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Research Article / Araştırma Makalesi

Clinical Characteristics, Treatment Approaches, and Complications in Children with Infective Endocarditis: A Single Center Experience From Turkey

İnfektif Endokarditli Çocuklarda Klinik Özellikler, Tedavi Yaklaşımları ve Komplikasyonlar: Türkiye'den Tek Merkez Deneyimi

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Abstract: In this study, we retrospectively evaluated the underlying risk factors, clinical and laboratory findings, treatment approaches, anticoagulation therapy experiences, and the complications that arose during the follow-up of patients diagnosed with infective endocarditis in our clinic between 2010–2018. Eleven patients with infective endocarditis were evaluated. The relevant features of the patients whom developed complications, given anticoagulant therapy in addition to antibiotherapy, underwent cardiac surgery, and showed a mortality course were determined. The youngest patient was 7 months old and the oldest was 14 years old (7.5 ± 4.6 years). All of the cases had congenital heart anomalies and there were no cases with rheumatic heart disease. A total of eight patients had embolic findings. Echocardiography showed vegetation in nine patients. In addition to antibiotherapy, anticoagulant treatment was applied to 2 patients. The most common microorganism in the blood culture was coagulase negative staphylococci with five cases. Five patients underwent early surgical treatment, one patient died due to multiple organ failure caused by systemic embolization, and one patient died due to sudden hemodynamic instability in the first week of follow-up. Infective endocarditis is a serious disease with life-threatening complications. In children, the main underlying risk factor is congenital heart disease unlike with adults. Once the diagnosis is made, appropriate antibiotherapy should be initiated as soon as possible to prevent septic embolism and mortality. The role of anticoagulation in the prevention of embolism and the treatment of ischemic stroke remains controversial.

Keywords: infective endocarditis, children, embolism, anticoagulation, surgery

Özet: Bu çalışma ile 2010-2018 yılları arasında kliniğimizde infektif endokardit tanısı almış hastalar altta yatan risk faktörleri, klinik ve laboratuvar bulguları, tedavi yaklaşımları, antikoagülan tedavi ile ilgili deneyimler ve izlemde ortaya çıkan komplikasyonlar açısından geriye dönük olarak değerlendirildi. İnfektif endokardit tanısı alan 11 hastaya ulaşıldı. Komplikasyon meydana gelen, antibiyoterapiye ilave olarak antikoagülan tedavi uygulanan, cerrahiye verilen ve mortal seyir gösteren hastaların özellikleri saptandı. En küçük hasta 7 aylık, en büyüğü 14 yaşındaydı (7.5 ± 4.6 yıl). Olguların 10'unda infektif endokardit için risk oluşturan konjenital kalp anomalisi mevcut olup, romatizmal kalp hastalığına sahip olgu yoktu. Toplam sekiz olguda embolik bulgular saptandı. Dokuz olguda ekokardiyografide vejetasyon izlendi. İki olguda antibiyoterapiye ilave olarak antikoagülan tedavi uygulandı. Koagülaz negatif stafilakok, beş olgu ile kan kültüründe en sık üreyen mikroorganizma idi. Beş olguya erken cerrahi tedavi uygulandı. Bir olgu sistemik embolizasyona bağlı gelişen çoklu organ yetmezliği, bir olgu ise izleminin birinci haftasında aniden gelişen hemodinamik bozulma nedeniyle öldü. İnfektif endokardit hayatı tehdit eden komplikasyonlar ile seyredebilen ciddi bir hastalıktır. Erişkinlerden farklı olarak, çocuklarda altta yatan başlıca risk faktörü konjenital kalp hastalıklarıdır. Tanı sonrasında, septik embolizasyon ve mortalitenin önlenebilmesi için olabildiğince erken uygun antibiyoterapi başlanmalıdır. Embolizmin önlenmesi ve iskemik inme tedavisinde antikoagülasyonun yeri ise tartışmalı bir konudur.

