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A Single-center Experience in Children with Acute Rheumatic Fever

Akut Romatizmal Ateşli Çocuklarda Tek Merkez Deneyimi

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Abstract

Objective: This retrospective study aimed to emphasize the importance of subclinical carditis in children with acute rheumatic fever before the revised 2015 Jones criteria.

Method: Throat culture, antistreptolysin O test, C-reactive protein and erythrocyte sedimentation titers, telecardiogram, electrocardiogram, and Doppler echocardiography findings of each patient were evaluated. Doppler echocardiography, examined by pediatric cardiologists was applied to each patient especially to screen subclinical carditis.

Results: In our study of 54 patients with acute rheumatic fever, the frequency of carditis including cases with subclinical carditis was found to be 74.1% (40 patients). And the other clinical findings were arthritis 70.3% (38 patients), Sydenham's chorea 13% (7 patients), erythema marginatum 1.9% (1 patient), while subcutaneous nodule was not seen in any of our patients. Cardiac involvement was not observed in 14 (25.9%) of 54 cases diagnosed with acute rheumatic fever. Of 54 acute rheumatic fever cases, isolated mitral valve regurgitation in 14 (25.9%), isolated aortic valve regurgitation in 2 (3.8%), and coexistence of mitral and aortic regurgitation in 24 (44.4%) cases were detected. Eighteen patients (45%) with mild carditis detected by echocardiography did not have clinical findings of carditis; these cases were considered as subclinical carditis.

Conclusion: To consider subclinic carditis long before 2015 Jones criteria provided our center to get more favourable outcomes in regard to morbidity and possible mortality in these patients. We think that physicians living in populations with moderate-and high-risk for acute rheumatic fever should pay more attentions to newly publicated issues related to carditis in addition to diagnostic criteria.

Keywords: Acute rheumatic fever, carditis, rheumatic arthritis

Öz

Amaç: Bu retrospektif çalışmanın amacı, revize edilmiş 2015 Jones kriterlerinden önce akut romatizmal ateşi olan çocuklarda subklinik karditin önemini vurgulamaktır.

Yöntem: Her hastanın boğaz kültürü, antistreptolizin O testi, C-reaktif protein ve eritrosit sedimantasyon titreleri, telekardiyogram, elektrokardiyogram ve Doppler ekokardiyografi bulguları değerlendirildi. Özellikle subklinik kardit taraması amacıyla her hastaya pediatrik kardiyologlar tarafından Doppler ekokardiyografi uygulandı.

Bulgular: Elli dört akut romatizmal ateş tanılı hastayı kapsayan çalışmamızda subklinik karditli olgulara dahil edildiğinde kardit sıklığı %74,1 (40 hasta), artrit %70,3 (38 hasta), Sydenham koresi %13 (7 hasta), eritema marjinatum %1,9 (1 hasta) idi. Hiçbir hastamızda deri altı nodül görülmedi. Akut romatizmal ateş tanısı alan 54 olgunun 14'ünde (%25,9) kardiyak tutulum yoktu. Kalp kapağı tutulumu olan 40 olgunun 14'ünde (%25,9) izole mitral kapak yetmezliği, 2'sinde (%3,8) izole aort kapak yetmezliği, 24'ünde (%44,4) mitral ve aort yetmezliği birlikteliği saptandı. Ekokardiyografi ile hafif kardit saptanan 18 hastanın (%45) klinik kardit bulgusu yoktu; bu vakalar subklinik kardit olarak değerlendirildi ve romatizmal kardit olarak kabul edilerek tedavi edildi.

Sonuç: Subklinik karditin 2015 Jones kriterlerinden çok daha önce dikkate alınması, merkezimizin bu hastalarda morbidite ve olası mortalite açısından daha olumlu sonuçlar almasını sağlamıştır. Akut romatizmal ateş açısından orta ve yüksek riskli popülasyonlarda yaşayan hekimlerin, tanı kriterlerinin yanı sıra kardit ile ilgili yeni yayınlanmış konulara daha fazla dikkat etmesi gerektiğini düşünüyoruz.

