A case of neonatal arterial thrombosis mimicking interrupted aortic arch

Hazım Alper Gürsu¹, Birgül Varan¹, Ayla Oktay¹, Murat Özkan²
¹Department of Pediatrics, Division of Pediatric Cardiology, Başkent University Faculty of Medicine, Ankara, Turkey
²Department of Cardiovascular Surgery, Başkent University Faculty of Medicine, Ankara, Turkey

Abstract
Neonatal arterial thrombosis is a very rare entity with clinical findings resembling coarctation of aorta or interrupted aortic arch. A two day-old male newborn was admitted to a different hospital with difficulty in sucking and sleepiness. On echocardiographic examination, a diagnosis of interrupted aortic arch was made and he was treated with prostoglandin E2. When the patient presented to our center, physical examination revealed that his feet were bilaterally cold. The pulses were not palpable and there were echymotic regions in the lower extremities. Echocardiography ruled out interrupted aortic arch. Computerized tomographic angiography revealed a large thrombosis and total occlusion of the abdominal aorta. Since there was no response to treatment with tissue plasminogen activator, we performed thrombectomy. Homozygous Factor V Leiden and Methylenetetrahydrofolate reductase mutations were found in this patient. Neonatal aortic thrombosis which is observed very rarely and fatal should be considered in the differential diagnosis of coarctation of aorta and interrupted aortic arch. (Turk Pediatri Ars 2015; 50: 118-22)

Keywords: Aortic arch, fibrinolysis, thrombosis, newborn

Introduction
Thrombosis in the descending aorta or abdominal aorta in the newborn is a very rare condition without an accompanying anatomical pathology. Its clinical findings are similar to coarctation of aorta (AC) or interrupted aortic (IA) and it is manifested with findings of severe heart failure in the first hours and days of life.

Case
A 2-day old male patient presented to a different hospital with complaints of difficulty in sucking and sleepiness. As a result of the tests and echocardiographic examination. The diagnosis of interrupted aortic arch type B was made and prostoglandin E2 (PGE2) was initiated at the age of seven days. He was referred to our clinic for further investigations and treatment. In the history, it was learned that the patient was born at the end of the 40th gestational week with a birth weight of 2350 g by cesarean section from the first pregnancy of a 31-year old mother. On physical examination, his general status was poor, respiratory sounds were normal, S1 and S2 were normal, cardiac sounds were rhythmical and the liver was palpable 3-4 cm in the midclavicular line. His feet were bilaterally cold. Arterial pulses were not palpable in the lower extremities and echymotic areas were present in bilateral lower extremities (more diffusely in the left side). The blood pressure was found to be 86/64 mmHg. The laboratory tests were as follows: Hb: 11.6 x10³/μL, MCV: 102 fl, RDW: 18.1%, glucose: 72 mg/dL, BUN: 87 mg/dL, creatinine: 3.04 mg/dL, uric acid: 8.4 mg/dL, sodium: 147 mmol/L, potassium: 5.2 mmol/L, total protein: 5.36 g/dL, albumin: 3.15 g/dL, ASR: 1039 U/L, ALT: 45 U/L, ALT: 68 U/L, C reactive protein: 7.4 mg/L, APTT: 44.5 s, PT: 40.4 s, INR: 4.05. 33% segemented neutrophils and 26 lymphocytes were observed on peripheral blood smear. Periton dialysis was initiated due to renal failure that was diagnosed with the abnormality in renal function tests and oliguria. Echocardiography (ECHO) revealed tricuspid failure (mild), patent ductus arteriosus and patent foramen ovale, but IA was not considered. Thrombosis in the ab-
dominal aorta was observed on angiographic examination by computerized tomography (Figure 1). Tissue plasminogen activator (t-PA) was initiated by the intravenous route (Figure 2). Meanwhile, it was observed that necrosis developed starting from the left toes. On the next day, t-PA infusion was started through the sheath placed in the femoral artery. Meanwhile, infusion with heparin was continued at the times when t-PA infusion was discontinued. Although increased abdominal aortic flow was observed on abdominal Doppler ultrasonography (USG) in the left lower extremity circulation was impaired and thrombectomy was performed in the abdominal artery and iliac artery on the second day of t-PA infusion by way of the femoral artery (Figure 3). Heparin infusion was initiated after the procedure of thrombectomy. On the third day after the procedure, heparin infusion was discontinued and enoxaparin and aspirin treatments were started. Meanwhile, the tests ordered for differential diagnosis of thrombosis were as follows: Anti Factor X: 0.13 IU/mL (normal: 0.1-1.2), lupus anticoagulant: 53.5 s (normal: 20-60), Antithrombin III:68% (normal: 80-120), Protein S: 73% (normal: 60-140), Protein C: 18% (70-140), Homocystein: 19.41 umol/L (normal: 4.5-15). In addition, the patient was found to be homozygous mutant in terms of Factor V Leiden and Methylentetrahydrofolate recutase (MTHFR) C677T. There was no known familial history of thromboembolic disease or prenatal risk factor. After thrombectomy the peripheral pulses became palpable. Renal function tests improved and urinary output reached the normal level. The progression in circulatory impairment of the left lower extremity ceased. The color and warmth of the extremity became normal. On bilateral Doppler ultrasonography, it was observed that the flow in the left leg was better. In addition, complications related with t-PA treatment were observed in the follow-up. The protein C value measured 6 months later was found to be 85%. Enoxaparin treatment was discontinued three months later. The patient is still being followed up under aspirin treatment.

