

A Tale of Two Sisters: Idiopathic Arterial Calcification of Infancy in Siblings

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Abstract

Idiopathic arterial calcification of infancy (IACI) is a rare disorder, characterized by extensive arterial calcification of large and medium sized arteries. We present two cases of IACI in siblings including the prenatal, postnatal and postmortem imaging, which is a hallmark of this disease.

Keywords: Idiopathic arterial calcification of infancy; Ectonucleotidepyrophosphatase/phosphodiesterase 1 (*ENPP1*) gene; Echocardiography

Introduction

Idiopathic arterial calcification of infancy (IACI) is a rare disorder, characterized by extensive arterial calcification and stenoses of large and medium sized arteries. Its complications include severe cardiac failure *in utero* with hydrops fetalis and postnatal respiratory failure and cardiomegaly. Recently, homozygous or compound heterozygous mutations for the ectonucleotidepyrophosphatase/phosphodiesterase 1 (*ENPP1*) gene have been reported as causative for the disorder, with 75% of affected individuals having mutations in this gene. *ENPP1* is a cell surface enzyme that generates extracellular pyrophosphate, which regulates vascular smooth muscle differentiation and inhibits soft tissue calcification. Thus, mutations in *ENPP1* lead to generalized calcification. IACI is inherited in an autosomal recessive pattern. Treatment with bisphosphonates, which are synthetic pyrophosphate analogues, has been proposed as a means of reducing arterial calcifications in IACI patients, but reported treatment regimens vary considerably both in terms of the specific bisphosphonate employed and the dose and duration of treatment [1-3].

Case Series

Case 1

This was the first baby born to non-consanguineous parents of mixed European descent at 37 weeks of gestation. The mother's family history was notable for 3 miscarriages involving her paternal half-brother. The father's family history was notable for a neonatal death to a paternal aunt and a maternal aunt with 2 miscarriages. The pregnancy was uncomplicated. The infant was reportedly well until day 20 of life, when she suddenly developed increased work of breathing and died suddenly. Post mortem examination demonstrated diffuse calcification of the coronary arteries, the aorta, and the pulmonary arteries. Her coronaries appeared prominent and were firm on palpation. All cardiac chambers were dilated. On histology, there was diffuse biventricular subendocardial infarction as well as widespread arterial calcification (Figures 1 and 2).

Case 2

Two months later, the mother became pregnant again with the same partner. Screening fetal echocardiogram at 31 weeks gestation revealed hyperechoic areas in the ascending aorta, main pulmonary arteries, mitral valve, and descending aorta, and accelerated flow in the right renal artery (Figure 3). In addition, there was a moderate pericardial effusion, hepatomegaly and polyhydramnios. The fetal

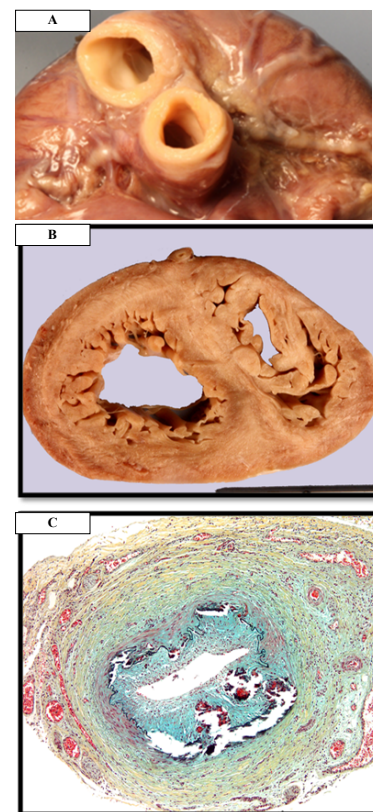


Figure 1: Autopsy findings in Case #1 a. Grossly prominent and calcified coronaries. b. Cross section of heart shows subendocardial infarction of the left and right ventricles. c. Intimal calcification and near-complete occlusion of the left anterior descending artery.