Anahtar kelimeler: Akut romatizmal ateş, kardit, romatizmal artrit

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Introduction

Acute rheumatic fever (ARF) is a late complication of upper respiratory tract infections due to *Group A Beta Hemolytic Streptococcus* and develops as a humoral (antibody-mediated) immune response. ARF mainly involves the joints and heart, less commonly the central nervous system, skin, and subcutaneous tissue. It is an inflammatory disease involving serous and serous surfaces. During the acute phase of rheumatic fever, there can be an increase in morbidity and even death in severe cases. However, in long-term outcomes seen in young adults, the main problem caused by ARF is rheumatic heart disease (RHD) (1-3).

ARF remained the leading cause of acquired heart disease in children until the late 20th century. Improvements in the general standard of living, hygiene and sanitation, a better understanding of the disease, appropriate antimicrobial use, and ease of access to healthcare have been seen with a significant reduction in the incidence of ARF and the prevalence of RHD (3). However, it remains a significant public health problem in moderate and high-risk populations and vulnerable colonies in low-risk populations (4).

With the widespread use of echocardiography in the last 20 years, subclinical (silent) carditis detection has come to the fore. In the 1992 Jones and 2002 World Health Organization (WHO) recommendations, subclinical carditis detected by Doppler echocardiography was not included as a diagnostic criterion (5,6). In 2015, the Jones criteria were updated to include different diagnostic criteria for low-risk and moderate-and high-risk populations. In the moderate and high-risk populations, including Turkey and low-risk populations, subclinical carditis was accepted as the major criterion by Doppler echocardiography (6).

This is a study emphasizing our clinical practice in which patients with subclinical carditis were also included at the time when the 2015 ARF diagnostic criteria were not published yet.

Materials and Methods

The study analysed retrospectively the files of 54 pediatric cases, who were diagnosed with ARF between January 2009 and April 2013. It did not include recurrent ARF cases or cases with uncertain diagnoses.

Ethical approval for this study was obtained from the Ethics Committee of Necmettin Erbakan University (date: 29.01.2013, approval number: 2013/345).

Patients with ARF were diagnosed using the 1992 Modified Jones criteria. Major criteria included carditis, migratory and aseptic polyarthritis, subcutaneous nodules, erythema marginatum, and Sydenham's chorea; minor criteria included PR interval prolongation on electrocardiogram (ECG), polyarthralgia, fever, C-reactive protein (CRP) and erythrocyte sedimentation (ESR) titers increase. In the evidence of preceding *Group A Streptococcal* infection, the diagnosis of ARF was made with the presence of 2 major or 1 major and 2 minor criteria. Polyarthritis was defined as swelling, redness, warmth, and limitation of movement in 2 or more joints. Sydenham chorea was diagnosed after other causes of chorea were excluded (7). Patients considered to have clinical carditis had a pathological murmur with or without heart failure, and also, aortic and/or mitral regurgitations were demonstrated by Doppler echocardiography. Cases without a murmur or clinical findings were screened for subclinical carditis to detect pathological mitral valve regurgitation and/or aortic valve regurgitation according to WHO criteria in Doppler echocardiography (8,9). Subclinical carditis was defined as mild carditis. Patients with moderate valvular regurgitation and murmur but no cardiomegaly were defined as moderate carditis. Patients with severe valvular regurgitation, murmur and cardiomegaly were defined as severe carditis.

Each patient's blood antistreptolysin O (ASO), CRP and ESR, throat culture, ECG, Doppler echocardiography, and telecardiogram findings were evaluated.

Statistical Analysis

Statistical Package for Social Sciences (SPSS for Windows Version 16.00, Chicago, IL, USA) package program was used to evaluate the findings. The conformity of all variables to the normal distribution was investigated using the Shapiro-Wilks test. Pearson chi-square test and Fisher's exact test was used to compare categorical variables between groups. A p-value of <0.05 was considered statistically significant.

