Case Report / Приказ болесника

Vesna Petrović1, Vesna Vujić-Aleksić2,3, Vojislav Parezanović4,5

Recurrent fever and anemia as manifestations of infective endocarditis in a 13-year-old girl with bicuspid aortic valve

Рекурентна температура и анемија као манифестације инфективног ендокардитиса код тринаестогодишње девојчице са бикуспидном аортном валидуом

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

Received: April 12, 2020
Revised: April 16, 2022
Accepted: April 27, 2022
Online First: May 5, 2022
DOI: https://doi.org/10.2298/SARH200412046P

*Accepted papers are articles in press that have gone through due peer review process and have been accepted for publication by the Editorial Board of the Serbian Archives of Medicine. They have not yet been copy-edited and/or formatted in the publication house style, and the text may be changed before the final publication.

Although accepted papers do not yet have all the accompanying bibliographic details available, they can already be cited using the year of online publication and the DOI, as follows: the author’s last name and initial of the first name, article title, journal title, online first publication month and year, and the DOI; e.g.: Petrović P, Jovanović J. The title of the article. Srp Arh Celok Lek. Online First, February 2017.

When the final article is assigned to volumes/issues of the journal, the Article in Press version will be removed and the final version will appear in the associated published volumes/issues of the journal. The date the article was made available online first will be carried over.

*Correspondence to:
Vesna PETROVIĆ
Dr Milorad Mika Pavlović Primary Health Care Center, Novosadska 21/73, 22320 Indija, Serbia
E mail: dr.vesna.petrovic@gmail.com
Recurrent fever and anemia as manifestations of infective endocarditis in a 13-year-old girl with bicuspid aortic valve

Рекурентна температура и анемија као манифестације инфективног ендокардитиса код тринаестогодишње девојчице са бикуспидном аортном валвулом

INTRODUCTION

Infective endocarditis (IE) is rare and life-threatening disease in 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 as 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 new murmur or change in the nature of 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, a 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 aim to prevent serious adverse events.

**CASE REPORT**

A 13-year-old girl with no significant past medical history appeared on sports preparticipation screening at primary care center with grade 2/6 systolic heart murmur. Electrocardiogram and routine laboratory tests were normal with exception of slightly lower hemoglobin concentration and hematocrit levels (Table 1). On cardiologist’s evaluation one month after, 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. Cardiologist had advised next exam for the six months and also recreational sport activities were permitted.

In the next three months a girl had three episodes of upper respiratory tract infection with fever, associated with iron-deficiency anemia. Oral antibiotics prescribed in every episode (azithromycin, amoxicillin and amoxicillin/clavulanic acid, respectively) improved symptoms, but she was unresponsive to iron supplementation (Table 1.). Peripheral blood smear showed hypochromic red blood cells with anisocytosis.

Three months after diagnosing BAV a 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. A girl was treated with oral antibiotic (cefpodoxime) and discharged home in good condition.

Few weeks following the first hospitalization a girl presented to hospital again with a four-day fever (39°C) and right thigh pain. Inflammatory markers were elevated and anemia
presented (Table 1.) On auscultation diastolic murmur appeared. Abdominal computerized tomography showed splenomegaly (131x52 mm) and TTE showed suspected verruca on the anterior mitral valve leaflet with mild mitral and aortic regurgitation. Infective endocarditis was suspected and empirical 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 penicillin G and gentamicin for 14 days. Girl’s condition slowly improved so she was discharged home after five weeks of hospitalization.

Two weeks after the second hospitalization the girl presented at 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 she was febrile (>38°C), had low blood pressure with a wide pulse pressure (100/20 mmHg) and diastolic murmur present. Inflammatory markers were elevated (Table 1.). One major and three minor modified Duke criteria for IE were established. Transoesophageal echocardiogram showed a circular formation (14 x 9 mm) on the anterior mitral valve leaflet (Figures 1 and 2). Also, suspected rupture of BAV coronary leaflet, as well as significant mitral and moderate aortic regurgitation, were present. Left ventricle was dilated with systolic function preserved (ejection fraction of 70%). Doppler ultrasound of legs as well as head computerized tomography were normal. Abdominal magnetic resonance imaging confirmed splenomegaly (140x47x67 mm). N-terminal pro-brain natriuretic peptide was 2672 pg/ml (normal range <178 pg/ml), and medical therapy for the acute congestive heart failure was initiated. The serial blood cultures were negative and empirical antibiotic therapy for blood culture-negative IE was initiated (ampicillin and gentamicin). After three weeks fever persisted, no reduction in vegetation was observed and antibiotic therapy was changed to penicillin G and amikacin. On the 30th day of hospitalization N-terminal pro-brain natriuretic peptide has doubled (5217 pg/ml) and repeated transesophageal echocardiogram showed suspected perforation of aortic and mitral valve. Finding was confirmed by multislice detector cardiac computerized tomography, which showed anterior-posterior BAV without raphe, thickened coronary cusp for about 2.5 mm, 4.3 mm leaflet perforation and two aortic valve aneurysms (4.8x5 mm and 11.5x12 mm). Additionally, a periannular abscess (19.8x6.2x14.6 mm) was present along the anterior wall of aortic root. The anterior mitral valve leaflet was thickened (2.5 mm) with an aneurysm (11x13 mm) at the site of previous vegetation and with 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, Minnesota, USA), along with aortic root augmentation and anterior mitral leaflet reconstruction. No vegetations were seen during operation. Antibiotic prophylaxis for bacterial endocarditis (cefazolin, amikacin, vancomycin) was administered after 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, a girl was asymptomatic, and TTE showed significantly lower size of the left ventricle, normal function of 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 for the publication of this case report and any accompanying images.

