Complications and outcome in left-sided endocarditis in children

Dursun Alehan, Süheyla Özkutlu, Canan Ayabakan, Arman Bilgiç, Şencan Özme
Sema Özer, Alpay Çeliker

Cardiology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey

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We retrospectively assessed the clinical course and outcome of left-sided endocarditis in pediatric patients to find out the prognostic significance of the presence and size of echocardiographically detected vegatations.

Among the children admitted to our institution with endocarditis between January 1987 and October 1999, 16 patients (mean age 9.03 ± 4.95 years) who met the Duke criteria for the diagnosis of infective endocarditis (IE) were included in this study. Rheumatic valvular disease was the most frequent underlying heart disease (10 patients: 62.5%). Five patients were operated at a mean of 13.9 months before endocarditis, and all had residual defects. Vegetation was detected in 11 cases (69%). Ten patients had major complications (within 2 weeks in 6 patients). Three patients developed congestive heart failure (CHF), six had intracranial and one had lower extremity emboli. Among them four were operated because of complications (CHF: 3 cases, intracranial emboli: 1 case). All the operated cases are doing well. The association between intracranial embolic events and echocardiographically detected vegetations was determined by calculating specificity (40%), sensitivity (100%), positive predictive value (50%), and negative predictive value (100%). No intracranial embolism occurred in patients without vegetations. All vegetations were ≤ 6 mm in patients with systemic embolism. There were four deaths, three of which were because of intracranial embolism.

This study suggests that intracranial emboli have a major risk of mortality in left-sided endocarditis. The larger size of the vegetation is not a predictor of complications; furthermore, the absence of vegetations predicts that the patient is safe from embolic events. Therefore all patients with left-sided IE should be considered for earlier surgical intervention.

Key words: infective endocarditis, left-heart, children, systemic emboli.

In recent years, the prognosis of patients with infective endocarditis (IE) has improved with better antimicrobial therapy, advances in diagnosis, earlier detection, and urgent surgical management of complications[1,2]. Congestive heart failure, severe valvular regurgitation and uncontrolled infection are strongly associated with poor outcome when no surgical treatment is applied[2,3]. Echocardiography, beyond comparison, is the accepted procedure for the diagnosis of IE, with which assessment of valvular dysfunction, hemodynamic status, and direct visulization of endocarditis-induced lesions are possible. Echocardiography also aids in decision of the necessity and timing of surgical intervention[4-7]. On the other hand, echocardiographically demonstrated vegetations or occurrence of systemic emboli are less agreed upon indications for surgical intervention during active IE[8].

Although it has been reported lately that there is a moderate increase in the global incidence of IE, it is still a relatively rare disease in infancy and childhood, especially during the first two years of life[9,10]. Furthermore, most studies about the timing and necessity of surgical interventions in active IE are done on adult patients. In view of the conflicting reports, we reassessed retrospectively the clinical course and outcome of left-sided IE in pediatric patients to find out the prognostic significance of size and the location of echocardiographically detected vegetations.

Material and Methods

We retrospectively reviewed the hospital records of 21 pediatric patients diagnosed with left-sided endocarditis between January 1987 and October 1999. Among these 21 patients, 16 who fulfilled the Duke criteria for the diagnosis of IE were included in this study[11]. All of the patients were evaluated with two-dimensional, M-mode, continuous wave and color Doppler transthoracic echocardiography for the site of vegetations, extension of intracardiac lesions, and presence of congestive heart failure. Each cardiac valve was especially evaluated for thickening, calcification, prolapse of leaflets and, in particular, for the presence or absence of typical vegetations. All echocardiographic examinations were performed with Toshiba Sonolayer SSH-160A using 5, 3.75 and 2.5 MHz transducers. The duration of medical treatment, the timing of the surgical treatment and the clinical outcome, emphasizing the systemic embolic events, were evaluated for all patients. Statistical analysis was done using frequencies of variables. The association between intracranial embolic events and echocardiographically detected vegetations was determined by calculating specificity, sensitivity, and positive and negative predictive values as follows:

(MR), one had aortic regurgitation (AR), and four had both MR and AR. Two patients had primum atrial septal defect (ASD) and mitral cleft. Other pathologies included 1) Shone's anomaly (mitral stenosis-MS, aortic stenosis-AS, coarctation of aorta), 2) AS and secondary hypertrophic cardiomyopathy, 3) Truncus arteriosus type I, and 4) tetralogy of Fallot, with each seen in one patient. Five patients were operated at an average of 13.9 months before the diagnosis of IE, but all had residual defects (Table I).