Results

A total of 54 patients, including 26 females and 28 males aged 5 to 18 years, were diagnosed with ARF. There were 22 patients aged 5-9 years (40.7%), 25 patients aged 10-14 years (46.3%), and 7 patients over 14 years old (13%). The mean age at the time of diagnosis was 10.1±2.88 years. The follow-up period of 54 ARF cases was 15.12±8.5 months in patients with carditis and 20.8±14.1 months in patients with arthritis.

Among the major criteria, 22 patients (40.7%) had only one major criterion; 9 (16.7%) had isolated carditis, and 13 (24%) had isolated polyarthritis. There were 32 patients (59.3%) with two major criteria; 24 (44.4%) had carditis and polyarthritis, 7 (13%) had carditis and chorea, and 1 (1.9%) had polyarthritis and erythema marginatum. No one had more than two major criteria.

Among the major criteria, the incidence of carditis and Sydenham's chorea was found to be higher in female cases, and polyarthritis was high in male cases ($p<0.05$) (Table 1).

There was no statistically significant difference in the incidence of carditis, arthritis, Sydenham's chorea, and erythema marginatum among all age groups ($p>0.05$).

Among the minor criteria, acute phase reactants increase was observed in 53 patients (98.1%) arthralgia in 41 (75.9%), fever in 7 (13%), and prolongation of PR interval on ECG in 6 patients (11.1%). Considering the distribution of supportive findings of previous streptococcal infection, ASO titre elevation was detected in 53 (98.1%) cases, and streptococcal growth was not observed in the throat culture of all cases. One patient had moderate carditis and Sydenham's chorea, but there was no increase in ASO titer as a supportive finding.

The distribution of the increase of acute phase reactants, the most common minor criterion in our cases, was most frequently observed in ESR titres, followed by the rise in CRP titers.

Cardiac involvement was not observed in 14 (25.9%) of 54 cases diagnosed with ARF. Of 54 ARF cases, isolated mitral valve regurgitation in 14 (25.9%), isolated aortic valve regurgitation in 2 (3.8%), and coexistence of mitral and aortic regurgitation in 24 (44.4%) cases were detected. Of patients with carditis (n=40), there was mild carditis in 18 patients (45%), moderate carditis in 12 patients (30%), and severe carditis in 10 patients (25%). Eighteen patients (45%) with mild carditis detected by echocardiography did not have clinical findings of carditis; these cases were considered subclinical carditis (Table 2).

Table 1. Distribution of major criteria by sex

	Male		Female		p-value
	n	%	n	%	
Carditis	14	53.8	26	92.9	0.001*
Polyarthritis	23	88.5	15	53.6	0.005*
Sydenham's chorea	0	0	7	25.0	0.007**
Erythema marginatum	1	3.8	0	0	0.481**

*: Pearson chi-squared test, **: Fisher's exact test was used to compare categorical variables

Only one of 54 cases diagnosed with rheumatic carditis did not return for a check-up after starting treatment. Therefore, it was not included in the evaluation of valve involvement by echocardiography after treatment. Among cases with carditis (n=39) 9 patients (23%) were completely healed in the cardiac findings at the end of the follow-ups. Carditis in the remaining patients persisted, albeit with a decrease. No ARF attacks were observed as our patients received secondary prophylaxis. When we evaluated mitral and aortic valve regurgitation separately, 10 (27%) of 38 patients with mitral valve regurgitation had improved entirely, 23 (62.2%) had decreased, and 4 (10.8%) had remained at the same level. Of the 32 patients with aortic valve regurgitation, 17 (43.5%) had completely recovered, 9 (23%) had decreased, and 6 (15.3%) had remained at the same level of aortic valve regurgitation (Table 3).