Discussion

Thromboembolism in the newborn is a rare condition reported with a rate of 2.4/1000 in pediatric intensive care units or 5.1/100 000 births (1, 2). The factors which cause to arter-
al thrombosis in the neonatal period are examined in three main groups: 1) hereditary thrombophilia, 2) presence of prenatal risk factors (asphyxia, diabetes in the mother, polysemia, sepsis, intravascular catheter applications), 3) syndromes with low cardiac output. Heterozygous carrier state of factor V Leiden mutation is the most common hereditary prothrombotic condition.

The main clinical characteristic of arterial thrombosis in the newborn are findings of severe heart failure in the first hours or days of life and symptoms suggesting AC or IA.

A diagnosis of IA was made in our patient as a result of the initial tests. When we screened the literature, we found 10 cases where AC or IA was considered initially, but a diagnosis of aortic thrombosis was made subsequently (Table 1) (3-11). In 9 of these 10 patients, the symptoms started in the first 48 hours of life as in our patient. The most common findings on physical examination include findings of heart failure, cyanosis, palor, coldness and absence of pulses in the legs.

The most common localizations of thrombosis include just above the aortic valve, ascending aorta, arcur aorta and left subclavian artery. In our patient, thrombosis was present in the abdominal aorta.

While antithrombin III, protein C and protein S deficiencies are the most common causes of thrombophilia, these factors were found to be normal in four patients (Table 1). Factor V Leiden gene mutation was found to be positive only in three

<table>
<thead>
<tr>
<th>Birth weight/gestational week</th>
<th>Gender</th>
<th>Onset</th>
<th>The initial diagnosis</th>
<th>Initial clinical finding</th>
<th>Absence of pulses</th>
<th>Localization of thrombus</th>
<th>Prothrombotic test</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metsvaht T et al. 2006 (3)</td>
<td>M</td>
<td>21h</td>
<td>AC/IA</td>
<td>HF</td>
<td>Cyanosis, FA</td>
<td>Asc.A</td>
<td>ATIII, PC, PS N, FVL mutation</td>
<td>S, H, t-PA</td>
<td>Exitus</td>
</tr>
<tr>
<td>Trowitzcsh et al. 1985 (4)</td>
<td>M</td>
<td>1h&gt;</td>
<td>IA</td>
<td>Cyanosis</td>
<td>All peripheral pulses</td>
<td>Above the aortic valve and lef SA</td>
<td>None</td>
<td>Exitus</td>
<td></td>
</tr>
<tr>
<td>Scott 1987 (5)</td>
<td>M</td>
<td>1h&gt;</td>
<td>IA</td>
<td>RDS, ht</td>
<td>All extremities and cortide artery</td>
<td>Above the aortic valve and lef SA</td>
<td>ATIII N</td>
<td>Surgery</td>
<td></td>
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<tr>
<td>Uva et al. 1993 (6)</td>
<td>M</td>
<td>5h</td>
<td>IA</td>
<td>Cyanosis, HF</td>
<td>Left BA and bilateral FA</td>
<td>Above the aortic valve and lef SA</td>
<td>Surgery</td>
<td>Exitus</td>
<td></td>
</tr>
<tr>
<td>Uva et al. (6)</td>
<td>M</td>
<td>48h</td>
<td>AC</td>
<td>HF</td>
<td>Bilateral FA</td>
<td>Distal part of the left BSA</td>
<td>ATIII, PC, PS N</td>
<td>Surgery</td>
<td></td>
</tr>
<tr>
<td>Evans 1994 (7)</td>
<td>M</td>
<td>24h</td>
<td>AC</td>
<td>Palor in the legs</td>
<td>Left BA and bilateral FA</td>
<td>Above the aortic valve and lef SA</td>
<td>ATIII, PC, PS N</td>
<td>Normal development</td>
<td></td>
</tr>
<tr>
<td>Baptista MJ et al. 2002 (8)</td>
<td>NB</td>
<td>AC</td>
<td></td>
<td>AA</td>
<td></td>
<td></td>
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<td>Normal development</td>
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<tr>
<td>Amaral F 1997 (9)</td>
<td>NB</td>
<td>AC</td>
<td></td>
<td>AA</td>
<td></td>
<td></td>
<td></td>
<td>Cystic encephalo-malacia</td>
<td></td>
</tr>
<tr>
<td>Guenthard J 1997 (10)</td>
<td>NB</td>
<td>AC</td>
<td></td>
<td>AA</td>
<td></td>
<td></td>
<td></td>
<td>Exitus</td>
<td></td>
</tr>
<tr>
<td>Kenny D et al. 2007 (11)</td>
<td>Term</td>
<td>96h</td>
<td>AC</td>
<td>Palor, coldness in the legs</td>
<td>Left FA</td>
<td>DA</td>
<td>ATIII low FVL mutation</td>
<td>H, t-PA</td>
<td>Normal development</td>
</tr>
<tr>
<td>Gürsu et al. 3350g/40w</td>
<td>M</td>
<td>48h</td>
<td>IA</td>
<td>HF, coldness in the legs</td>
<td>Bilateral FA</td>
<td>AA</td>
<td>FVL and MTHFR mutation</td>
<td>H, t-PA, surgery</td>
<td>Left foot amputation</td>
</tr>
</tbody>
</table>