Anahtar Kelimeler: enfektif endokardit, çocuklar, embolizm, antikoagülasyon, cerrahi

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1. Introduction

Infective endocarditis (IE) is still an important cause of childhood mortality, with the overall mortality rate in the world reported to be 15–25% (1). Although increased advanced treatment approaches in recent years include early surgical intervention, there has not been a decrease in the IE-related mortality rate even in children (2). Compared with the adult population, the prevalence of IE remains low in the pediatric setting, and has a quite different epidemiological profile. The estimated annual incidence of pediatric IE in the United States ranges from 3.3 per 100,000 per year among infants <1 year old to 0.3 to 0.8 per 100,000 per year in older children and adolescents (3). Children with congenital heart diseases (CHD), especially those with cyanotic heart disease, are at increased risk of developing IE. The risk of IE is highest in patients with complex cyanotic heart disease, especially in those who have had surgical intervention (4). In developed countries, since the incidence of rheumatic heart disease has declined, in the modern era rheumatic heart disease is an uncommon predisposing condition for IE in children. And also, the prolonged life expectancy of children with congenital heart disease (CHD) an increase in the number of cases of CHD-associated IE has been observed (5) Elbey ve ark.'nın 2005-2012 yıllarını kapsayan, Türkiye'de farklı bölgerde yer alan 13 tane 3. basamak hastaneye ait verilerin dahil edildiği çok merkezli çalışmaları, yetişkin yaş grubunda infektif endokarditin Türkiye'deki epidemiyolojik özelliklerini tanımlayan önemli bir kaynaktır.
(6). The multicenter study of Elbey and et al.'s which contains experience of the thirteen tertiary hospitals located in the variable regions in Turkey and covering the period between 2005-2012 is one of the valuable source of the epidemiological characteristics of infective endocarditis in adult population. Unfortunately, there is no study about the epidemiological features as the incidence, underlying risk factors and prognosis of infective endocarditis in children in Turkey except a few available reports about the experience of the certain clinics (7,8).

In this study, we retrospectively evaluated the underlying risk factors, clinical and laboratory findings, microbiological profil, treatment approaches, and the complications that arose during the follow-up of patients diagnosed with IE at our clinic (a tertiary hospital located at the middle part of Turkey) for last eight year period. In addition, we shared our limited experience about the anticoagulant therapy, as a relative contraindicated in the treatment of infective endocarditis in adult guidelines (9). This is the first study including the epidemiological features of infective endorditis in children in the part of middle region of Turkey.

2. Method

The data from patients who were coded as IE in the ICD-10 Diagnosis Information System between 2010–2018 were retrospectively obtained. Depending on the presence of an underlying predisposing factor, patients were classified into high-, medium-, and low-risk groups following the recommendations made by the American Heart Association (AHA) and the European Society of Cardiology (ESC) Guidelines for Infectious Endocarditis Risk Classification (2,10) Demographic data, the presence of a predisposing cardiac disease, presentation with complaints, clinical and laboratory findings, blood culture results, treatment plans, evolving complications, and the echocardiographic data of patients were examined. The diagnoses were evaluated for compliance with the Duke Criteria. The relevant features of the patients with complications, of those having anticoagulant therapy in addition to antibiotherapy, those who underwent surgery, and those who showed a mortality course were determined. Categorical variables are presented as absolute values and proportions. Continuous variables are presented as mean standard deviations. This study was conducted in accordance with the principles outlined in the Declaration of Helsinki and approved by local Ethical Committee (09.10.2018 dated and 25403353/050 numbered).