Table 2. Distribution of valve involvement according to clinical degrees at the time of diagnosis

Patient number/percentage		n	%
Subclinical carditis n=18	Mild AR	2	5.0
	Mild MR	7	17.5
	Mild MR+ mild AR	9	22.5
Clinical carditis n=22	Moderate AR	6	15.0
	Severe MR	1	2.5
	Moderate MR+ mild AR	4	10.0
	ModerateMR+ moderate AR	2	5.0
	Severe MR+ mild AR	7	17.5
	Severe MR+ moderate AR	1	2.5
	Severe MR+ severe AR	1	2.5
Total		40	100

MR: Mitral valve regurgitation, AR: Aortic valve regurgitation

Table 3. Distribution of valve involvement according to clinical degrees after treatment

Patient number/percentage	n	%
No valve involvement	9	23
Mild AR	3	7.7
Mild MR	12	30.8
Moderate MR	2	5.1
Severe MR	1	2.6
Mild MR+ mild AR	6	15.4
Moderate MR+ mild AR	3	7.7
Moderate MR+ moderate AR	1	2.6
Mild MR+ moderate AR	2	5.1
Total	39	100

MR: Mitral valve regurgitation, AR: Aortic valve regurgitation

Table 4. Frequency of Modified Jones Criteria detected in studies

		Ravisha et al. (13) n/%	de Loizaga et al. (14) n/%	Karaaslan et al. (15) n/%	Erdem et al. (16) n/%	Yılmaz et al. (17) n/%	Our study n/%
Major criteria	Isolated poliarthritis	101 (40.4%)	208 (30.4%)	88 (32.1%)	47 (12.5%)	11 (16.9%)	13 (24%)
	Isolated Carditis	37 (14.8%)	336 (49.1%)	-	56 (14.9%)	49 (75.4%)	9 (16.7%)
	Sydenham's chorea	47 (18.8%)	254 (37.1%)	19 (7%)	14 (3.7%)	-	-
	Subcutaneous nodules	3 (1.2%)	24 (3.5%)	-	-	-	-
	Erythema marginatum	-	59 (8.6%)	-	1 (0.3%)	-	-
	Arthritis, carditis	68 (27.2%)	-	135 (49.2%)	219 (58.1%)	5 (7.7%)	24 (44.4%)
	Carditis, S. chorea	-	-	30 (10.9%)	25 (6.6%)	-	7 (13%)
	Arthritis, E. marginatum	-	-	-	-	-	1 (1.9%)
	Carditis, S. nodules	-	-	2 (0.7%)	1 (0.3%)	-	-
	Carditis, E. marginatum	-	-	1 (0.4%)	1 (0.3%)	-	
	Carditis, arthritis, S. chorea	-	-	-	12 (3.2%)	-	-
Minor criteria	Fever	-	330 (48.2%)	-	194/376 (51.6%)	-	7 (13%)
	Arthralgia	-	131 (19.2%)	-	268/377 (71.1%)	-	41 (75.9%)
	Prolongation of PR interval	-	63 (9.2%)	-	115/297 (38.7%)	-	6 (11.4%)
	APR elevated	-	315 (46.1%)	-	221/312 (70.8%)	-	53 (98.1%)

S. chorea: Sydenham's chorea, S. nodules: Subcutaneous nodules, E. marginatum: Erythema marginatum, APR: Acute phase reactants (C-reactive protein and erythrocyte sedimentation titers) PR interval: The time from the beginning of the P wave to the beginning of the QRS complex in electrocardiography

Discussion

In the 2005 systematic review, there were 471,000 new cases of ARF each year, with 15.6-19.6 million existing RHD cases and 350,000/year ARF deaths as a result of RHD (3). Tibazarwa et al. (10), in a study conducted in 10 countries, found that the average global incidence of ARF was 19/100,000, and the frequency was variable according to geographical regions and societies. Organisation for economic co-operation and development countries were grouped under 3/100,000 cases as a low-risk society, 3-25/100,000 cases as a moderate-risk group, and over 25/100,000 cases as high risk. Turkey was in the moderate-risk group with a prevalence of 21/100,000 (11). In a study of the first attack of 1103 ARF patients in Turkey in 2016, the estimated incidence rate of ARF was 8.84/100,000 (12).

In 2018, WHO identified actions to improve living conditions, effectively treat upper respiratory tract infections, diagnose the disease in its early stages, and prevent recurrent attacks by fully implementing penicillin prophylaxis. ARF and RHD have been unanimously accepted as a global health priority (4).

