A Diagnostic and Clinical Approach to Acute Myopericardial Syndromes in Children and Adolescents

Çocuk ve Adölesanlarda Akut Miyoperikardiyal Sendromlara Tanısal ve Klinik Yaklaşım

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ABSTRACT

Objective: Acute myopericardial syndromes (myopericarditis and perimyocarditis) are among the most challenging diseases to diagnose and treat in pediatric cardiology. The true incidence of the diseases is unknown because the disease can be subclinical or mild enough to go unrecognized in the context of a viral syndrome. The clinical manifestations of acute myopericardial syndromes vary widely from typical chest pain and electrocardiogram changes to atypical chest pain, non-specified electrocardiography changes and subclinical left ventricular dysfunction. The aim of this study is to help pediatricians in the evaluation and management of these common and complex clinical syndromes.

Material and Methods: Patients who had been diagnosed with myopericarditis or perimyocarditis at Dr. Sami Ulus Maternity, Children's Health and Diseases Training and Research Hospital between 2010 and 2019 were retrospectively evaluated. Patients who had a fulminant form of myocarditis or progressing to dilated cardiomyopathy were excluded from the study. The medical records of the patients were examined, and their age, gender, diagnostic tests and diagnosis were all evaluated.

Results: During the study period, the records of 260 patients were obtained. 47 patients were excluded from the study because of fulminant myocarditis and progression to dilated cardiomyopathy. Of the remaining 213 patients, 68% were male, 32% were female and the median age was 156 months (32 to 212 months). Patients diagnosed with perimyocarditis and myopericarditis had been admitted with a complaint of chest pain and the diagnosis was made according to their history, physical examination, electrocardiography and echocardiography findings.

Conclusion: Pediatricians should be aware of the clinical signs and symptoms that increase the index of suspicion for acute myopericardial syndromes because prompt referral to the emergency department and access to specialists with expertise in the care and support of these patients is imperative.

Key Words: Children, Myocarditis, Pericarditis

ÖZ

Amaç: Akut miyoperikardiyal sendromlar (miyoperikardit ve perimiyokardit) pediatrik kardiyolojide tanı ve tedavisi en zorlayıcı hastalıklardır. Bu hastalıkların gerçek insidansı bilinmemektedir, çünkü viral bir sendrom ile ilişkili olarak belirtileri hafif veya subklinik olabilir. Akut miyoperikardiyal sendromların klinik bulguları tipik göğüs ağrısı ve elektrokardiyografi değişikliklerinden, atipik göğüs ağrısı, özgün olmayan elektrokardiyografi değişiklikleri ve subklinik sol ventrikül disfonksiyonuna kadar değişkenlik gösterir. Bu çalışmanın amacı çocuk doktorlarının bu yaygın ve karmaşık klinik sendromları değerlendirmesine ve yönetmesine yardımcı olmaktır.

Gereç ve Yöntemler: 2010-2019 yılları arasında Dr. Sami Ulus Kadın Doğum ve Çocuk Sağlığı ve Hastalıkları Eğitim ve Araştırma Hastanesinde miyoperikardit veya perimiyokardit tanısı alan hastalar geriye dönük olarak değerlendirildi.

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Fulminan form miyokardit olan veya dilate kardiyomiyopatiye ilerleyen hastalar çalışma dışı bırakıldı. Hastaların tıbbi kayıtları incelendi ve yaş, cinsiyet, tanısal testleri ve tanıları değerlendirildi.

Bulgular: Çalışma süresi boyunca 260 hastanın bilgilerine ulaşıldı, 47 hasta fulminan miyokardit ve dilate kardiyomiyopatiye ilerleme nedeniyle çalışma dışı bırakıldı. Kalan 213 hastanın % 68'i erkek,% 32'si kadın ve ortanca yaş 156 ay (32-212 ay)'dı. Perimiyokardit ve miyoperikardit tanısı alan hastalara göğüs ağrısı yakınması ile başvurmuş ve tanı öykü, fizik muayene, elektrokardiyografi ve ekokardiyografi bulguları ile konulmuştu.

