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Fatal Outcome of Two Siblings with Idiopathic Arterial Calcification of Infancy Diagnosed In Utero

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Abstract. Idiopathic arterial calcification of infancy (IACI) is a rare condition characterized by extensive arterial calcification and stenoses of large and medium-sized arteries. Its complications include severe cardiac failure diagnosed *in utero* as hydrops fetalis or postnatally as respiratory failure combined with cardiomegaly. Two newborn male siblings with IACI are described. *In utero,* echocardiography revealed poor ventricular function and hyperechogenic foci in arterial walls. Both had fatal outcome during the newborn period. At autopsy, medial calcifications in the walls of great arteries, in coronary arteries, in glomeruli, and in subendocardium were detected. In addition, an inflammatory process in the shoulder joint was determined to be large periarticular tissue calcifications. Because of an autosomal recessive inheritance pattern of IACI, fetal echocardiography is recommended in future pregnancies of all affected families.

Key words: Idiopathic arterial calcification of infancy — Fetal echocardiography

Idiopathic arterial calcification of infancy (IACI) is an extremely rare form of vascular calcification, which is inherited in an autosomal recessive pattern [1]. The etiology of the disease is unknown. Clinical presentation is variable; cardiac failure, which may be found prenatally or immediately after birth, is the most common clinical finding [1, 4, 5]. Hypertension is usually present and may be refractory to medical therapy [3, 9]. The prognosis is poor; coronary artery involvement leads to death within 6 months [4, 5, 12].

We report two infants of IACI diagnosed *in utero.* Both died during the newborn period. In autopsy, severe calcifications in the walls of the great arteries, in the coronary arteries, and in the glomeruli were found. In addition, large periarticular calcifications in the shoulder of the first sibling are demonstrated.

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Case Report

The two patients were the second and third children of unrelated Finnish parents. The first child, a girl, is healthy. The mother had been treated with carbamazepin for epilepsy prior and during all pregnancies. She had had no epileptic seizures during pregnancies.

Case 1

A hydroptic male infant of 29 weeks' gestation, weighing 1740 g, was delivered by emergency cesarean section for poor beat to beat variability. Two days before delivery the mother developed preeclamptic symptoms. Prior to delivery the ultrasound examination showed severe fetal hydrops and pericardial effusion. Regurgitation of both atrioventricular valves was noticed. The Apgar scores were 2 and 3 at 1 and 5 minutes, respectively. After intubation, bilateral chest and pericardial tubes were placed and abdominal paracentesis was performed, with each tube draining clear serous fluid. A chest roentgenogram showed extremely dilated heart. Echocardiography revealed a structurally normal heart with myocardial hypertrophy (3 SD) and poor ventricular function (fractional shortening of 12%).

Ventilatory support and inotropic medication were started. In x-ray an inflammatory process in the right shoulder was suspected (Fig. 1), and because of elevated c-reactive protein (62 mg/L) and a low trombocytic consentration of 44 antibacterial medication was started. During the next few days, despite cardiac failure systemic hypertension with a mean arterial pressure of 80 to 100 mmHg was noticed and nifedipine was administered.

Urinary organic acid examination and consentration of β-long-chain 3-hydroxyacyl coa dehydrogenase showed normal findings. Viral and bacterical cultures of blood and pleural and peritoneal fluids were uniformly negative. In muscle biopsy specimens the mitochondrial enzymes of the respiratory chain were normal. Furthermore studies of cultured skin fibroblasts revealed normal finding. Cranial ultrasound revealed symmetrical ventriculomegaly. Two-dimensional and Doppler ultrasound of the kidneys was normal.

At the age of 6 days the condition of the patient was better and he was extubated. However, at 14 days the hemodynamic situation became worse and respiratory treatment was started again. Echocardiography revealed cardiomegaly and poor movement of the left ventricular walls (fractional shortening of 10%). In the aortic wall there were hyperechogenic foci in the ascending and descending aorta. Despite intensive support, the baby developed increasing cardiac failure and died at 24 days of age.

