value <0.05 was considered as statistically significant.

Results

Patients

Of the 158 patients included in the study, 38.6% were male and 61.4% were female. The mean age and body weight were 10.5 years and 36.6 kilograms, respectively. Detailed demographic and clinical characteristics of the patients are given in Table I. Heart rate was within the normal range in all of the patients. Among the major modified Jones criteria, erythema marginatum and subcutaneous nodules were not present in any of the patients.

Initial Echocardiography Findings

Table II shows the echocardiographic findings of the patients at the time of diagnosis. Left ventricular end-diastolic diameter, left ventricular end-systolic diameter, fractional shortening, and ejection fraction were within normal ranges in all patients¹⁷. The majority of the patients had isolated mitral insufficiency, and severity of insufficiency was mild in most of the cases (84.4%). Morphological changes in

Table I. Demographic and Clinical Characteristics of the Patients at the Time of Diagnosis (n=158)

Characteristics	
Age (y), mean±SD (range)	10.5±2.9 (4-17)
Male gender	61/158 (38.6%)
Body weight (kg), mean±SD (range)	36.6±12.3 (17-68)
ARF criteria	
Absence of any ARF criteria	109/158 (69.0%)
Presence of major criteria	
Arthritis	15/158 (9.5%)
Chorea	30/158 (19.0%)
Presence of minor criteria	
Fever	4/158 (2.5%)
Arthralgia	27/158 (17.1%)
Prolonged PR interval	9/140 (6.4%)
Elevated acute phase reactants	28/84 (33.3%)
Laboratory findings	
Anemia	12/108 (11.1%)
Leukocytosis	12/106 (11.3%)
Elevated ESR	23/96 (24.0%)
Elevated CRP	24/89 (27.0%)
Positive throat culture	5/40 (12.5%)
Elevated ASO	58/91 (63.7%)

Unless otherwise stated, data are presented as number of patients/number of patients with available data (percent).

ARF: Acute rheumatic fever. CRP: C-reactive protein. ASO: Antistreptolysin-O. ESR: Erythrocyte sedimentation rate. SD: Standard deviation.

the mitral valve, including prolapsus, thickening and nodularity were most frequently located at the anterior leaflet. At the time of initial examination, frequency of morphological changes in the mitral valve was significantly lower in patients with at least one additional Jones criterion compared to those without Jones criteria (48.8% vs. 13.3%, $p=0.01$). Aortic insufficiency was detected in 22 of the patients, and the insufficiency was defined as mild in all. Four patients had moderate tricuspid insufficiency.

Follow-Up

The mean duration of follow-up from initial echocardiographic evaluation was 32.6 ± 26.1 (3-110) months. Data on follow-up echocardiography was available in 135 patients (85.4%), with 111 (82.2%) having less than and 24 (17.8%) having more than five years of follow-up. The mean jet size for mitral insufficiency (12.0 ± 8.8 versus 18.2 ± 5.5 mm, $p<0.01$) and aortic insufficiency (4.1 ± 4.0 versus 14.0 ± 5.8 mm, $p=0.008$) significantly

decreased compared to baseline; however, mean jet velocity for mitral insufficiency did not change. Data on follow-up of mean jet velocity for aortic insufficiency was not available. Improvement in mitral and aortic insufficiency was evident in 64.4% and 68.4% of patients, respectively, with available follow-up data. Improvement in mitral insufficiency was significantly more frequent among patients with more than five years of follow-up (82.6% versus 60.0%, $p=0.039$). Although patients with or without any additional Jones criterion did not differ with regard to improvement in mitral insufficiency ($p=0.25$), morphological changes in the mitral valve were less frequent among patients with additional Jones criterion (arthritis or chorea) (43.5% versus 27.8%, $p=0.11$), similar to baseline.

Discussion

Carditis is the only sign of acute rheumatic fever that can cause permanent functional and morphological impairment. Recurrences increase morbidity and mortality by increasing

Table II. Echocardiography Findings of the Patients at the Time of Diagnosis (n=158)

Echocardiography finding	
Isolated MI	136/158 (86.1%)
Isolated AI	6/158 (3.8%)
Combined AI and MI	16/158 (10.1%)
Posterolateral MI jet direction	62/85 (72.9%)
Central MI jet direction	23/85 (27.1%)
Morphological changes in mitral valve	58/158 (36.7%)
MI jet size (mm), mean±SD (range)	18.2±5.5 (10-38)
MI jet velocity (m/sec), mean±SD (range)	3.5±0.7 (2.5-5.2)
AI jet size (mm), mean±SD (range)	14.0±5.8 (5-24)
AI jet velocity (m/sec), mean±SD (range)	3.0±0.7 (1.3-3.8)

Unless otherwise stated, data are presented as number of patients/number of patients with available data (percent). Data on MI jet size, MI jet velocity, AI jet size, AI jet velocity were available in 131, 97, 17, and 13 patients, respectively.