Bacteriological Data

Blood cultures were positive in 10 patients (62.5%). Staphylococcus aureus (n = 5; 31.2%) and Streptococcus viridans (n = 4; 25%) species accounted for the majority of cases. One patient (6.3%) had Candida albicans growth in multiple blood cultures. Valve tissue was also culture positive in two patients who underwent surgery (Cases 9 and 14). Four of the remaining six patients, who were culture negative, had received empirical antibiotic treatment of various durations before presenting to our hospital.

Echocardiography

Vegetations were observed in 11 of the 16 patients (69%), and all were on native valves. Four patients had vegetations on the mitral valve (Fig. 1) (one of them also had vegetation on interatrial patch), three of them on the aortic valve (Fig. 2), and two of them on both aortic and mitral valves. There were extravalvular vegetations in the remaining two patients (1 in left atrium, and the other in left ventricular outflow tract). Size of the vegetations ranged from 3 mm to 17 mm in diameter (mean: 4.93 ± 5.05 mm). Among the six patients operated during active IE, four patients had vegetations at preoperative echocardiography. The

$$\text{Sensitivity} = \frac{\text{Emboli with vegetations (veg)}}{\text{Emboli with veg + Emboli without veg}}$$

$$\text{Specificity} = \frac{\text{No emboli without veg}}{\text{No emboli without veg + No emboli with veg}}$$

$$\text{Positive predictive value} = \frac{\text{Emboli with veg}}{\text{Emboli with veg + No emboli with veg}}$$

$$\text{Negative predictive value} = \frac{\text{No emboli without veg}}{\text{No emboli without veg + Emboli without veg}}$$

Results

The age range of nine male and seven female patients was from 1 to 17 years (mean: 9.03 ± 4.95 years). All patients had preexisting cardiac abnormalities. Rheumatic heart disease (RHD), with occurrence in 10 patients (62.5%), was the most frequent underlying heart disease. Five patients with RHD had mitral regurgitation

Table I. Details of the Study Group

Case	Age	Sex	Cardiac pathology	Operation/residual defect	Location/size of vegetation	Blood culture	Complication/day of complication	Surgery	Outcome
1	13	M	TOF	Total correct/VSD, PS	LV outflow tract 3 mm	Negative	Uncontrolled infection	Redo total correction	Cure
2	14	M	MR*	MVR/MR	Mitral 4 mm	C. albicans	Intracranial emboli/9	None	Died
3	12	F	MR*	None	Mitral 6 mm	S. aureus	Intracranial emboli/14	None	Cure
4	1.5	F	Mitral cleft, primum ASD	MVR, ASD closure/MR	LA 11 mm	S. viridans	None	None	Cure + elective surgery
5	1	M	Truncus type I	None	None	S. aureus	None	None	Cure + elective surgery
6	7	F	Shone's anomaly (MS, AS, coarctation (Ao)	Patch angioplasty of Ao/MS, AS, recoarctation	None	S. aureus	Lower extremity emboli/48 + CHF/69	None	Died
7	13	F	AR, MR+	None	None	Negative	None	None	Cure + elective surgery
8	17	M	AR*	None	Aortic 17 mm	Negative	Uncontrolled infection	AVR	Cure
9	7	M	MR*	None	None**	S. viridans	CHF/17**	MVR	Cure
10	9	M	AR, MR*	None	Aortic 3 mm	Negative	Intracranial emboli/27	None	Died
11	15	F	AR, MR*	None	Aortic-Mitral 3-13 mm	Negative	None	None	Cure
12	7	M	MR*	None	None**	S. aureus	CHF/35***	MVR	Cure
13	7	F	AS, HCMP	None	Aortic 5 mm	S. viridans	Intracranial emboli/1	None	Cure
14	4	M	MR*	None	Mitral 5 mm	S. aureus	Intracranial emboli/2	None	Died
15	13	M	MR, AR*	None	Aortic-Mitral 4-7 mm	S. viridans	CHF/10	MVR	Cure
16	4	F	Mitral cleft, primum ASD	Mitral cleft + ASD closure/MR	Mitral 5 mm	Negative	Intracranial emboli/1	Redo closure of mitral cleft and primum ASD	Cure

* Rheumatic heart disease.
** Perforation of anterior mitral valve leaflet.
*** Rupture of chordae tendineae of anterior mitral valve.

