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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Association of recurrent fever and anemia with infective endocarditis in a 13-year-old girl with bicuspid aortic valve

Vesna Petrović[1], Vesna Vujić-Aleksić[2,3], Vojislav Parezanović[4,5]

[1]Dr. Milorad Mika Pavlović Primary Health Care Center, Inđija, Serbia;
[2]Republic of Srpska Agency for Certification, Accreditation and Quality Improvement in Health Care, Banja Luka, Republic of Srpska, Bosnia and Herzegovina;
[3]University of Banja Luka, Faculty of Medicine, Department of Pharmacology, Toxicology and Clinical Pharmacology, Banja Luka, Republic of Srpska, Bosnia and Herzegovina;
[4]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[5]University Children's Hospital – Tiršova, Department of Cardiology, Belgrade, Serbia

SUMMARY
Introduction Infective endocarditis is relatively rare in pediatric population, but can result in significant morbidity and mortality. Children with bicuspid aortic valve are at higher risk of developing infective endocarditis as compared to the general population. Our objective is to emphasize the importance of rapid diagnosis and proper treatment of infective endocarditis in patients with bicuspid aortic valve with the aim of preventing serious adverse events.
Case outline We report a case of a 13-year-old girl with a newly diagnosed bicuspid aortic valve who developed infective endocarditis with severe complications and underwent cardiac surgery. Recurrent fever and anemia, as well as cardiac murmur, were present for six months prior to diagnosing infective endocarditis. During the course of illness, only one of many blood cultures taken was positive for *Streptococcus sanguinis*.
Conclusion Patients with bicuspid aortic valve require careful evaluation for infective endocarditis, especially if recurrent fever associated with anemia is present. Delayed diagnosis of infective endocarditis is associated with serious complications.
Keywords: endocarditis; congenital heart defect; children; case report

INTRODUCTION

Infective endocarditis (IE) is a rare and life-threatening disease in the pediatric population. The predominant underlying condition of IE in children nowadays is congenital heart disease, of which bicuspid aortic valve (BAV) is common. Bicuspid aortic valve occurs predominantly in men, and currently is considered an intermediate-risk factor for IE. The presentation of IE in children may be fulminant, but more often has slow progress, with prolonged low-grade fever, and a variety of somatic complaints. Consequently, diagnosing IE in children is challenging and frequently delayed. However, the presence of a new murmur or a change in the nature of a preexisting one is significant [1, 2].

We report a case of a 13-year-old girl with newly diagnosed BAV, who developed IE with severe complications and underwent cardiac surgery. Recurrent fever and anemia, as well as cardiac murmur, were present six months prior to IE diagnosis. During that period, the girl was hospitalized three times and received six courses of antibiotic therapy. Numerous blood cultures were taken, but only one was positive for *Streptococcus sanguinis*. Our objective is to emphasize the importance of rapid diagnosis and proper treatment of IE in BAV patient with the aim to prevent serious adverse events.

CASE REPORT

A 13-year-old girl without significant medical history appeared at a sports preparticipation screening at a primary care center with grade 2/6 systolic heart murmur. Electrocardiogram and routine laboratory tests were normal with the exception of slightly lower hemoglobin concentration and hematocrit levels (Table 1). On the cardiologist's evaluation one month later, the transthoracic echocardiogram (TTE) showed BAV with aortic insufficiency grade II. The diameter of the aortic annulus was normal, with normal flow rate and an eccentric insufficiency jet. The cardiologist advised next examination in six months, with permitted recreational sport activities.

During the next three months, the girl had three episodes of upper respiratory tract infection with fever, associated with iron-deficiency anemia (Fe 3.9 μmol/l). In every episode, oral antibiotic treatment (azithromycin, amoxicillin, and amoxicillin/clavulanic acid, respectively) improved the symptoms, but the patient was

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Correspondence to:
Vesna PETROVIĆ
Dr. Milorad Mika Pavlović Primary Health Care Center
Novosadska 21/73
22320 Inđija, Serbia
dr.vesna.petrovic@gmail.com