Sonuç: Çocuk doktorlarının, miyoperikardiyal sendromların klinik belirti ve bulguları için farkındalıklarını ve şüphe eşiklerini artırmaları, bu hastaların erken dönemde acil servise ve bu hastalıkların tanı ve tedavisi konusunda uzman merkezlere ulaşımı için önemlidir.

Anahtar Sözcükler: Çocuk, Miyokardit, Perikardit

INTRODUCTION

Myocarditis is an inflammatory disease of the cardiac muscle caused by myocardial infiltration of immunocompetent cells following any kind of cardiac injury (infectious, autoimmune, toxic, drug-induced/hypersensitive and vasculitis) (1). Acute pericarditis is an inflammatory pericardial syndrome with or without pericardial effusion (2). Clinically, acute pericarditis and myocarditis commonly coexist (3). As the pericardial sac has two layers, a fibrous parietal layer and a serous visceral layer also known as the epicardium, adhering to the surface of the myocardium (4). Furthermore, their clinical manifestations are similar, and they are often associated with chest pain, increased cardiac biomarkers and ST-segment elevation, ST-T changes in electrocardiography (5). Specific considerations apply to cases with pericarditis and concomitant myocardial inflammatory involvement, usually referred to in literature as myopericarditis (3,6). Myopericarditis is defined as a primarily pericarditic syndrome with concomitant myocardial involvement and inflammation (3). Perimyocarditis specifies a primarily myocarditic syndrome with pericardial involvement (7,8). Patients with acute myopericarditis present a sudden onset of chest pain, which is sharp in nature and usually in the precordial/retrosternal area (8,9). Pain is classically worsened with inspiration and is often positional, increased when supine, and relieved with sitting or leaning forward (10). Myopericarditis may involve the phrenic nerve which innervates the trapezius muscles, resulting in pain in the back and shoulders. The pain may radiate to the neck, left shoulder, and jaw (10). Symptoms can be associated with cough, rhinorrhea, low-grade fever, and shortness of breath (8-10). The clinical manifestations of perimyocarditis can range from atypical chest pain with non-specific electrocardiographic abnormalities in the setting of normal left ventricular systolic function to subclinical left ventricular dysfunction and arrhythmia (7,8). Acute perimyocarditis and myopericarditis commonly coexist in the clinical setting because they share common causal agents, mainly cardiotropic viruses (11). Although they can have the same etiologies and symptoms often overlap, their prognosis and treatment differ significantly. Early suspicion and recognition of signs and symptoms are important because their follow-up, prognosis and treatment differ significantly. This study aims to reveal the key points that may help in the differential diagnosis of perimyocarditis and myopericarditis by investigating the clinical signs and symptoms, diagnostic tests, and natural history of these diseases.