TOF : Tetralogy of Fallot.
HCMP: Hypertrophic cardiomyopathy.
Ao : Aorta.
MR : Mitral regurgitation.
AR : Aortic regurgitation.
AVR : Aortic valve replacement.
AS : Aortic stenosis.
LA : Left atrium.
MVR: Mitral valve replacement.
VSD : Ventricular septal defect.
MS : Mitral stenosis.
LV : Left ventricle.
CHF: Congestive heart failure.
ASD: Atrial septal defect.
PS : Pulmonary stenosis.

diagnosis was confirmed at surgery. Chordae tendineae rupture of the anterior mitral leaflet and perforation of the anterior mitral leaflet accompanying severe congestive heart failure were diagnosed echocardiographically in the remaining two patients.

Fig. 1. A 13 mm vegetation (arrows) is observed on the anterior leaflet of the mitral valve of a 15-year-old female patient (Case 11) (long-axis view). LV: left ventricle, IVS: interventricular septum, AO: aorta, LA: left atrium.

Fig. 2. A 3 mm vegetation is observed on aortic valve of a nine-year-old male patient (Case 10) (long-axis view). LV: left ventricle, LA: left atrium, AO: aorta.

Complications

All 16 patients were medically treated for a mean period of 32 ± 21 days (range: 2-69 days) after hospitalization for IE. During the in-patient follow-up period complications were observed in 10 patients (62.5%) on the 1st-69st days (mean: 20 ± 14 days) of the treatment. Clinical evidence of systemic embolism was present in seven patients (43.8%) (Table I). Intracranial embolism occurred in six patients, and one patient had lower extremity embolism. The association between intracranial embolic events and echocardiographically detected vegetations was determined by calculating specificity, sensitivity, and positive and negative predictive values. The sensitivity of occurrence of intracranial embolic events in the presence of vegetation was 100%. The specificity, positive predictive value, and negative predictive value were 40%, 50% and 100%, respectively. It is of note that no intracranial embolism occurred in patients without vegetations on echocardiographic examinations. However, a postoperative patient with Shone's anomaly had lower extremity embolism on the 48th day of treatment although no vegetation was detected on echocardiography. Among the patients with intracranial embolism, four patients had vegetations on the mitral valve, and two patients had vegetations on the aortic valve. The average size of the vegetations was 4.4 mm. An important finding of the study was that all vegetations were ≤ 6 mm in patients with systemic embolism. Two of these patients, however, had embolism before the initial echocardiographic examination (location: aortic valve in 1 patient, mitral valve in the other; vegetation size: 5 mm in both cases). One of them was treated only with medical therapy, while the other was treated with both medical and surgical therapy. Patients were discharged after six and five weeks of treatment, respectively.

There were three deaths among patients with cranial embolism. None of these patients was surgically treated during acute IE. Two of them died within 10 days of medical treatment, and one patient died on the 27th day of treatment. The patient with lower extremity embolism died on the 69th day of treatment because of severe congestive heart failure.

Three cases with severe congestive heart failure were operated during acute IE, and none of them died. One of these patients had vegetations at echocardiography (4 mm on aortic and 7 mm on mitral valve). The other two patients had perforation of the anterior mitral valve leaflet and rupture of the chordae tendinea, respectively. The echocardiographic diagnosis was confirmed histopathologically in these patients.

Surgical Treatment

Cardiac operation was undertaken in six (37.5%) of the 16 patients. The indications for cardiac surgery were severe congestive heart failure (n = 3), intracranial embolism (n = 1), and uncontrolled infection (n = 2). There were no intraoperative or perioperative deaths among these patients. Three mitral valve replacements, one aortic valve replacement, and one mitral cleft surgery and interatrial patch revision were performed. Total correction for tetralogy of Fallot was redone in one patient. Vegetations were demonstrated surgically in all of the echocardiographically diagnosed patients.

In-Hospital Mortality

There were four in-hospital deaths (25%). Three patients died because of intracranial embolism. One patient (with lower extremity embolism) died due to severe congestive heart failure. This patient initially was operated for Shone's anomaly (MS, AS, coarctation of aorta). She had residual AS, MS, and recoarctation 4.5 months after that operation. None of the operated patients died intraoperatively or perioperatively.