On pathological examination, the body was that of a normally formed male infant weighing 1350 g. The size of the heart was larger

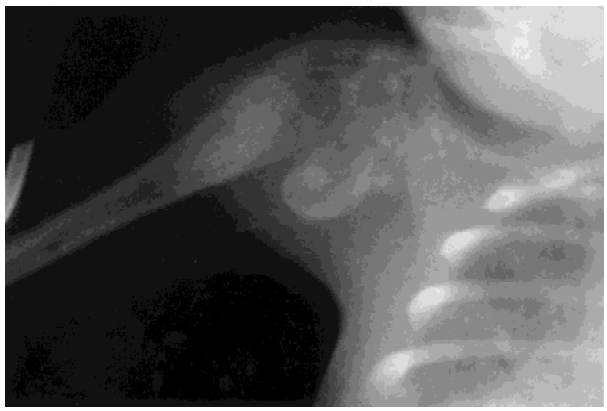

Fig. 1. X-ray of the right shoulder of patient 1 reveals a large area of tissue calcifications. The section of the shoulder joint showed abundant periarticular calcifications.

Fig. 2. Microscopy of aortic wall containing intimal calcifications, which are situated near the internal elastic lamina but also in intima and throughout media. In adventitia, an inflammatory infiltrate with lymphocytes could be seen. Calcifications were surrounded by giant cells.

than normal, and it weighed 33 g (normal 9.6 ± 3.3 g). The color of the muscle was light brown. Coronary arteries were macroscopically normal. The liver was of normal size, weighing 72 g. Cut surface was brownish-green in color.

Light microscopy revealed small areas of coagulation necrosis subendocardially. Medial calcifications were detected in ascending and descending aorta and in pulmonary arteries. In a section containing a coronary artery slight perivascular lymphocyte infiltration was found. No inflammatory reaction was seen. A biopsy from kidney contained calcified foci in glomeruli and tubules. Section of humerus showed abundant tissue calcification but no inflammatory infiltrations. Bacterial and viral cultures from heart, liver, or lung tissue were all negative, as was mycobacterial culture from the shoulder joint.

Case 2

A male sibling of case 1 was born 2 years later at 30 weeks' gestation. During this pregnancy, preeclamptic symptoms started at 29 gestational weeks. Five days before delivery fetal echocardiography revealed a structurally normal heart with severe myocardial dysfunction in both ventricles with fractional shortening of 12%. All four cardiac chambers were dilated and severe regurgitation in both atrioventricular valves was observed. Hyperechogenic foci were seen in the walls of both atrias and in atrioventrilar valves. The wall of ascending aorta was thickened and hyperechogenic plagues were seen. Due to severe cardiac failure accompanied with pericardial effusion transplacental digitalization with intravenous infusion was started. After 3 days of treatment there was no improvement in fetal echocardiography.

A grotesquely hydropic male infant weighing 2430 g was delivered by secarean section after 5 days of digitalization with Apgar scores of 6 and 7 at 1 and 5 minutes, respectively. Immediately after birth he required ventilatory support. A chest roentgenogram showed extremely dilated heart and pleural effusion. Echocardiography confirmed severe myocardial dysfunction and cardiac failure. The child could not be ventilated and died after 1 hour of life.

On pathologic examination, a hydropic male infant weighing 2400 g was seen. The heart was enlarged, weighing 23 g (normal 17.7 ± 4.2 g). Pericardial effusion was noted with a color of bright yellow. Lungs were hypoplastic weighing 28.8 g (normal 45 ± 5 g). Both ventricles of the heart were dilated. The aortic wall was thickened and white plaques were seen in ascending and descending aortic walls as well as in the orifices of bigger arteries.

Microscopically, calcifications were seen in the aorta (Fig. 2) and in pulmonary and coronary arteries (Fig. 3). Mostly, they were situated near the internal elastic lamina but were also seen in intima and throughout media. Sometimes calcifications were surrounded by giant cells. In adventitia a mild, mixed inflammatory infiltrate with lymphocytes accompanied with macrophages, plasma cells, and eosinophils could be seen. In the heart, calcifications were detected subendocardially between muscle fibers. In addition, lamellar, round calcified foci were noticed in the glomeruli and tubuli of the kidneys, in adrenal zona reticularis, in a thyroid follicle, and in the thymus near Hassel's bodies. In liver, some pale stained, ischemic hepatocytes surrounding the central veins contained small calcifications.

On the grounds of macroscopic and microscopic findings, a diagnosis of IACI was established in both infants.