patients including our patient, but MTHFR gene mutation was observed only in our patient (Table 1). In recent years, the association between thromboembolic events in the newborn and Factor V Leiden gene mutation has started to be observed with a gradually increasing rate. However, clinical findings develop only in 5% of the children in whom this mutation is positive and in 40% of the adults (12). Currently, it is predicted that 3-10% of the population are heterozygous in terms of this gene and 60-250/1000000 are homozygous (13). Another hereditary risk factor in terms of arterial thrombosis is MTHFR C677T mutation. The frequency of homozygous MTHFR C677T mutation has been found to be 10,6% in healthy children (14). In our patient, both Factor V Leiden and MTHFR C677T gene mutations were found in association.

The fact that the majority of the patients were male as our patient shown that sex-linked inheritance was efficient in development of arterial thrombosis in the newborn (Table 1). In addition, continuance of thrombosis despite intensive thrombolytic treatment suggested that prenatal factors might have been involved in development of thrombus. However, our patient had no prenatal risk factor. Wieland et al. (15) reported that there were no neonatal risk factors in two newborns who had thrombus in the arcus aorta in the case presentation they published in 2013 and both patients had heterozygous Factor V Leiden mutation.

Metsvaht et al. (3) reported that they found congenital obstructive thrombosis in the arcus aorta and ascending aorta on angiography in a one-day old patient who was investigated because of suspicious AC in 2006. Findings of cardiopulmonary failure started in the first 48 hours of life as in our patient, bilateral femoral pulses were palpable, renal functions tests and transaminase levels were increased and PEG2 infusion was initiated considering AC or IA with ECHO findings. In the same patient, heterozygous carrier state for Factor V Leiden mutation was found to be the only prothrombotic risk factor. In the same patient, MTHFR C677T gene mutation was not found in contrast to our patient.

The prognosis of arterial thrombosis in the newborn depends on the area involved, involvement of the other vessels and presence of neurological complications (6). When we examined the patients, we found that thrombosis was frequently localized above the aortic valve and left subclavian artery in patients who ended up with mortality (Table 1).

Surgical or medical treatment is preferred as the first-line therapy. In medical treatment, heparin or fibrinolytic agents are used. Knöfler et al. (16) reported that fibrinolytic t-PA was efficient and safe when used at an appropriate dose in the treatment of thrombosis. Surgical treatment is performed successfully in organized and calcified partial arcus aorta thrombosis without harming the other vessels. Kawahira et al. (17) reported a patient who had thrombus in the abdominal aorta and its branches and who underwent Fogart thrombectomy, but who was lost because of sepsis. In our patient, thrombolytic treatment was performed initially. Since the response was not sufficient, thrombectomy was performed subsequently.

We tried to emphasize that obstructive thrombotic events in the aorta should also be considered in addition to congenital structural abnormalities of the aorta including AC and IA in newborns presenting with findings of acute ischemia in the extremities.

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