Discussion

Infectious endocarditis remains a common and serious condition. Echocardiography is the only noninvasive method available today allowing direct visualization of endocarditis-induced lesions. The combination of M-mode and two-dimensional echocardiography imaging allows identification of vegetations in 13% to 78% of cases[12-16]. Transesophageal approach is important in patients whose transthoracic echocardiography fails to provide adequate imaging quality, as in patients who have advanced obesity, chest deformity or emphysema, or who are seen early after thoracic surgery or under artifical ventilation[4]. In our study group, vegetations were identified in 69% (11 patients) of the patients using the transthoracic approach. The presence of the vegetation was confirmed pathologically in all four patients who were operated during acute IE. Two other patients (Cases 9 and 12) without echocardiographically demonstrated vegetations were correctly diagnosed preoperatively by echocardiography as having mitral valve leaflet perforation and rupture of mitral chordae tendineae, respectively. Transthoracic echocardiography provided a reliable noninvasive diagnosis of IE-related lesions.

It has been suggested that the presence of echocardiographically identified vegetations may be associated with an impaired prognosis, based on a higher incidence of congestive heart failure, systemic embolism or death[12,13,17,18]. Recently, some studies have reported that prognostic implications are more dependent on vegetation size than on the presence or absence of vegetation[12-14,18-21]. In contrast, a relation between the size of vegetation and the incidence of complications has not been found in other studies[5,17,22,23].

Absolute indications for surgical treatment during active IE include severe heart failure, the presence of an infecting organism that is not susceptible to available antimicrobial agents, and unstable infected prosthetic valve[1,2,8]. Two or more embolic events and vegetations large enough to be demonstrated with echocardiography are less agreed upon, and are among the relative indications for surgical intervention during active IE. Valvular vegetations are hypothesized to increase the risk of systemic embolic events in left-sided IE[12,15,16]. The estimated cumulative incidence of such events ranges from 22% to 43%[21,24]. The neurologic complications due to cerebral embolism represent a major factor associated with an increased mortality rate in this disease[8,24]. If death does not occur after intracranial embolism, neurological deficit is usually the consequence. There is certain debate on the association of higher incidence of embolic events with larger vegetations (i.e. vegetations > 10 mm). Some of the studies did[12-14,18-21], and others did not[5,17,22,23], find an association with embolic events and vegetation size. Müge et al.[4] could not clearly associate the embolic events and vegetation size; on the other hand, when they considered the location of the vegetation, larger vegetations on mitral valves were significantly associated with increased risk of systemic embolism.

In our study, intracranial embolism was observed in six of the 11 patients with vegetations (54.5%) (Cases 2, 3, 10, 13, 14, and 16). None of these embolisms was recurrent and none of these patients had large vegetations by transthoracic echocardiography. The echocardiographic examination was performed after the embolic event in two patients (Cases 13 and 16). Although an embolic event might have reduced the size of the vegetations in these patients, all the remaining patients still had vegetations < 6 mm. Systemic embolic events other than cerebral embolisms were not considered to have increased mortality since the cause of death in the patient with lower extremity emboli was not the embolism itself, but congestive heart failure. The association between intracranial embolic events and echocardiographically detected vegetations was determined by calculating specificity, sensitivity, and positive and negative predictive values. The sensitivity of occurrence of embolic events in the presence of vegetation was 100%. The specificity, positive predictive value, and negative predictive value were 40%, 50% and 100%, respectively. In other words, in our study, the absence of vegetations clearly predicted that the patient was safe from embolic events, and detection of vegetation by echocardiography was 100% sensitive for an embolic event. Intracranial emboli were significantly associated with mortality. Death occurred in three of the six patients (50%) with intracranial emboli on the 2nd, 9th, and 27th day of the medical treatment (Cases 2, 6, and 10). None of these patients was treated surgically for IE. Three patients with vegetations were operated for reasons other than intracranial embolism (Cases 1 and 8 because of uncontrolled infection and Case 15 because of congestive heart failure). If these patients had not been operated for other reasons, and if their vegetations had not been removed surgically, they might have been at increased risk of systemic or intracranial embolism.