3. Results

The demographic characteristics, clinical symptoms, and the findings from eleven pediatric patients with IE are shown in Table 1. The youngest patient was 7 months old and the oldest was 14 years old (7.5 □ 4.6 years). Four cases had cyanotic CHD, four had a ventricular septal defect (VSD), two had a bicuspid aortic valve (BAV) with aortic insufficiency, and one patient had a secundum atrial septal defect (ASD) that was not considered as an increased risk factor for IE. Three patients with cyanotic CHD were treated with corrective cardiac surgery in the infantile period but were considered as high risk due to the presence of residual lesions. A total of eight patients had embolic findings; five at the time of admission and three at follow-up. Nine patients received antibiotics prior to admission. One of the three patients whose source of bacteremia was apparent was in the second week of post-cardiac surgery, one of them had a history of skin infection from two weeks previously, and there was a history of tooth extraction with IE prophylaxis in one patient who had viridans group streptococci (VGS) positivity in his blood cultures. In all cases, the body temperature of the patients was above 38°C and there were murmurs with varying sound intensities ranging from 2–4/6°. Oxygen saturation, as measured with pulse oximetry, was < 85% in three patients: one was diagnosed with congenitally-corrected transposition of the great arteries (c-TGA) with VSD, one with severe pulmonary hypertension plus VSD, and the other with VSD plus widespread pulmonary embolization. In three patients, tachypnea and crackles in the basal portions of the lung were detected. One patient with BAV, severe aortic insufficiency, and moving vegetation on the aortic valve was lethargic and presented with findings of shock at the time of admission, and had myocardial ischemia findings on the electrocardiogram, and cerebral, cerebellar, hepatic, renal, and splenic infarct areas supporting diffuse systemic embolization, as seen in the cranial magnetic resonance imaging (MRI) and abdominal computed tomography (CT) scans. There was a loss of strength both in the left arm and leg in a 7-month-old patient with known secundum ASD and mitral valve vegetation, and in one patient with a BAV, aortic valve vegetation, and severe aortic valve insufficiency, as shown through echocardiography, who was sent to pediatric cardiology for a consultation with a murmur when evaluated for fever and organomegaly.

The laboratory, microbiological, echocardiographic, and clinical follow-up results of the cases are shown in Table 2. Streptococcus viridans was detected in four patients as the causative agent. The most common microorganism was coagulase negative Staphylococcus aureus (CNSA) in five cases

Table 1. Demographic and clinical characteristics of cases

Variables	IE cases (n)	(%)
Age (year)		
1<	1	(9.1)
1-7	5	(45.4)
8-11	2	(18.1)
10-14	3	(27.2)
Gender		
Male	6	(54.5)
Female	5	(45.4)
Congenital heart disease		
VSD	4	(36.3)
d-TGA+VSD	3	(27.2)
BAV + AR	2	(18.1)
c-TGA+VSD+PS	1	(9.1)
History of cardiac surgery		

Rastelli	2	(18.1)
Jaten	1	(9.1)
Clinical signs and symptoms		
Fever	11	(100)
Tachypnea	5	(45.4)
Neurological findings	3	(27.2)
Arthralgia	1	(9.1)
Rash	2	(18.1)
Chest pain	1	(9.1)
Cyanosis	3	(27.2)
Murmur	11	(100)
Hepatomegaly	3	(27.2)
Splenomegaly	1	(9.1)
Embolization		
Yes	8	(72.7)
Pulmonary	5	(45.4)
CNS	3	(27.2)
CNS+Renal+Hepatic+Coronary	1	(9.1)
No	3	(27.2)
Prior antibiotic use		
Yes	9	(81.8)
No	2	(18.1)

VSD, ventricular septal defect; d-TGA, corrected transposition of the great arteries; BAV, bicupit aortic valve; c-TGA, congenitally corrected transposition of the great arteries; PS, pulmonary stenosis; AR, aortic regurtation; CNS, central nervous system.
'Two patients underwent the Rastelli procedure, and one underwent Jaten procedure.

Table 2. Laboratory, echocardiographic findings and prognosis of the patients

	IE cases	
Variable	**(n)**	**(%)**
Laboratory		
ESR>20 mm/h	10	(90.9)
CRP>5 mg/dl	11	(100)
RF(+)	5	(45.4)
Leukocytosis	8	(72.7)
Anemia	7	(63.6)
Albumin<3.5 g/dl	7	(63.6)
Microbiological		
Blood Culture (+)	10	(90.9)
CNSA	3	(27.2)
Staf.epidermidis	2	(18.1)
Strep.viridans	2	(18.1)
Strep.mitis	1	(9.1)
Strep.oralis	1	(9.1)
Neisseria	1	(9.1)
Blood Culture (-)	1	(9.1)
Echocardiography		
Vegetation (+)	9	(81.8)
Aort	2	(18.1)
Tricuspid	3	(27.2)
Pulmonary	2	(18.1)
Mitral	1	(9.1)
Pulmonary conduit*	1	(9.1)
Vegetation (-)	2	(18.1)
Surgery	5	(45.4)
Result		