ARF was seen most commonly in children between the ages of 5-15 years (3). In the study conducted by Ravisha et al. (13) on 550 patients in India between 1971 and 2001, the mean age was 9.6 years. In a retrospective review of 947 cases in 22 US pediatric institutions between 2008 and 2018, the mean age was 9 years (14). In the study conducted by Karaaslan et al. (15) in Konya between 1993 and 1998 on 274 patients, the mean age was 12.7±2.9 years. In a retrospective review of 377 cases diagnosed with ARF in Çukurova/Turkey between 1997 and 2017, the largest age group were between 9 and 12 years and the mean age was 11±2.6 years (16). In our study, the mean age of the patients diagnosed with ARF was 10.1±2.88 years. The youngest patient was 6 years old, and the oldest was 15 years old, which is consistent with the literature.

In the literature, the most common significant clinical finding in ARF was arthritis, while carditis was the second most common clinical finding. Sydenham's chorea occurs in 30% of cases (3). In 1971-2001, Ravisha et al. (13) examined patients with ARF as the most common arthritis, second most commonly carditis. de Loizaga et al. (14) examined in 2008-2018, carditis was the most common in their patients and Sydenham's chorea was the second most common. Karaaslan et al. (15) found the most common arthritis in their patients between 1993-1998 and carditis was the second most common. Erdem et al. (16) found the most common carditis and arthritis was the second most common finding. Yılmaz et al. (17) found the most common carditis in their patients between 2010-2014 (Table 4). Gürses et al. (12) found the incidence of clinical carditis 53.5%, subclinical carditis 29.1%, polyarthritis 52.8%, aseptic monoarthritis 10.3%, polyarthralgia 18.6% and Sydenham's chorea 7.9%. In our study of 54 patients with ARF, the frequency of carditis, when including the cases with subclinical carditis, was 74.1% (40 patients) and then arthritis in 70.3% (38 patients). Sydenham's chorea was in 13% (7 patients) and erythema marginatum in 1.9% (1 patient). At the same time, subcutaneous nodules were not seen in any of our patients. The coexistence of arthritis and carditis was observed in 44.4% (24 patients), the coexistence of carditis and Sydenham's chorea in 13% (7 patients), and the coexistence of arthritis and erythema marginatum in 1.9% (1 patient). Carditis was present in all of Sydenham's chorea patients. We thought that the reason why carditis was detected more often than arthritis was that subclinical carditis was taken into consideration in our centre at that time and that most of the cases with arthritis were treated in primary or secondary care centres. However, cases with suspected carditis were mainly referred to our tertiary health centre.

When we researched the literature, apart from Sydenham's chorea (more common in females), there was no significant sex difference in major findings in other Jones criteria (18). In the study of Karaaslan et al. (15) in 1993-1998, arthritis and carditis showed an equal distribution between the sexes, while Sydenham's chorea was more common in female patients. In the multicenter study of Orsini et al. (19), in which the psychiatric conditions of patients diagnosed with ARF were evaluated, Sydenham's chorea was more common in the female sex. In our study, carditis and Sydenham's chorea incidence was statistically higher in female patients than in males. Although the reason for this association was not completely clear, it can be explained by intrinsic factors such as autoimmune susceptibility.

Of our patients with carditis (n=40), 38 (95%) had mitral valve regurgitation, and 32 (80%) had aortic valve regurgitation. Isolated mitral valve regurgitation was observed in 14 patients (35%), isolated aortic valve regurgitation in 2 patients (5%), and coexistence of mitral and aortic valve regurgitation in 24 patients (60%). In the study of Erdem et al. (16) in 1997-2017, the most commonly affected valve was isolated mitral valve regurgitation (54.9%), followed by a coexistence of mitral and aortic valve regurgitation (34%) and isolated aortic valve regurgitation (5.7%). In the study of Yılmaz et al. (17) in 2010-2014, out of 65 patients diagnosed with ARF, 54 had carditis. Isolated mitral valve regurgitation was observed in 14 patients (21.5%), isolated aortic valve regurgitation in 10 patients (15.4%), and coexistence of mitral and aortic valve regurgitation in 22 patients (33.9%). In our study, compatible with other studies, mitral valve involvement was the most common, followed by the aortic valve.