AI: Aortic insufficiency. MI: Mitral insufficiency. SD: Standard deviation.

the extent of cardiac injury. Some researchers have argued that valvular insufficiency may be present in up to 90% of the patients even in the absence of clinical signs of carditis^{14,18,19}. Although reported figures for concomitant occurrence of subclinical carditis with isolated chorea, isolated arthritis or arthralgia in the first episode are quite variable, the estimated frequency was reported as 16.8% in a comprehensive literature review²⁰.

When Duckett Jones proposed his diagnostic criteria for acute rheumatic fever in 1944, echocardiography had not yet been introduced for clinical use, and at that time, only a few reports on subclinical carditis were present. However, in subsequent years, an increasing number of studies on this diagnostic entity appeared in the literature. In 2000, the Task Force on Rheumatic Fever declared that subclinical carditis should not be considered a major diagnostic criterion for acute rheumatic fever due to possibility of “over-diagnosis”, on the basis of the assumption that subclinical carditis could be easily confused with physiological mitral and aortic insufficiency. The most recent guidelines rely on auscultation findings. However, if echocardiography is not performed in subjects with arthritis or arthralgia, or in subjects with typical or atypical signs and symptoms of acute rheumatic fever, a diagnosis of subclinical carditis can be overlooked, resulting in recurrences or severe cardiac involvement in young patients due to the absence of prophylaxis⁶. Accordingly, in a

community-based surveillance study in rural Pakistan with 9,430 participants, 54 cases of rheumatic cardiac disease were detected, of whom approximately 20% were not aware of the condition and only 8% were receiving secondary prophylaxis²¹. In a field study from Mozambique and Cambodia, a 10-fold increase in the number of diagnosed cases of rheumatic carditis was observed with the use of echocardiography vs. physical examination²². Accurate diagnosis of acute rheumatic fever is crucial for determining the need for secondary prophylaxis and its duration, indicating the importance of the diagnosis of subclinical carditis. In a study from India in which a predetermined set of echocardiographic criteria were used, a diagnosis of subclinical carditis was made by echocardiography in 15.6% of the patients in the absence of positive Jones criteria, with a reported sensitivity and specificity of 81% and 93%, respectively⁵. On the other hand, another study from India showed presence of carditis in only 86% of patients with a suspicion of clinical carditis¹¹. Echocardiography is useful for making a diagnosis of subclinical carditis and for confirming auscultation findings, and allows for estimation of the severity of myocarditis, pericarditis, and valvular regurgitation.

Subclinical carditis is a major diagnostic criterion in the guidelines in New Zealand and Australia^{23,24}. As stated earlier, subclinical carditis is considered a major diagnostic criterion by some authors⁵⁻¹¹ while others consider it a minor criterion¹²⁻¹⁵. Inclusion

of subclinical carditis among major criteria is expected to result in an 11-16% increase in the diagnosis of acute rheumatic fever, while decreasing the number of patients without a diagnosis⁶. Similarly, inclusion of monoarthritis and subclinical carditis as major criteria and mild fever as a minor criterion in the current diagnostic criteria has been reported to cause an increase in the number of acute rheumatic fever diagnoses²⁵. We also hold the view that subclinical carditis should be included among the major criteria and that these patients should be given secondary prophylaxis^{9,19}, since subclinical carditis does not appear to be a temporary and benign condition. For instance, in a prospective study, pathological valvular regurgitation detected by echocardiography was found to persist in 4/9 and 3/6 of Chilean patients with subclinical carditis after one and five years of follow-up, respectively⁷.

