Myocardial infarction and arterial thrombosis in identical newborn twins with homozygosity for the PAI-1 4G/5G polymorphism

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Received 29 January 2008; accepted 3 May 2008

Abstract

Myocardial infarction in the perinatal period, in the absence of congenital heart disease or coronary artery lesions, is rare. The most common etiology described are the thromboembolism and perinatal asphyxia. We report a case of monozygotic twins who developed, after birth, acute vascular events and both had PAI-1 4G/4G homozygosity.

Keywords: Myocardial infarction; Thrombosis; Newborn twins; PAI-1/4G/5G Polymorphism

1. Introduction

Myocardial infarction (MI) in children is rare overall in patients without congenital structural cardiac disease or Kawasaki disease. Reports of neonatal arterial thrombosis are also extremely rare [1–8]. We report a case of monozygotic twins who shortly after birth both developed acute vascular events and were found to have a prothrombotic genetic disposition.

2. Case descriptions

A pair of twin males was delivered by cesarean section at 34 weeks of gestation, complicated by an abortion threat at 29 weeks. The mother was a 25 year old gravida 1 and the parents were of different ethnic groups and unrelated.

Twin A, a 2380 g male infant, with Apgar score 4 at 1 and 5 min respectively, was immediately intubated and ventilated due to respiratory distress. During the first hours of life the newborn developed cardiac failure. Quantitative determination of cardiac troponin (cTnI), creatine kinase (CK) and creatine kinase MB (CK-MB) were performed and values resulted higher than normal range (cTnI 14 ng/ml, CK 966 IU/L and CK-MB 197 ng/ml; normal range cTnI 0–0.04 ng/ml, CK 20–170 IU/L and CK-MB 0.5–3.2 ng/ml). The patient received inotropic therapy and continuous infusion of heparin (25 U/Kg/h). Arterial blood gas measurement showed normal PaO2 and PaCO2 with pH 7.35 and bicarbonate—5.8 mmol/L. Electrocardiographic findings were consistent with myocardial infarction with sinus tachycardia, Q wave on DI, aVL and chest leads V4 to V6. An echocardiographic examination showed a structurally normal heart with severely depressed global ventricular performance (LVEF 35%), anterior and septal hypokinesia and lateral and apical akinesia. Significant laboratory values included CK 718 IU/L, CK-MB 36.7 ng/ml and cTnI 2.89 ng/ml. Complete blood count, basic chemistry...
and lipid panel were normal. At 3 days of life the infant underwent coronary angiography. The first injection in the ascending aorta showed a thrombotic sub-occlusion of the left anterior descending coronary artery with left circumflex and right coronary artery patent. A second aortography (Fig. 1), performed 5 min later, showed a spontaneous complete thrombotic occlusion of the right coronary artery. Immediately after this second injection, the infant developed signs of inferior myocardial lesion, second and third degree AV block with subsequent cardiac arrest. During cardiopulmonary resuscitation, intra-aortic infusion of Urokinase was administered (single bolus of 4100 U/Kg, followed by a continuous infusion of 4100 U/Kg/24 h) in an attempt to restore myocardial perfusion. Cardiac enzymes were again risen with CK 1076 IU/L, CK-MB 79.4 ng/ml and cTnI 15.51 ng/ml. Echocardiogram showed inferior akinesia with worsening of global left ventricular function. The patient was transferred to the Intensive Care Unit and treated with inotropic agents, intravenous nitrates and low molecular weight heparin with progressive improvement of his cardiac and general condition. A control aortography performed 20 days later revealed patent coronary arteries. At this time echocardiogram showed an improvement of global ventricular function (LVEF 52%). The patient was discharged 48 days post admission, prescribed take home drugs were low molecular weight heparin, salicylic acid, carvedilol and diuretics.

At one year follow-up, low molecular weight heparin therapy was stopped. The patient was in good clinical condition with LVEF 50%, on therapy with carvedilol.

At two years follow-up, the infant underwent cardiac Magnetic Resonance (MR) that showed anterior and lateral subendocardial necrosis of the left ventricle (Fig. 2).

Twin B, a 2540 g male infant, APGAR scores 4 and 10 at 1 and 5 min, developed acute left external iliac and common femoral artery thrombosis at birth and underwent unsuccessful thrombolysis and catheter embolectomy. He was discharged on low molecular weight heparin therapy and treated with this therapy for one year. At one year follow-up, he had residual occlusion of his left common femoral artery. At two years follow-up, the patient underwent MR angiography of the lower limbs that evidenced proximal external iliac artery occlusion and recanalization of superficial femoral artery through collateral vessels (Fig. 3).

Both twins were found to be homozygous (4G/4G) for the deleted allele of the plasminogen activator inhibitor-1 (PAI-1) gene.

3. Comments

Few studies have reported neonatal myocardial infarction or ischemia that can be a possible cause of early neonatal death [1–8]. The most common etiology described are the thromboembolism and perinatal asphyxia. It was assumed that a deficiency of natural anticoagulant factors could be a cause of perinatal myocardial infarction [9]. This case report describes the development of acute vascular events after birth in identical twins who both had PAI-1 4G/4G homozygosity, that could be the most plausible risk factor for the arterial thrombotic events.

The gene for PAI-1 has an insertion/deletion polymorphism at position −675 in the promoter region, the 4G allele resulting in increased mRNA transcription in response to cytokine stimulation compared to the 5G allele, while there is little or no difference under basal conditions [10].

Indeed, patients who are homozygous for the 4G allele have higher plasma PAI-1 antigen levels or activity levels than patients who are either heterozygous or homozygous for the 5G-allele, and there is considerable evidence for the relevance of increased PAI-1 activity in thrombotic disorder [10–13].

Importantly, neonates and infants with underlying cardiac disease who are homozygous for the 4G/4G variant of the PAI-1 promoter polymorphism are at high risk of developing early thromboembolism during cardiac catheterisation or insertion of central venous lines for major surgery [14]. Recently, intreventricular hemorrhage associated with sinus venous thrombosis has been reported in a full-term neonate with PAI-1 4G/4G genotype [15]. In addition, Baumeister et al. described deep cerebral venous infarction in a preterm infant homozygous for PAI-1 4G/4G promoter polymorphism [16]. On the other hand, PAI-1 expression is dramatically induced by stress or mild hypoxia. As even an uncomplicated partum involves mild hypoxia, it may further increase PAI-1 concentrations in babies whose genetic background already endows them with high PAI-1 plasma concentrations [15].

In conclusion, our findings suggest that PAI-1 4G/4G genotype may be a genetic risk factor for perinatal thrombosis. Further attention and larger prospective studies are required to establish the relevance of PAI-1 promoter 4G/5G polymorphism in the pathogenesis of neonatal myocardial infarction and any other perinatal thrombotic complications, especially during cardiac catheterisation.

Acknowledgements

The authors thank Elaine Lows for linguistic editorial help.

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Please cite this article as: De Lucia V, et al, Myocardial infarction and arterial thrombosis in identical newborn twins with homozygosity for the PAI-1 4 G/5 G polymorphism, Int J Cardiol (2008), doi:10.1016/j.ijcard.2008.05.030