In 2000, the American Hearth Association (AHA) emphasised the importance of subclinical carditis, which can be detected by echocardiography, as an indicator of ARF. However, the authors concluded that there was insufficient evidence to include subclinical carditis as a diagnostic criterion. It was also emphasised that the detected subclinical carditis might reduce the specificity of Jones criteria and lead to the diagnosis of excessive ARF and the overuse of long-term penicillin prophylaxis due to the diagnosis (20). These prevalence studies have been conducted since then, emphasising the importance of subclinical carditis among patients with ARF. In a meta-analysis of 23 studies in 2007, 16.8% of subclinical carditis was shown in ARF, and 44.7% of these patients had worsened valve involvement over time (21). It had been emphasised that valvular regurgitation findings may represent early RHD due to the pathological prevalence of subclinical carditis detected in Doppler echocardiography according to the diagnostic criteria recommended by WHO for RHD at the time of diagnosis (22).

RHD, the only long-term consequence of ARF, continued unabated among middle-income and low-income communities (22). Subclinical carditis was relatively common in ARF. The reported prevalence of subclinical carditis in ARF was ranges from 0 to 53%. Since 2004, the WHO had recommended echocardiographic screening for RHD and ARF in high-prevalence regions (8,9). In 2005, a joint WHO and National Institutes of Health working party established insufficient experience with normal echocardiographic findings in children and the

concern that echocardiography might be overly sensitive in some children with standard valvular structure and function variation. It had accelerated the development of an internationally validated, evidence-based echocardiographic diagnostic guideline for RHD. The 2012 World Heart Federation aimed to reduce the burden of RHD worldwide by defining minimum echocardiographic criteria for diagnosing RHD (22). Therefore, since we had already performed echocardiography on every ARF patient with arthritis, carditis, and Sydenham's chorea, we accepted subclinical carditis as carditis according to the echocardiographic criteria 2012. After screening for subclinical carditis with Doppler echocardiography, we thought that we missed no case of carditis according to the new Jones criteria. Therefore, we revealed that morbidities and also possible mortalities might be prevented with the follow-up of these patients as carditis long before the 2015 Jones criteria. However, there might be missed cases in patients with isolated monoarthritis or monoarthralgia.

In 2015, the AHA recommended stating the population as low and moderate/high-risk groups with a successful revision, applying echocardiography to patients with suspected ARF, and accepting subclinical carditis as the major criterion in all risk groups (23). In our study between 2009 and 2013, as recommended by WHO, we applied the Doppler echocardiography criteria for pathological mitral and/or aortic valve regurgitation to detect subclinical carditis. Thus, owing to successful management and follow-up of these patients was provided to obtain more favourable outcomes. The Modified Jones Criteria, published later and renewed in 2015, also showed the accuracy of our approach at that time.

Study Limitations

Our study has some limitations. The last patient recruitment was completed in 2013. Unfortunately, we could not collect the 10-year results because some of the patients passed to other centres for follow-up and also transitioned into adulthood.

Conclusion

We suggest that investigating cardiac involvement with Doppler echocardiography is so crucial when any major findings of ARF are suspected, especially in moderate- and high-risk populations. Appropriate treatment and prophylaxis for those with carditis will significantly contribute to the reduction of morbidity and mortality due to RHD. Between 2009 and 2013, we followed and treated our patients by recognising subclinical carditis as a major criterion, showing the accuracy of our approach prior to the 2015 Modified Jones Criteria. Therefore, we think that physicians living in populations with moderate-and high-risk for ARF should pay more attention to newly publicated issues related to carditis in addition to diagnostic criteria.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the Ethics Committee of Necmettin Erbakan University (date: 29.01.2013, approval number: 2013/345).

Informed Consent: Consent was obtained from the formal guardians.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: N.B., Concept: N.B., F.Ş., T.B., Design: N.B., F.Ş., T.B., Data Collection or Processing: N.B., Analysis or Interpretation: F.Ş., T.B., Literature Search: N.B., Writing: N.B.

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