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Received July 12, 2013; Accepted August 22, 2013; Published August 26, 2013

Citation: Bishnoi R, Nigrini E, Shapiro JR, Crosson JE (2013) A Tale of Two Sisters: Idiopathic Arterial Calcification of Infancy in Siblings. J Clin Exp Cardiol 4: 266. doi:10.4172/2155-9880.1000266

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echo findings and the sibling's findings were most consistent with a diagnosis of IACI. The mother was started on oral etidronate 1200 mg orally daily at 32 weeks gestation. Repeat echo at 34 weeks of gestation was unchanged other than a slightly larger pericardial effusion. Delivery was induced at 36 weeks. Birth weight was 2495 g. The baby was non-dismorphic and had normal physical findings. Postnatally, bisphosphonate (etidronate) 20 mg/kg orally was initiated immediately. Serial ECGs were normal. Her post-natal echocardiogram showed a structurally normal heart with diffusely hyperechoic ascending aorta, transverse arch, descending aorta, main pulmonary artery, proximal branch pulmonary arteries, crux of the heart and tricuspid valve annulus (Figure 4). She had normal biventricular function. There was increased echogenicity of the right coronary artery on the second neonatal echo; the left coronary artery was not well seen. Ultrasound showed diffusely hyperechoic abdominal aorta, common iliac arteries and renal arteries, generalized and diffuse calcification of the carotid arteries and increased echogenicity in the anterior cerebral and middle

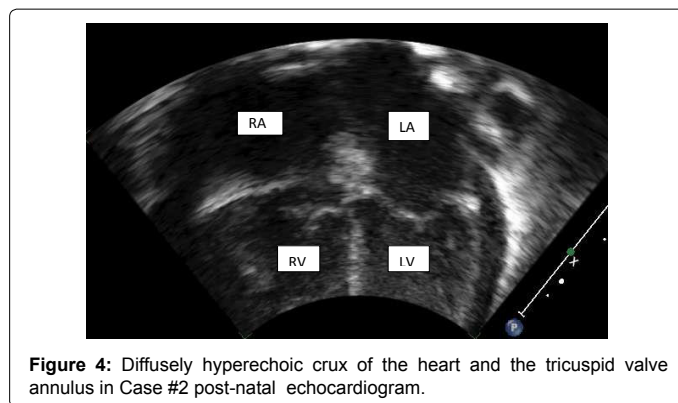


Figure 4: Diffusely hyperechoic crux of the heart and the tricuspid valve annulus in Case #2 post-natal echocardiogram.

cerebral arteries, all with normal Doppler velocities. DNA sequencing of the *ENPP1* gene showed a homozygous mutation in exon 14 at c.1412A>G, a mutation previously reported as disease-causing for IACI [1-3]. DNA analysis in each parent demonstrated heterozygosity for the same defect. The child remained hemodynamically stable throughout hospitalization, and was discharged on day of life 26. The pericardial effusion resolved by 3 weeks of life. She is now 10 months old and remains asymptomatic, with normal growth and development. Her echocardiogram continues to show unchanged diffuse increased echogenicity with normal ventricular function and ECGs have been unremarkable. She continues on 20 mg/kg daily of etidronate orally. She has not shown any biochemical, radiological or clinical evidence of rickets or osteoporosis. Her calcium and alkaline phosphatase levels have been normal.

Discussion

IACI was initially described by Bryant and White in 1901 [4]. The incidence is unknown, but approximately 180 cases have been reported to date and many cases are presumed to go undiagnosed or unreported. Most reported cases of IACI have been diagnosed at autopsy [5]. Antenatal diagnosis of IACI by fetal echocardiography has also been reported [5,6]. Dystrophic calcification in IACI results in decreased vessel compliance, with resultant hypertension, ischemia, myocardial infarction and cardiac failure [7]. Fetal heart failure can result in polyhydramnios, fetal hydrops, and demise during the early half of the last trimester of pregnancy [5,6]. Coronary artery involvement can be lethal within the first 6 months. Several case studies have described patients who survived into adulthood with persistent hypertension and cardiovascular squealae; however, approximately 85% of affected infants do not survive beyond 6 months of age [1].

Medical management of cardiovascular effects has generally been unsuccessful. However, in a case report by Ciana et al. [7], prostaglandin E1 infusion promptly controlled hypertension in a premature baby with IACI. Some infants treated with bisphosphonate postnatally have survived [8]. In addition, spontaneous remission of the disorder has also been reported [9]. However, to date curative therapy for children with IACI is not proven. Treatment with bisphosphonates has been proposed as a means of reducing arterial calcifications in IACI patients. Here, etidronate was administered based on previous reports and the fact that unlike currently available nitrogen-containing bisphosphonates, etidronate is recognized to impair tissue mineralization while decreasing bone resorption. Our second case received bisphosphonates during fetal life starting at 32 weeks. The maternal dose was based on an adult dose known to cause a mineralization defect in bone for non-IACI indications; no literature was available to guide fetal therapy.