Discharged	9	(81.8)
Death	2	(18.1)

ESR, erythrocytes sedimentation rate; CRP, C-reactive protein; RF, rheumatoid factor; CNSA, coagulase-negative Staphylococcus aureus.
***** The patient who was applied the Rastelli procedure*

An embolectomy and corrective surgery were performed in two of the cases with recurrent pulmonary embolization findings and a large vegetation diameter (> 15 mm), and, in two cases, this was due to no reduction in the vegetation size and a lack of improvement in clinical findings despite appropriate antibiotherapy, even though one patient underwent aortic valve replacement surgery because of the high risk of systemic embolization and a lack of reduction in the vegetation size following appropriate treatment. One case involving vegetation of the BAV and infarct areas in the cerebral and cerebellar hemispheres due to diffuse embolization, as detected by cerebral diffusion MRI, died because of multiple organ failure 12 hours post-admission. A patient with VSD plus systemic pulmonary hypertension (PHT) without vegetation on echocardiography but having CNSA reproduction in her blood cultures died after a sudden onset of respiratory arrest on the 6th day of the follow-up.

Anticoagulant therapy was given to two patients with stroke findings in one and high risk of cerebral embolization in the other. In patient with serebral embolism, after anticoagulant therapy stroke symptoms had been regressed and surgery became unnecessary. Unfortunately, we decided to perform surgery because of the lack of reduction in vegetation size, the high mobility of the vegetation, and the decrease in the left ventricular ejection fraction despite the appropriate antibiotherapy and anticoagulation treatment for the other patient.

4. Discussion

In our clinic, eleven patients with IE were followed up over an 8-year period. Ahmadi and Daryushi, from Iran, published 5-year retrospective follow-up results of 17 children with IE in their study (11). There were only 47 children in the study by Johnson et al., in which they published 60 years of data from a single center in the United States (12). Thus, in developed countries, the incidence of endocarditis would appear to be significantly lower than it is in developing countries (12). In Turkey, Izmir, Tavli et al. (7) reported on 28 patients between 2003–2005, 3 of whom had rheumatic heart disease and 25 of whom had CHD; from Ankara, Hizli and Bilgic (8) published the data on 33 child patients between 1987–1998, including 11 patients with rheumatic heart disease, and 22 with CHD. Altough rheumatic heart diseases reported as a predisposing factor, CHD were the most common predisposing factor for children in both of the studies, unlike with previously reported in adults from Turkey (6). The number of patients included in our study is lower than in these two studies, but it can be explained by the fact that the incidence of IE may vary, even from city to city, and at the same time, there has been a decrease in the incidence of IE in recent years compared to previous years in Turkey. Although, the incidence of rheumatic heart disease in children in Turkey not exactly known, this reduction may be explained by the fact that the underlying risk factor in IE has shifted from rheumatic heart disease to CHD, similar to developed countries. Indeed, in our study, unlike the other two Turkish studies, there are no cases with rheumatic valvular disease.

The riskiest cardiac conditions for IE are a history of endocarditis, the presence of an artificial heart valve ring, cyanotic CHDs, CHDs that have been operated on leaving a residual defect, and the first 6 months of CHD without a residual defect (13). Dinela Rushani et al. reported that high-risk CHDs for the development of IE were cyanotic CHD, an endocardial cushion defect, and left heart lesions, respectively, in a retrospective study of 136 child patients who were diagnosed with IE and CHD, of whom 22 (16%) had a history of cardiac surgery (14). In nine of our eleven patients diagnosed with IE, valvular vegetation was detected via echocardiography, three patients had a history of corrective cardiac surgery. One case was in the second post-operative week. The other

seven patients had no history of operations, but the presence of VSD, BAV with aortic insufficency, and c-TGA with PS were underlying risk factors for IE. In our 7-month-old patient who was diagnosed with secundum ASD, mitral valve endocarditis developed secondarily to drug extravasation, and venous thrombophlebitis developed secondarily to parenteral treatment due to gastroenteritis. The most common predisposing factor in our patients was CHDs, and cyanotic CHD and VSD were equal in frequency.