Embolism occurs most commonly in patients infected with virulent organisms, an event more likely to be seen within two weeks in the course of this infection[5,24]. In our group the intracranial embolic complications were observed on the 1st to 27th day after the diagnosis (within 2 weeks in 5 of the 6 patients-83.3%). A lower extremity embolism was observed in one patient, on the 48th day. The microorganisms grown on blood cultures of these patients were as follows: S. aureus in three patients, Candida albicans in one patient, and S. viridans in one patient. No microorganism grew on blood cultures of the remaining two patients; both of them had received antibiotic treatment before admission and diagnosis of IE.

Blood cultures may be negative in 15% of all IE patients[25]. In our study group 37.5% of all the IE patients and 28.6% of the patients with embolism had negative blood cultures. Anerobic bacteria, fungi, or previously administered antibiotics may have been responsible for negative cultures.

The management of patients with clinical evidence of embolic disease remains unclear. There is no data to suggest that a patient with one major embolism is at an increased risk of having more[8]. As Lerner[24] states, one also must not forget that a single clinically evident embolus may be accompanied by clinically inapparent emboli, so a criterion of multiple emboli as indication for valve surgery seems to be inappropriate. None of our patients experienced recurrent intracranial embolism, but half of them died shortly after the first embolic event. On the other hand, all the patients operated during acute IE, including the patient with a single intracranial embolism episode, were successfully cured. There were four cases of severe congestive heart failure due to IE in our group (Cases 6, 9, 12, and 15). Two of these four cases had chordae tendineae, or mitral valve ruptures. Three of them were operated with no in-hospital mortality. Case 6 died on the 69th day of treatment due to congestive heart failure. Similar to recent reports, our study indicates that early operation during active infection may be safely performed before the classical antibacterial therapy is completed[1,26].

Chordal rupture due to IE has been reported in 8.5 to 45% of patients in various studies[28,29]. On the other hand Roberts and Buchbinder[27] state that cuspal perforations are always indicative of IE whenever they are seen. There is higher incidence of ruptured chorda to the posterior leaflet in the spontaneous group. In patients with floppy mitral valve, IE tends to results in chordal rupture of the posterior cusp as well. In IE involving normal or rheumatic valves, however, the anterior cusp is most commonly affected, with chordal rupture often occurring in association with cusp perforation[28]. In our study, one patient (Case 12) had rupture of the chorda to the anterior mitral valve, and another patient (Case 9) had perforation on the anterior mitral valve leaflet. Both patients developed severe congestive heart failure and were operated for this reason. No case of mycotic aneurism or ring abscess was observed.

One of the most striking changes that has occurred in infantile and childhood IE has been the virtual disappearance of rheumatic heart disease (RHD) as a predisposing factor. The introduction of antibiotics, especially penicillin, not only provided a most effective form of treatment for streptococcal infections, thereby dramatically reducing the incidence of RHD, but also provided an effective means of prophylaxis against IE in individuals with RHD. Congenital heart disease, on the other hand, has become the major predisposing factor in development of IE during childhood[9,10]. In conflict with this data, our study disclosed that 10 of the 16 patients (62.6%) had valvular defects due to previous RHD as a predisposing pathology. We think that the changing patterns of IE cannot be applied globally. The clinical aspects and the prognosis of this disease may be different in developing countries like Turkey, where RHD is still considerably frequent. Furthermore, in a setting with higher incidence of RHD, IE involving mitral and aortic valves (i.e. left-sided IE) may be observed more frequently even among pediatric patients.

Limitations of the study

This study, like earlier reported studies, has some unavoidable limitations. There is remaining uncertainty regarding the true vegetation size when measurements are based on transthoracic echocardiography. The additional use of transesophageal echocardiography may improve detection rate and the accuracy of measurements. It is well known that some embolic events remain silent during the course of IE. This study was a retrospective one, with a relatively small study group, selected among the patients seen at a tertiary referral center.

In conclusion, the disease scope varies greatly in pediatric and adult patients as well as in different countries. Left-sided IE has a high rate of complications in children, which are mostly fatal or debilitating. RHD is still a frequent predisposing factor of IE in our population. There is limited information in literature focusing on pediatric patients, and collective information concentrating on left-sided IE in children is needed. Our study suggests that presence of an echocardiographically detected left-sided vegetation has high sensitivity and positive predictive value of an embolic event, irrespective of vegetation size. Therefore, we propose early surgical treatment in pediatric patients with echocardiographically discovered left-sided vegetations in an attempt to prevent systemic embolic events and, therefore, decrease mortality and morbidity of IE.

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