MATERIALS and METHODS

We performed a single-center retrospective observational study in Dr. Sami Ulus Maternity, Children's Health and Diseases Training and Research Hospital over a 9-year period from 2010 to 2019. Data were obtained from a review of medical records and included the age, gender, symptoms at presentation, final discharge diagnosis, peak troponin values and physical examination features. The cut-off value of elevated troponin was >0.06 ng/ml. The degree of troponin elevation was classified as mild (<1ng/ml), moderate (1-50 ng/ml) and severe (>50 ng/ml). The results of the cardiac diagnostic studies were recorded including electrocardiogram (ECG), chest X-ray, echocardiogram, cardiac magnetic resonance imaging (MRI) and rhythm Holter monitor. Left ventricular (LV) end-diastolic and end-systolic dimension, interventricular septum and left ventricle posterior wall thickness dimensions in systole and diastole, ejection fraction (EF) and fractional shortening (SF) were calculated from two-dimensional guided M-mode echocardiographic tracings obtained at the parasternal long axis position using Teicholz formula (12). LV dysfunction was defined as LV EF<54% and LV SF<28%. LV dilatation increased and decreased LV wall thickness were determined according to pediatric echocardiography normagrams (12,13). The regional wall motion abnormalities were evaluated with two-dimensional echocardiography and visual assessment (12). The eventual final diagnoses were documented based on the clinical impression of the attending cardiologist. Patients who had a fulminant form of myocarditis and progressing to chronic dilated cardiomyopathy were excluded from our study. Myopericarditis was diagnosed by the presence of elevated troponin levels and at least two of the following criteria: pericarditis-related chest pain, pericardial friction rub, characteristic 4 stage ECG abnormalities (First, diffuse ST-segment elevation that occurs in all leads (except for V1 and aVR) with diffuse PR segment depression; second, the ST segment returns to baseline and the T wave flattens; third, the T wave inverts and there is potential ST-segment depression; and fourth, the ECG returns to normal over the course of weeks or months), and/or pericardial effusion (14). Perimyocarditis was diagnosed by the presence of elevated troponin levels, non-specific chest pain, resting tachycardia,

non-specific ST segment changes and T-wave inversion, increased ventricular end-systolic or diastolic dimensions, reduced shortening or ejection fractions, atrioventricular and semilunar valve regurgitation and regional wall motion abnormalities (15). Some of patients with perimyocarditis had persistent echocardiographic abnormalities (LV dilatation and/or dysfunction) although their ECG features and troponin values returned to normal. The diagnosis of perimyocarditis was confirmed in these ten patients by the presence of delayed myocardial enhancement as seen on performing cardiac MRI (16). The distinction of perimyocarditis and acute coronary syndrome was made according to chest pain characteristics and ECG findings. Differential characteristics of perimyocarditis may be listed as; non-anginal chest pain (sudden-onset sharp pain, lasts over 30 minutes, not radiates to the left arm/shoulder, jaw and neck, can radiate to the ridges of both trapezius muscles, worsens with inspiration, increases with supine and relieves with sitting), diffuse ST-segment elevation without reciprocal ST depression, concave ST-segment morphology, ST-segment elevation in lead II greater than III, without any ST depression in aVL, ST/T-wave ratio in V6 greater than 0.25 and no new Q waves (17).The study was approved by the local ethics and research committee (Protocol: 2019/11-21).

Statistical Methods

The statistical analysis was performed by SPSS (Statistical Package for the Social Sciences, Chicago, IL, and version 21.0). Categorical data were presented using frequencies and percentages, while continuous data were analyzed and presented with mean (and standard deviation, SD) or median (and interquartile range, IQR) depending on the normality of distribution. Normal distribution of samples was detected by Kolmogorov-Smirnov analysis. Comparisons of peak troponin I values of myopericarditis and perimyocarditis patients were performed using two independent sample t tests for normally distributed variables and by Mann–Whitney U test for non-normally distributed ones. Statistical significance for all analyses was assumed at $p<0.05$.