Table 1. Laboratory results during the course of illness

Variable	Sports Exam	Febrile illness after sports exam					First Hosp.	First Discharge	Second Hosp.	Third Hosp.
		A month after	Two months after	Three months after	Four months after	Four months after				
SE (mm/h)	-	-	-	-	46	46	55	65	-	-
Hgb (g/l)	111	103	93	90	84	80	85	91	84	111
Hct (l/l)	0.35	0.32	0.297	0.291	0.272	0.26	0.257	0.30	0.27	0.36
Er ($\times 10^{12}$/l)	4.46	4.2	4.09	4.07	3.91	3.77	4.01	4.3	4.03	5.05
MCV (fl)	78.5	76.7	72.5	71.5	69.7	68.9	67.8	-	67.0	-
Le ($\times 10^9$/l)	6.2	6.8	8.0	5.5	7.8	7.3	12.5	11.7	10.36	12.2
Tr ($\times 10^9$/l)	231	313	280	218	187	222	360	362	210	274
CRP (mg/l)	-	12	48	12	> 96	> 96	59.7	42.4	133.1	149.2

SE – erythrocytes sedimentation rate during first hour; HgB – hemoglobin; Hct – hematocrit; Er – erythrocytes; MCV – mean corpuscular volume; Le – leucocytes; Tr – thrombocytes; CRP – C-reactive protein

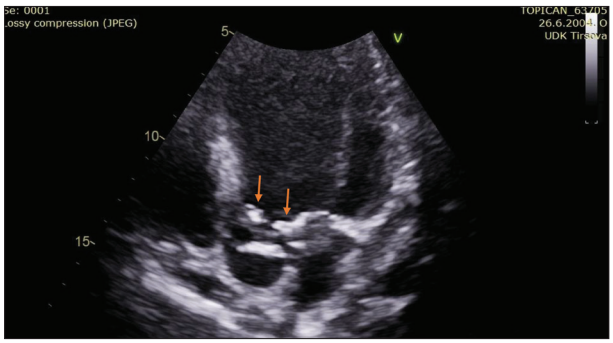


Figure 1. Five-chamber transesophageal echocardiography view of the patient with a bicuspid aortic valve showing vegetations in the left ventricular outflow tract (indicated by the arrows)

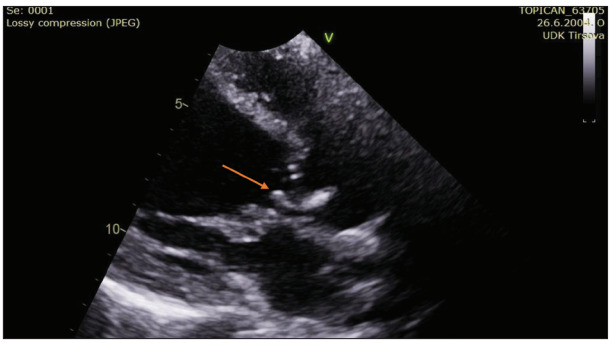


Figure 2. Parasternal long axis transesophageal echocardiography view of the patient with a bicuspid aortic valve showing vegetation in the left ventricular outflow tract (indicated by the arrow)

unresponsive to iron supplementation (Table 1). Peripheral blood smear showed hypochromic red blood cells with anisocytosis.

Three months after diagnosing BAV, the girl was hospitalized due to five-day fever (> 38°C) with nausea, vomiting, dizziness, weakness, and leg pain. Inflammatory markers were elevated and anemia got worse (Table 1). All blood cultures were negative and the TTE cardiac findings were unchanged as compared to the baseline. The girl was treated with an oral antibiotic (cefpodoxime) and discharged home in good general condition.

A few weeks following the first hospitalization, the girl presented to hospital again with a four-day fever (39°C) and right thigh pain. Inflammatory markers were elevated and anemia present (Table 1). On auscultation, a diastolic murmur was heard. Abdominal computerized tomography demonstrated splenomegaly (131 × 52 mm) and TTE suspected verruca on the anterior mitral valve leaflet with mild mitral and aortic regurgitation. Infective endocarditis was suspected and empirical intravenous (IV) antibiotic therapy initiated (linezolid and gentamicin for 14 days). Out of several blood cultures taken, only one was positive for *Streptococcus sanguinis* and the antibiotics were changed to IV penicillin G and gentamicin for 14 days. The girl's condition slowly improved and she was discharged home after five weeks of hospitalization.