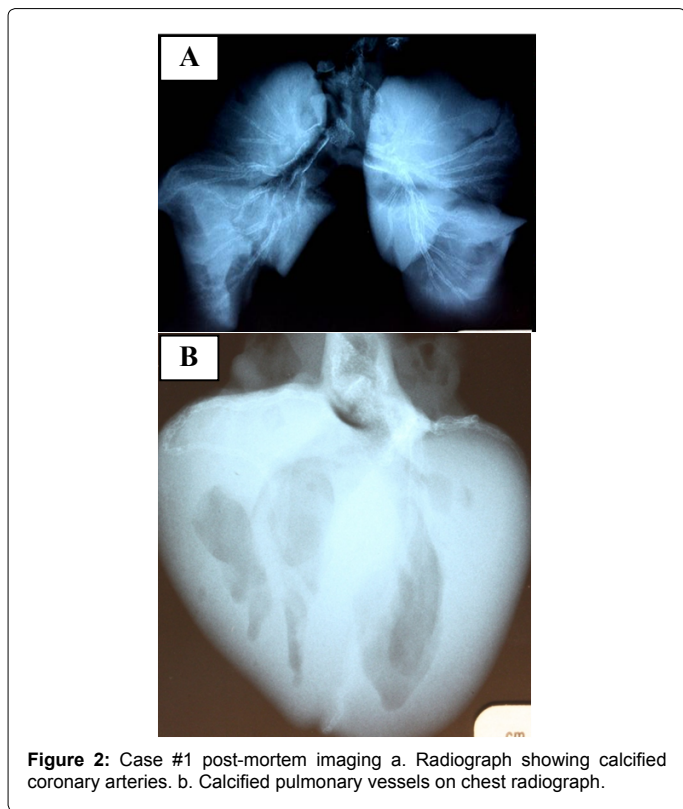


Figure 2: Case #1 post-mortem imaging a. Radiograph showing calcified coronary arteries. b. Calcified pulmonary vessels on chest radiograph.

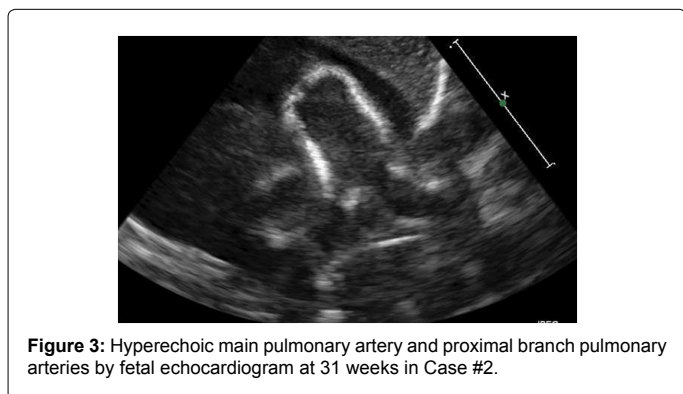


Figure 3: Hyperechoic main pulmonary artery and proximal branch pulmonary arteries by fetal echocardiogram at 31 weeks in Case #2.

The case reports of postnatal treatment with bisphosphonates have shown mixed outcome, with some resolution of the arterial calcifications in long-term survivors in some cases and infant death following treatment with or without resolution of the calcifications in others. Reported risks of long term postnatal treatment have included rickets, hypocalcemia and pulmonary alveolar microlithiasis [3,10].

Although the diagnosis of IACI is based on clinical features and echocardiographic and typical radiographic features, molecular analysis of ENPP1 is highly recommended for genetic counseling in an affected family. Early screening including fetal genetic testing and echocardiography is recommended in future pregnancies of all affected families.

Conclusion

IACI can cause rapidly progressive ischemic heart disease in affected infants, and carries a very high mortality risk. The diagnosis must be considered in the appropriate clinical context and confirmed by genetic testing and characteristic echocardiographic and radiographic findings. Currently, there is no definitive therapy, although the use of diphosphonates may be useful. Fetal therapy is unproven but was well-tolerated in our patient.

Acknowledgment

We would like to thank Dr. Pamela E. Southall from the office of the chief medical examiner, Maryland and Dr. Renu Virmani and Bob Kutys from the CV pathology for providing the autopsy images.

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