Our study points to the existence of cases in the community with no symptoms despite having subclinical carditis; thus, there may be undiagnosed asymptomatic cases of subclinical carditis who have never sought medical help. In our study, morphological changes of the mitral valve were detected in 36.7% and 38.1% of the subjects at the time of diagnosis and follow-up, respectively. In patients with additional major diagnostic criteria plus subclinical carditis, morphological changes were less frequent both at diagnosis and during follow-up, compared to those without having additional Jones diagnostic criteria. This might be because patients without additional Jones criteria could have been diagnosed as having “subclinical carditis” after the emergence of morphological changes, with no initial clinical signs such as joint disease or chorea. On the other hand, patients with major diagnostic criteria usually have manifest clinical signs such as joint disease or chorea resulting in a shorter course of disease before echocardiographic evaluation, which provides these patients with a chance to receive anti-inflammatory treatment and/or a chance to begin antibiotic prophylaxis before the occurrence of morphological changes. The rate of morphological changes in our patient group is similar to that in previous reports^{1,26}. Despite the absence of clinical carditis in our patients, structural mitral and aortic valve changes were observed at a similar frequency with some other studies involving

primarily patients with pansystolic murmur, suggesting that our findings were more likely to represent pathological rather than physiological changes, thus ruling out the possibility of “over-diagnosis”. The presence of the posterolateral direction of mitral insufficiency jet in 72.9% of our patients in the color Doppler examination provides additional evidence for the pathological character of these findings. This particular finding has been shown to increase diagnostic specificity for subclinical carditis¹².

Similar to previous studies, which included a follow-up for patients with subclinical carditis, improvement in mitral and aortic regurgitation was observed in the majority of subjects (64.4% and 68.4%, respectively)^{9,27}. In one of these studies, steroid use as an anti-inflammatory treatment resulted in faster improvement⁹. However, the average follow-up duration was longer in our study (32.6 months) when compared to these two studies (8.5 and 18.1 months). In addition, the proportion of patients with partial or total disappearance of mitral regurgitation was 60% in patients with a follow-up duration less than five years and 82.6% in those with a follow-up duration of five years or more. As all our patients received secondary prophylaxis, no recurrence among the study group was observed. Our literature search for subclinical carditis revealed only a few studies reporting long-term results, mostly in a small number of patients^{1,7}.

In the present study, patients diagnosed using recognized Jones criteria of joint findings (arthritis and arthralgia) and chorea and patients diagnosed with signs of previous subclinical carditis showed a similar degree of improvement in the long term. This result provides supportive evidence for the accuracy of the diagnosis of carditis and for the inclusion of subclinical carditis among the diagnostic criteria for acute rheumatic fever.

Antibiotic prophylaxis for the prevention of recurrences and early diagnosis of valvular insufficiency are prerequisites for reducing mortality and morbidity. However, use of echocardiography in the diagnosis, during the acute stages, and during follow-up of acute rheumatic fever and the duration of secondary prophylaxis in subclinical carditis are not well defined^{16,22}. Until more evidence is established with well-designed studies,

clinicians have to make their own decisions²⁰. On the other hand, WHO defines subclinical carditis as “possible rheumatic heart disease” and recommends secondary prophylaxis¹⁶. Recently, a recommendation has been made to continue secondary prophylaxis for at least 10 years after the last episode and/or until 25 years of age²⁸. In our institution, we continue secondary prophylaxis until 30 years of age.

Our study has several limitations, including inability to access some patient files, missing data in some files, and the small number of patients with long-term follow-up. However, improvement or disappearance of mitral insufficiency in patients with long-term follow-up suggests that subclinical carditis is not a physiological condition. The absence of objective criteria defining morphological changes observed in rheumatic fever is another limitation of our study. Further multicenter studies are needed involving a larger number of patients regarding the natural course and evolution of the morphological changes observed during the course of rheumatic fever.

In conclusion, echocardiography is clearly superior to auscultation in the assessment of presumed carditis. In suspicious cases of acute rheumatic fever, an echocardiographic evaluation should be performed for a definitive diagnosis in the early phase and for prognostic estimations during follow-up. Subclinical carditis is not a benign and temporary condition, and thus should be included among the major diagnostic criteria for acute rheumatic fever. These patients should be given secondary prophylaxis for a definitive period of time. In addition, patients with no congenital, systemic or infectious etiology for pathological mitral and/or aortic insufficiency as detected by Doppler echocardiography (conventional and color) should be carefully evaluated with detailed history and clinical findings; if an assumption of a diagnosis of previous subclinical carditis can be made, they should be given secondary prophylaxis.

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