Two weeks after the second hospitalization, the girl presented at a tertiary hospital reporting three-day fever (up to 38.8°C), acute onset of severe headache, and right leg pain that made walking difficulties. On admission, the patient was febrile (> 38°C), had low blood pressure with a wide pulse pressure (100/20 mmHg), and a diastolic murmur was present. Inflammatory markers were elevated (Table 1). One major and three minor modified Duke criteria for IE were established. Transesophageal echocardiogram (TOE) showed a circular formation (14 × 9 mm) on the anterior mitral valve leaflet (Figures 1 and 2). In addition, a suspected rupture of BAV coronary leaflet as well as significant mitral and moderate aortic regurgitation were present. The left ventricle was mildly dilated with preserved ejection fraction of 70%. Doppler ultrasound of the legs as well as computerized tomography of the head were normal. Abdominal magnetic resonance imaging confirmed splenomegaly (140 × 47 × 67 mm). N-terminal pro-brain natriuretic peptide was 2672 pg/ml. The serial blood cultures were negative and empirical antibiotic therapy for blood culture-negative IE was initiated (IV ampicillin and gentamicin). Fever persisted for three weeks and repeated TOE showed no reduction in vegetation. Antibiotic therapy was changed to IV penicillin G and amikacin. On the 30th day of hospitalization, N-terminal pro-brain natriuretic peptide was doubled (5217 pg/ml) and TOE showed suspected perforation of the aortic and mitral valve. The finding was confirmed by multislice detector cardiac computerized tomography, which showed an anterior–posterior BAV without raphe, thickened coronary cusp (2.5 mm), 4.3 mm leaflet perforation, and two aortic valve aneurysms (4.8 × 5 mm and 11.5 × 12 mm).

Additionally, a periannular abscess (19.8 × 6.2 × 14.6 mm) was present along the anterior wall of the aortic root. The anterior mitral valve leaflet was thickened (2.5 mm) with an aneurysm (11 × 13 mm) at the site of previous vegetation and a medial cusp perforation (2 mm in diameter).

On the 58th day of hospitalization, the patient underwent aortic valve replacement with 19 mm bileaflet mechanical prosthesis (St Jude Medical, St Paul, MN, USA), along with aortic root augmentation and anterior mitral leaflet reconstruction. No vegetations were present at surgery. Antibiotic prophylaxis for bacterial endocarditis (IV cefazolin, amikacin, vancomycin) was administered following the operation. Subsequent laboratory tests and electrocardiogram were normal. The patient recovered uneventfully and was discharged asymptomatic on the 18th postoperative day.

At one-year follow-up, the girl was asymptomatic, and TTE showed significantly lower size of the left ventricle, normal function of the mechanical valve and residual moderate regurgitation at the place of the anterior mitral leaflet reconstruction.

This case report was approved by the institutional ethics committee, and written consent was obtained from the patient's parent/guardian for the publication of this case report and any accompanying images.

DISCUSSION

Despite improvements in diagnostics and management, IE remains associated with significant morbidity and mortality. Congenital heart diseases predispose to the development of IE. Bicuspid aortic valve is the most common form, with a prevalence of 0.5–2% in the general population and is currently considered intermediate-risk cardiac condition for IE [1, 2]. Some studies showed that the risk of IE was markedly greater for BAV than tricuspid aortic valve patients [3]. Patients with IE and BAV were also significantly younger and had similar rates of intracardiac complications as high-risk patients [4]. As of recently, we must also consider that COVID-19 infection and acute endocarditis may present similarly, yet with very different treatments [5].

The presence of non-specific febrile illness, irrespective of the duration of the fever, fever pattern, or the resolution of fever with antipyretics, in children with congenital heart disease should be considered as suspected IE [6]. Routine laboratory findings in IE are non-specific, such as elevated inflammatory markers and anemia, usually normocytic and normochromic, which reveals the disease activity and is well known as anemia of inflammation [7]. Our patient had hypochromic and anisocytic anemia, but also slightly lower hemoglobin concentration and hematocrit levels present six months prior to IE. Although anemia was mild, it cannot be ruled out it was associated with the development of IE. One analysis has shown that iron-deficiency anemia changed oral microbiota by decreasing overall bacterial diversity and altered taxonomic composition but it did not identify whether iron deficiency anemia can raise the risk of IE [8]. A new-onset systolic murmur was also discovered prior to BAV diagnosis in our patient. Nevertheless, the typical murmur of aortic insufficiency, revealed on TTE one month afterwards, is diastolic. Mitral and aortic regurgitation were developed later in the course of illness alongside with the diastolic murmur. The abovementioned limits us from drawing a firm conclusion on the association of the new-onset cardiac murmur with the beginning of IE. A study by N'Guyen et al. [9] showed that the time interval between IE first symptoms and the diagnosis is closely related to the IE clinical presentation, patient characteristics, and the causative microorganism.