RESULTS

A total of 260 patients were identified who had been diagnosed with myopericardial syndromes over the 9-year study period. A total of 47 were then excluded due to fulminant myocarditis and progression to dilated cardiomyopathy, leaving 213 patients as our study group. The median age at presentation was 180 months in and 138 months in group. Most patients were male in both groups (63% myopericarditis and 79% perimyocarditis group). First presentation place was emergency department in most of patients. Chest pain was the most common complaint for both groups (94% myopericarditis and 85% perimyocarditis group). Systemic complaints at presentation (fever, fatigue, and myalgia) were markedly more common in myopericarditis patients (85% versus 15%). On the other hand history of a viral illness was more common in perimyocarditis patients (85% versus 12%). The physical examinations of all patients were within normal limits except five patients with myopericarditis who had mild tachypnea and dyspnea. Patient demographic data are described in Table I. The most common ECG findings of myopericarditis patients were four stage ECG changes (90%) and PR segment elevation (42%). Perimyocarditis patients had most commonly nonspecific ST-T abnormalities (95%) and sinus tachycardia (85%) in ECG. The most common chest X-ray findings were cardiomegaly in both groups. All patients underwent an echocardiographic evaluation; myopericarditis patients had normal LV function and pericardial effusion (25%), perimyocarditis patients had LV dysfunction (40%), LV dilatation (34%). No further investigations (cardiac MRI, and 24-hour rhythm Holter monitor) were performed in myopericarditis patients. Cardiac MRG findings of ten perimyocarditis patients were as follows; the locations of late gadolinium-enhancement LV posterolateral wall (n:8), LV apex (n:1) and interventricular septum (n:1), LV end-diastolic volume 53.8±3.9 ml, LV end-systolic volume 27.4±2.8 ml, LV EF 52.8±4.8 Cardiac MRG findings of ten perimyocarditis patients were as follows; the locations of late gadolinium-enhancement LV posterolateral

Table I: Subject demographic and clinical characteristics.

Diagnosis	Myopericarditis (n=150)	Perimyocarditis (n=63)
Age median (Interquartile range) months	180 (60-214)	138 (32-216)
Sex %		
Female	37	21
Male	63	79
Place of presentation %		
Pediatric Emergency Department	72	75
Pediatric Cardiology Clinic	18	11
Transfer from another hospital	10	14
Clinical Presentation %		
Chest pain	94	85
Palpitation	16	95
Systemic complaints (fever, fatigue, myalgia) %	85	15
History of a viral illness %	12	85

Table II: Distribution of peak troponin I levels.

Diagnosis		Peak Troponin I (ng/ml)			
	Total number n	**Median**	**Interquartile range**	**Maximum**	**Minimum**
Myopericarditis	150	0.23	0.7	50	0.06
Perimyocarditis	63	13	29.9	50	3.4

Table III: The distribution of ECG and Echocardiography findings and degree of troponin elevation according to diagnosis.

	Myopericarditis n (%)	**Perimyocarditis n (%)**
ECG Findings		
Sinus Tachycardia	8 (5%)	54 (85%)
Atrial or Ventricular Arrhythmias	-	13 (20%)
Decreased QRS Voltage	15 (10%)	26 (42%)
Conduction Delay or Block	-	8 (12%)
Non-specific ST-T abnormalities	15 (10%)	60 (95%)
Four stages ECG changes	135 (90%)	-
PR segment elevation	63 (42%)	-
Electrical alternans	30 (20%)	-
Echocardiography Findings		
LV dysfunction	-	25 (40%)
LV dilatation	-	21 (34%)
Increased LV wall thickness	-	3 (5%)
Decreased LV wall thickness	-	22 (35%)
Regional wall motion abnormalities	-	5 (8%)
Pericardial effusion	38 (25%)	-
Degree of Troponin Elevation		
Mild (<1 ng/ml)	126 (84%)	5 (9%)
Moderate (1-50 ng/ml)	21 (14%)	48 (76%)
Severe (>50 ng/ml)	3 (2%)	10 (15%)