**DISCUSSION**

Despite improvements in diagnostics and management, IE remains associated with a significant morbidity and mortality. Congenital heart diseases predispose to the development of IE. BAV is the most common form with 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 23 times 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, such as abscess, fistula, or valve perforation as high-risk patients [4].

Diagnosing IE in children is challenging. It often presents as a subacute infection, with low-grade fever and non-specific symptoms that may mislead initial assessment and result in IE late diagnosis. Recently we must also consider that COVID-19 infection and acute endocarditis may present similarly, both with shortness of breath and vital sign abnormalities, yet they require very different treatments [5]. However, in children with congenital heart disease the presence of non-specific febrile illness, irrespective of the duration of fever, fever...
pattern, or the resolution of fever with antipyretics should be considered as suspected IE [6]. Routine laboratory findings in IE are non-specific, such as elevated inflammatory markers and anemia, which is usually normocytic and normochromic and reveals disease activity, such in our case [7]. Some comparative analysis showed that iron-deficiency anemia changed oral microbiota by decreasing overall bacterial diversity and altered taxonomic composition. However, this analysis didn't identify whether iron deficiency anemia can raise the risk of IE [8]. At our patient iron-deficiency anemia was present six months prior to IE diagnosis. It was mild following BAV diagnosis, but during the course of IE got worsened. The presence of new cardiac murmur was discovered prior to BAV diagnosis at our patient. Also, murmur was present for six months prior to IE diagnosis. A study by N'Guyen et al. showed that the time interval between IE first symptoms and diagnosis is closely related to the IE clinical presentation, patient characteristics and causative microorganism [9].

Infective endocarditis in BAV patients is mostly community acquired with oral cavity viridans group streptococci as the most common causative microorganisms [1, 2, 5]. Our patient denied any dental procedures, nevertheless, even routine daily dental hygiene could cause oral bacteria enter into the bloodstream. History of excessive antibiotic use at our patient might have been the one of the reasons why only one out of numerous blood cultures was positive for *Streptococcus sanguinis*. The other possible reasons for negative blood cultures may include infections with highly fastidious bacteria or IE caused by virus or fungi. Culture negative IE is rare and described in patients with clinical and echocardiographic evidence of IE, with blood cultures yields no organisms [10]. In our patient, no vegetations were seen during the cardiac surgery and histopathological and microbiological evaluation of resected valvular tissue was not done. The diagnosis of IE is based on modified Duke criteria which require history, clinical examination, blood cultures, laboratory results and echocardiography [10]. Our patient was diagnosed with IE according to 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 cases of native valve endocarditis and represents the most common indication for surgery. It is more often present when IE affects the aortic than the mitral valve [10]. Patients with BAV IE have a high risk of perivalvular abscesses and thus prompt diagnosis and timely surgery might
be required to prevent the perivalvular abscess formation and its extension [11]. Even though antibiotic therapy for IE was administered appropriately for age, dose and duration, our patient underwent cardiac surgery due significant insufficiency of both, aortic and mitral valves as well as other intracardiac complications.

It is worth mentioning that according to Sievers classification, our patient had the anterior-posterior BAV type 0 with no raphes, which is rare [12]. Large multicenter study showed that the presence of raphe is risk factor for significant both aortic stenosis and regurgitation and subsequent need for aortic valve and aortic surgery [13]. Considering BAV phenotypes according to the fusion of leaflets, our patient had fusion of right and left coronary cusp which is defined as the coronary cusp fusion. All other types of BAV are defined as the mixed cusp fusion and are considered as one of risk factors for the occurrence of aortic stenosis and associated aortopathy, which could result in significant hemodynamic changes [2].

Diagnose of IE may be difficult due to non-specific symptoms. However, presence of cluster of symptoms in patient with BAV requires careful evaluation for IE. If recurrent fever and anemia present in children with BAV, IE should always be suspected. Late IE diagnose is associated with high risk of serious complications and development of indications for surgical treatment.

**Conflict of interest:** None declared.
REFERENCES


**Table 1.** Laboratory results during course of illness

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>SE (mm/h)</td>
<td>-</td>
<td>-</td>
<td>46</td>
<td>65</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hgb (g/l)</td>
<td>111</td>
<td>103</td>
<td>90</td>
<td>84</td>
<td>85</td>
<td>91</td>
</tr>
<tr>
<td>Hct (l/l)</td>
<td>0.35</td>
<td>0.32</td>
<td>0.291</td>
<td>0.26</td>
<td>0.257</td>
<td>0.30</td>
</tr>
<tr>
<td>Er (×10^{12}/l)</td>
<td>4.46</td>
<td>4.2</td>
<td>4.07</td>
<td>3.77</td>
<td>4.01</td>
<td>4.3</td>
</tr>
<tr>
<td>MCV (fl)</td>
<td>78.5</td>
<td>76.7</td>
<td>71.5</td>
<td>68.9</td>
<td>67.8</td>
<td>-</td>
</tr>
<tr>
<td>Le (×10^9/l)</td>
<td>6.2</td>
<td>6.8</td>
<td>5.5</td>
<td>7.3</td>
<td>12.5</td>
<td>11.7</td>
</tr>
<tr>
<td>Tr (×10^9/l)</td>
<td>231</td>
<td>313</td>
<td>218</td>
<td>222</td>
<td>360</td>
<td>362</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>-</td>
<td>12</td>
<td>&gt;96</td>
<td>&gt;96</td>
<td>59.7</td>
<td>42.4</td>
</tr>
</tbody>
</table>

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 transoesophageal 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 transoesophageal echocardiography view of the patient with a bicuspid aortic valve showing vegetation in the left ventricular outflow tract (indicated by the arrow)