Discussion

IACI was described by Bryant and White in 1901 [2]. The incidence is unknown, but approximately 100 cases have been reported to date. Most reported cases of IACI have been diagnosed at autopsy [1, 5]. However, in previous papers antenatal diagnosis of IACI by fetal echocardiography has also been demonstrated [5, 10]. Hajdu et al. [5] found hyperechogenic and hypokinetic walls in both atria and enlargement of the great vessels. The fetus died *in utero.* Samon et al. [10] diagnosed IACI antenatally by detection of hyperechogenicity of the proximal aorta and central pulmonary vessels. Hypertrophic cardiomyopathy was evident [10]. In our two fetuses with IACI, all cardiac chambers were dilated and severe myocardial dysfunction accompanied by atrioventricular valve regurgitation was evident. In addition, there were hyperechogenic foci in the walls of both atrias and great arteries.

Dystrophic calcification in IACI results in decreased vessel compliance and hypertension, with resultant cardiac failure and hypertrophy [3]. Fetal heart failure re-

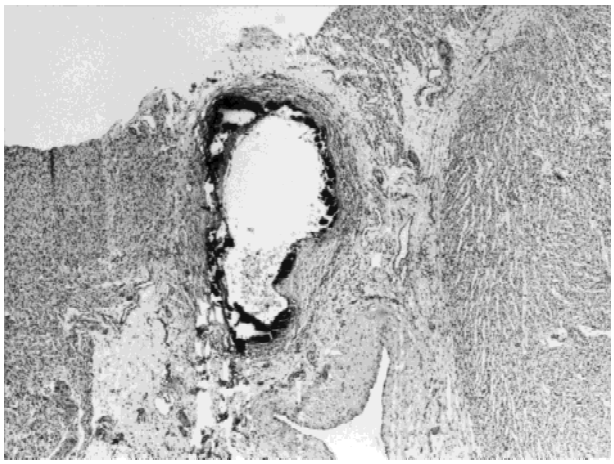

Fig. 3. Intimal calcifications in a coronary artery. A perivascular lymphocyte infiltration was found.

sults in polyhydramnios, fetal hydrops, and demise during the early half of the last trimester of pregnancy [1, 5, 10]. Premature delivery is common. In this case report of two siblings, preeclamptic symptoms in the mother started at 29 weeks' gestation. In case 2, due to severe fetal cardiac failure, transplacental digitalization was started. However, no improvement in cardiac function was noticed. Both infants were delivered prematurely because of poor beat to beat variability and fetal hydrops.

Postnatally, the clinical findings of IACI include severe congestive heart failure and refractory hypertension [3, 8, 9]. Medical management of cardiovascular effects is generally unsuccessful. However, in a case report by Ciana et al. [3], prostaglandin E_1 (PGE_1) infusion promptly controlled hypertension in a premature baby with IACI. Some infants treated with diphosphonate (an inhibitor of calcium salt precipitation) [8] or a combination of corticosteroids, estrogens, and thyroid hormone [9] have survived. In addition, spontaneous remission of the disorder has been reported [11]. In case 1, systemic vascular hypertension soon after birth was evident. A calcium antagonist, nifedipine, was started but no clear evidence of the effectiveness was noticed. Case 2 died after 1 hour of life with cardiac failure that did not respond to inotropic medication.

Interestingly, in case 1 x-ray revealed an inflammatory process in the right shoulder. Due to elevated c-reactive protein and decreased thrombocytes in the blood, antibacterial medication was started. However, no evidence of viral or bacterial infection was demonstrated in autopsy. The section of the shoulder joint showed abundant periarticular calcifications. The tissue calcifications are known to be secondary phenomena in IACI and should be taken into consideration in differential diagnostics between infection and calcifications [4].

Microscopically, in IACI arterial calcifications are usually detected in the media of large and medium-sized arteries [1]. In contrast, atherosclerotic plaques are mainly seen in the intima, and they contain foamy macrophages, myointimal proliferation, and sometimes inflammatory cells. In our cases, subendocardial calcifications were also seen without signs of myocarditis. In addition, surprisingly large periarticular calcifications were noticed without evidence of arthritis.

The mechanism of calcification in IACI is not understood. Altered iron metabolism [9], degeneration of elastin fibers [12], abnormal response to vascular injury [7], altered prostaglandin dysfunction [3, 6], and disorders of calcium–phosphorus metabolism [13] are the suspected causes of vascular injury in IACI. Because of an autosomal recessive inheritance pattern, a family history may be remarkable for stillborn of affected infants. Fetal echocardiography is recommended in future pregnancies of all affected families. However, to date curative therapy neither during pregnancy nor postnatally is available for children with IACI.

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