Prevention of IE via prophylaxis is a controversial issue, with the prophylaxis recommendation from the AHA's and ESC's current guidelines being limited to cardiac conditions in which the risk of IE and its complications are high (2). In a study investigating the effects of the AHA's 2007 guidelines on the incidence, clinical course, hospital stay, and mortality rate, no significant difference was found in the incidence of IE and the severity of the disease in the 5-year period after the new guidelines had been introduced but it was reported that VGS were detected in increasing frequency as the IE agent in children aged > 10 years (15). Similarly, Pant et al. (16) reported an increase in the incidence of IE caused by streptococci in the post-guideline period. They thought that the decrease in the use of IE prophylaxis for low-risk patients in the post-guideline period might have led to this increase (15). As a result of the increased incidence mostly occurring in older children, they emphasized that the age ranges in which patients more frequently undergo dental treatment should be taken into consideration (15). In 2008, the recommendation in the UK was to discontinue prophylaxis, including in those patients with a high risk of developing IE, and it was reported that 2 years post-recommendation, there had been no significant change in the incidence of IE, but a significant increase occurred after 5 years (17,18). Therefore, detailed studies covering long periods are needed to determine the effectiveness of prophylaxis (which is limited to specific cardiac conditions in the current IE prophylaxis guidelines) in order to correctly determine how it affects the frequency and course of the disease. Considering the fact that mortality rates have not decreased worldwide despite improvements in the treatment of IE, the importance of the prevention of the basic disease, and therefore of the bacteremia, is understood in terms of it reducing the mortality rate. Therefore, in our clinical practice, we still recommend IE prophylaxis for all risk groups prior to pre-defined dental procedures, unlike the recommendations put forward in the current guidelines.

Clinical suspicion is particularly effective in the diagnosis of children with risk factors, and the use of the modified Duke Criteria provides for an objective assessment and early recognition of suspected cases of endocarditis (19). Of the patients diagnosed in our clinic, nine were consistent with IE according to the Duke Criteria, and two were compatible with possible IE. In nine patients, the co-existence of positive blood culture results for IE and endocardial involvement following echocardiography led to definitive diagnoses. Although transthoracic echocardiography showed no vegetation in patients with possible IE, fever and structural heart disease, as well as the presence of microorganisms compatible with IE in their blood cultures supported the diagnosis. Our study, in which we detected blood culture positivity in nine patients, demonstrates that microbiological evidence is of great importance in the diagnosis of IE. Adriana Topan et al. (19), in their study of 6-year data from a single center in Romania, reported that 137 patients were found to be definite cases, 79 patients were found to be compatible with possible IE following clinical evaluation, and the negative blood culture rate was found to be 71%. In this study, they stated that 93.67% of the possible IE cases met the definite IE criteria when there was major culture-positive microbiological evidence, and if the cases were culture-negative, 32.85% of definite IE cases could be considered as possible IE; thus, they wanted to emphasize the importance of major culture-positive microbiological criteria for a clinical diagnosis. In these and many other studies, antibiotic treatments given prior to obtaining blood samples were reported as the most important cause of culture negativity (19,20). Walid Jomaa et al. (20), in their study on the prognosis and epidemiological features of IE in Tunisian children, were able to detect reproductive IE-compatible microorganisms:

17 of them were staphylococcus strains in 31 (42.5%) of 73 children with IE. We detected typical culture positivity for IE in nine of our eleven patients and IE-compatible microorganisms in one patient, so we determined the culture positivity of the causative microorganisms in ten patients. Although nine patients received antibiotics for at least one week prior to admission, we thought that the significant high positivity in their blood cultures could be associated with insufficient sensitivity to the antibiotics used and/or an inappropriate dosage. The most common agent responsible was CNSA with five cases. The incidence of endocarditis caused by CNSAs has been reported to be 5% and it may be fatal and the most frequently responsible pathogen has been identified as Staphylococcus epidermidis (21). In recent years, an increase in the frequency of bacteremia and endocarditis caused by CNSA has been reported, including native valve endocarditis (22). Maria et al. (23) reported that the prevalence of CNSA-related IE was 16% and the frequency of native valve endocarditis was 35% in their adult studies, which included 13 years of data. In our study, CNSA was the most frequent IE agent with five cases (45.5%), where three patients had native valves and two had condiut valves. S. epidermidis was defined as a pathogen in three cases. One of the cases with native valve endocarditis caused by CNSA died within the first 12 hours and the other died on the 6th day of follow-up. In accordance with the literature, CNSA was present at a high frequency in our IE cases and was the responsible agent in our patients with mortal disease.