wall (n:8), LV apex (n:1) and interventricular septum (n:1), LV end-diastolic volume 53.8±3.9 ml, LV end-systolic volume 27.4±2.8 ml, LV EF 52.8±4.8%. All perimyocarditis patients had 24-hour rhythm Holter monitoring during hospitalization and outpatient follow-up. The most common findings of 24 hours rhythm Holter monitor were premature ventricular beats (18%) and first and/or second-degree atrioventricular blocks (9%). The perimyocarditis patients had higher peak troponin I levels than myopericarditis patients (Table II). Furthermore, the degree of troponin elevation was mild to moderate (98%) in majority of myopericarditis patients and moderate to severe (91%) in majority of perimyocarditis patients. The distributions of ECG and echocardiography findings and degree of troponin elevation according to diagnosis were listed in Table III. The duration of return to normal troponin I level was significantly longer in perimyocarditis patients when compared to myopericarditis patients (7.3±3.6 days versus 2.1±1.8 days, p<0.001). The comparisons of peak troponin I levels and troponin normalization times of both groups were showed in Table IV. The treatment of myopericardial syndromes was made according to clinical scenario. The first line treatment for all patients with myopericardial syndromes was rest until any symptoms had been resolved. Non-steroidal anti-inflammatory therapy (ibuprofen or naproxen sodium) for 1-2 weeks were used for the symptomatic relief of pericardial pain and to suppress the inflammatory process in most patients with myopericarditis. However, four patients with myopericarditis had incessant or recurrent symptoms and inflammation and needed colchicine treatment for recurrent idiopathic pericarditis. Urgent pericardiocentesis was performed on five patients with myopericarditis for the treatment of tamponade physiology. The median volume of drained pericardial effusion was 150 mL (100-500 mL). The macroscopic appearance of pericardial fluids were serofibrinous in all samples. The pericardial fluid analysis showed exudate (the fluid total protein was >3 g, fluid/serum protein ratio >0.5, fluid/serum LDH >0.6) in all patients. The cell-count analysis of pericardial fluids showed leukocytosis with predominance of lymphocyte. All samples were negative for microbial culture, cytology, Ehrlich-Ziehl-Neelsen and Gram staining. Perimyocarditis patients were not treated with standard anti-inflammatory therapy and only paracetamol was given for pain relief if needed. Angiotensin-converting enzyme inhibitors (ACEis) were given to perimyocarditis patients if the patient had mild left ventricular dilatation and/or dysfunction. Avoidance of strenuous physical activity was recommended to all patients for a minimum of 6 months after the onset of symptoms. Before returning to strenuous activities, the patient should be symptom free, with normal cardiac biomarkers, normal ECG, and echocardiography findings.

Table IV: Comparison of the peak troponin I values and time to negative troponin between myopericarditis and perimyocarditis.

Diagnosis	Myopericarditis	Perimyocarditis	p
Troponin I value ng/ml Median (min-max)	0.23 (0.06-50)	13 (3.4-50)	<0.001
Return to normal troponin I level day Mean±SD (min-max) (day)	2.1±1.8 (3-14)	7.3±3.6 (3-21)	<0.001

DISCUSSION

The main findings of this study were that myopericardial syndromes in children and adolescents are uncommon in clinical practice and have a good short and long-term prognosis. Similarly, Kobayashi et al.(18) showed that myopericardial syndromes are associated with a benign course and a lack of short-term sequelae. Although troponin I levels may be markedly elevated at presentation, they do not appear to be associated with adverse outcomes (18). For these patients a thorough history remains the primary screening step. Secondary physical examination, careful electrocardiography interpretation and echocardiography are needed to make an accurate diagnosis, exclude concomitant disease and for the proper disposition of patients. Troponin testing should be performed on all pediatric patients with suspected myopericarditis or perimyocarditis. The higher initial troponin I levels and slower normalization of troponin I may be used to help in the differential diagnosis of myopericarditis and perimyocarditis.