Infective endocarditis in BAV patients is mostly community acquired with oral cavity viridans group streptococci as the most common causative microorganisms. Our patient denied any dental procedures; however, even routine daily dental hygiene could cause oral bacteria enter the bloodstream [1, 2, 10]. History of excessive antibiotic use in our patient might have been the reason for only one *Streptococcus sanguinis*-positive blood culture out of numerous taken. Other possible reasons for negative blood cultures may include infections with highly fastidious bacteria or IE caused by a virus or a fungus. Culture-negative IE is described in patients with clinical and echocardiographic evidence of IE, with blood cultures yielding no organisms [11]. In our patient, no vegetations were found during the cardiac surgery and pathological examination of the resected valvular tissue was not done. Nevertheless, histological diagnosis of IE remains the gold standard according to the guidelines [11]. Our patient's IE diagnosis is based on one major (echocardiogram positive for IE) and three minor modified Duke criteria (fever, predisposing heart condition, positive blood culture).

Surgical treatment is used in approximately half of patients with IE due to severe complications. Heart failure is the most frequent complication of IE, observed in 42–60% of native valve endocarditis cases and represents the most common indication for surgery. It is more often present when IE affects the aortic rather than the mitral valve [11]. Patients with BAV IE have a high risk of perivalvular abscesses and thus prompt diagnosis and timely surgery might be required [12]. Even though antibiotic therapy for IE was administered appropriately for the age, dose, and duration, our patient underwent cardiac surgery due to significant insufficiency of both the aortic and the mitral valve, as well as other intracardiac complications.

It is worth mentioning that according to the Sievers classification, our patient had the anterior–posterior BAV type 0 with no raphes, which is rare [13]. A large multicenter study showed that the presence of raphe is a risk factor significant for both aortic stenosis and regurgitation and subsequent aortic valve and aortic surgery [14]. Considering BAV phenotypes according to the fusion of leaflets, our patient had a fusion of the right and the left coronary cusp (coronary cusp fusion). All other types of BAV (mixed cusp fusion) are considered to be one of the risk factors for the occurrence of aortic stenosis and associated aortopathy, which could result in significant hemodynamic changes [2].

Diagnosing IE may be difficult due to non-specific symptoms. However, the presence of a cluster of symptoms in a patient with BAV requires careful evaluation for IE. If recurrent fever and anemia are present in children with BAV, IE should always be suspected. Late IE diagnosis is associated with a high risk of serious complications and higher rates of surgical interventions.

Conflict of interest: None declared.

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Повезаност рекурентне температуре и анемије са инфективним ендокардитисом код тринаестогодишње девојчице са бикуспидном аортном валвулом

Весна Петровић[1], Весна Вујић-Алексић[2,3], Војислав Парезановић[4,5]

[1]Дом здравља „Др Милорад Мика Павловић", Инђија, Србија;
[2]Агенција за сертификацију, акредитацију и унапређење квалитета здравствене заштите Републике Српске, Бања Лука, Република Српска, Босна и Херцеговина;
[3]Универзитет у Бањој Луци, Медицински факултет, Катедра за фармакологију, токсикологију и клиничку фармакологију, Бања Лука, Република Српска, Босна и Херцеговина;
[4]Универзитетска дечја клиника, Служба за кардиологију, Београд, Србија;
[5]Универзитет у Београду, Медицински факултет, Београд, Србија

САЖЕТАК

Увод Инфективни ендокардитис је редак у педијатријској популацији, али узрокује значајано оболевање и смртност. Деца са бикуспидном аортном валвулом имају већи ризик од развоја инфективног ендокардитиса у односу на општу популацију. Наш циљ је да истакнемо важност брзе дијагнозе и правилног лечења инфективног ендокардитиса код болесника с бикуспидном аортном валвулом, у циљу спречавања озбиљних нежељених догађаја.

Приказ болесника Приказујемо случај тринаестогодишње девојчице са новодијагностикованом бикуспидном аортном валвулом која је развила инфективни ендокардитис са тешким компликацијама и била подвргнута кардиохируршкој операцији. Рекурентна температура и анемија, као и срчани шум, били су присутни шест месеци пре постављања дијагнозе инфективног ендокардитиса. Током болести, само једна од многобројних узетих хемокултура била је позитивна на *Streptococcus sanguinis*.

Закључак Болесници са бикуспидном аортном валвулом захтевају пажљиву процену у погледу инфективног ендокардитиса, посебно ако је присутна рекурентна температура удружена са анемијом. Одложено постављање дијагнозе инфективног ендокардитиса је повезано са озбиљним компликацијама.

Кључне речи: ендокардитис; урођена срчана мана; деца; приказ болесника