Embolization is a frequent complication that can occur in 50% of patients with IE, 40% of whom show symptoms in the first 10 days and 75% of whom show symptoms in the pre-antibiotic period (24). Of the eight patients with embolization findings, three had pulmonary, one had CNS, and another had systemic embolization findings at the time of diagnosis, which is consistent with the literature. The relationship between S. aureus infection, vegetation size (> 10 mm), mitral valve anterior leaflet involvement, and embolization frequency has been clearly defined, and the risk decreases after antibiotherapy (25). Therefore, the most effective treatment for the prevention of embolization is the rapid initiation of antibiotherapy. In the present study, the empirical treatment was started as a vancomycin plus gentamicin combination due to the presence of a pulmonary conduit in two patients and severe sepsis findings in one patient, and the other eight patients were started with a penicillin G plus gentamicin combination and appropriate changes were made according to the antibiogram results. The treatment was continued for at least 4 weeks. Despite adequate antibiotherapy, three more patients developed embolization at the follow up and were applied the corrective surgery to two of them.

The use of anticoagulant therapy (ACT) to reduce the risk of embolization especially in patients with left sided infective endocarditis (IE) remains a controversial issue due to the reason of the increased probability of intracranial hemorrhage. It should be considered for ischaemic stroke without haemorhage and Staphylococcus aureus IE even in the absence of stroke according to ESC guidelines (9). The existing experiences with this issue includes to adult patients (25,26) Rasmussen et al. were reported no increased risk of cerebral haemorrhage in Staphylococcus aureus IE patients receiving anticoagulation. Furthermore, they have reported a lower incidence of ischemic stroke in the patients taking anticoagulation at admission (26). On the other hand, Lee et all. suggested that anticoagulant therapy reduce the embolic potential of septic vegetation if only use before antibiotic therapy (25). They argued that anticoagulation in patients on antibiotic treatment for IE may increase the risk of hemorrhagic complications. There are also case reports supports that anticoagulant therapy is useful in ischemic stroke. Preston et al. reported that dysphagia and a loss of strength in the right arm and leg rapidly resolved with anticoagulant therapy in addition to antibiotherapy in a 23-year-old female patient with multiple cerebral infarct areas with 5-mm diameter vegetation on the mitral anterior leaflet (27). Despite the presence of central infarct findings, a combined antibiotherapy and anticoagulation therapy was preferred to prevent the

recurrence of embolic events when considering the absence of additional surgical indications. In our smallest 7-month-old patient who had stroke findings as a loss of strength in the left hand and leg due to Staphylococcus aureus IE, we preferred to initially treat the patient with antibiotics and unfractionated heparin when considering a vegetation diameter of < 10 mm (7 mm) on the mitral anterior leaflet, less movement, and an absence of both hemodynamic instability and severe valve dysfunction. We obtained a marked reduction in the size of the vegetation and a regression in the signs of lateralization. We continued anticoagulant therapy with low-molecular-weight heparin and completed the treatment period at 12 weeks. Altough, the limited evidence suggests that anticoagulation is useful in patients such as ours, more studies, especially randomized trials in a larger population should be undertaken to support to anticoagulant therapy in patient with thromboembolic stroke or high risk for embolic serebrovascular event in infective endocarditis.

In conclusion, IE is a serious disease with life-threatening complications as septic embolism and congestif heart failure. The number of at-risk patients due to CHD as the main underlying risk factor for children are gradually increasing and thus the mortality rate has not decreased despite improved medical and surgical treatment procedures. Therefore, to prevent complications, clinical suspicion and rapid initiation of the appropriate antibiotherapy following the diagnosis is of great importance.

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