Myopericarditis is primarily a pericarditic syndrome with minor myocardial involvement. Perimyocarditis specifies a primarily myocarditic syndrome with pericardial involvement (3,17). The incidence rates of acute myopericarditis and perimyocarditis are higher two-fold in male compared to females (14). Similarly, we found a male predominance with 2-3-fold in the present study. Acute myopericarditis and perimyocarditis commonly coexist in the clinical setting because they share common causal agents, mainly cardiotropic viruses. Viral infections seem to be the most common cause of myopericarditis in developed countries (14). Due to ST-segment elevation in electrocardiography, acute perimyocarditis and myopericarditis can mimic ST-segment elevation myocardial infarction and thus distinguishing between acute myopericarditis/perimyocarditis and ST-elevation myocardial infarction may prove difficult (19,20). Commonly taught ECG findings of acute perimyocarditis and myopericarditis are diffuse ST-segment elevation without reciprocal changes, concave ST-segment morphology, ST-segment elevation in lead II greater than III, without any ST depression in aVL, ST/T-wave ratio in V6 greater than 0.25 and no Q-wave. Early repolarization also has precordial ST-elevation but cardiac enzymes are normal and the ST-segment/T wave amplitude ratio is below 0.25 (14-21). We also used these all ECG findings to differentiate between myopericardial syndromes and acute coronary syndrome. Most of patients with myopericarditis had characteristic ECG pattern with four stages and there was no ischemia or infarct sign on ECG of any patients. Echocardiography is a crucial imaging technique for detection of decreased ventricular function, regional wall motion abnormalities, ventricular dilatation and pericardial fluid and its hemodynamic effects on the heart (14). European Society of Cardiology guidelines for pericardial diseases 2015, routine transthoracic echocardiography is recommended in all patients with acute myopericardial syndromes (14). In the present study the distinction between acute myopericarditis and perimyocarditis was made according to echocardiography findings. If there was focal or diffuse LV dysfunction, the diagnosis was predominantly interpreted as perimyocarditis. If there was pericardial effusion, the diagnosis was considered as a myopericarditis. As a result, acute pericarditis with known (increased levels of troponin I) or suspected concomitant myocardial involvement should be referred to as myopericarditis. Evidence of new-onset focal or diffuse reduction of left ventricular function in patients with positive troponins and clinical criteria for acute pericarditis suggests predominant myocarditis with pericardial involvement and should be referred to as perimyocarditis.

The treatment of acute myopericarditic syndromes is in 2 categories: the treatment of any hemodynamic issues (mainly pericardial effusion and tamponade) and the symptomatic relief of pericardial pain (17). The recommended first line treatment of myopericarditis is rest until any symptoms have been resolved in conjunction with aspirin or NSAIDs (14). Colchicine has been found to be a promising adjunct to conventional treatment in patients with acute and recurrent myopericarditis (3). Colchicine has been added as first line therapy with NSAIDs to improve efficacy and combat recurrences by guidelines (17). It is recommended that corticosteroids be avoided due to their increased risk of adverse effects and recurrences, unless there is a specific indication due to a systemic, usually autoimmune, disease that requires corticosteroid use. (22,23). We used naproxen sodium or ibuprofen as anti-inflammatory therapy for all myopericarditis patients. But four patients needed a second anti-inflammatory drug because of incessant or recurrent symptoms, and we added colchicine to their therapies. In perimyocarditis the use of NSAIDs should be evaluated against the degree of myocardial involvement, because in animal models of myocarditis, NSAIDs are not effective and may enhance the myocarditic process and increase mortality (24,25). In clinical practice lower anti-inflammatory doses are considered mainly to control symptoms (15). Therefore, we used only paracetamol for pain relief in perimyocarditis patients if they needed. Renin-angiotensin system blockade with ACE is improves cardiac remodeling and outcomes (26, 27). So we

used ACEis to reduce scar formation in perimyocarditis patients with LV dilatation and/or dysfunction.

CONCLUSION

Overall, this study has tried to ensure useful information for pediatricians when confronted with a child or an adolescent in whom myopericardial syndromes are suspected. A careful clinical history, physical examination, ECG interpretation and application of echocardiography are necessary to make an accurate diagnosis, exclude concomitant disease and for the proper disposition of patients. The goals of therapy for acute myopericarditis and perimyocarditis are to relieve symptoms, decrease inflammation and prevent recurrences. NSAIDs are the mainstay of therapy, colchicine should be considered in addition to standard therapy for incessant or recurrent cases. This will usually result in the reduction of symptoms and the prevention of recurrence of the disease.

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