Idiopathic infantile arterial calcification in two siblings: failure of treatment with diphosphonate

Graham Stuart, Christopher Wren, Hugh Bain

Abstract
Two siblings with idiopathic infantile arterial calcification are reported. The fetal and postnatal echocardiographic features were a large pericardial effusion, thickened pulmonary and aortic valves, poor pulsation of the descending aorta, and calcification of the great vessels. In one patient calcification was first detected at 33 weeks' gestation. Despite treatment with disodium etidronate both children died.

Idiopathic infantile arterial calcification is a rare congenital disorder that is usually fatal in the first six months of life. It is characterised by widespread fibrous proliferation in elastic and muscular arteries and is associated with areas of patchy calcification of elastic tissue. Myocardial ischaemia resulting in refractory cardiac failure is the usual cause of death. We report two siblings with this disorder; in one the diagnosis was made by fetal echocardiography. Both children died despite treatment with diphosphonate.

Case reports
PATIENT 1
This was the first child of unrelated teenage parents. The pregnancy was complicated by hydramnios and hypertension at 34 weeks. Spontaneous labour developed at 35 weeks and despite intravenous salbutamol a 2580 g girl was delivered vaginally one week later. Within a few hours she became tachypnoeic and required oxygen for cyanosis. On examination she had biventricular hypertrophy, heart sounds were single, and there was a grade 2/6 pulmonary ejection murmur. Only the femoral and axillary pulses were palpable and examination of the abdomen showed firm 4 cm hepatomegaly and 3 cm splenomegaly. The chest x ray showed cardiomegaly with normal pulmonary vascularity and the electrocardiogram was normal. A cross sectional echocardiogram showed normal cardiac connections with a large pericardial effusion and dense echoes reflected from the pulmonary and aortic valves. In addition, echocardiographic examination of the descending aorta showed very poor vessel pulsation. At cardiac catheterisation there was pulmonary hypertension but no stenosis of the pulmonary or aortic valves. When pulmonary artery calcification was seen on fluoroscopy the chest x ray was reviewed and linear calcification was detected in both axillary arteries and the descending aorta. A biopsy specimen of the posterior tibial artery showed calcium deposition within the internal elastic lamina and confirmed the diagnosis of idiopathic infantile arterial calcification. Further investigation showed a low plasma concentration of pyrophosphate (0-6 μmol/l (normal range in adults 1-6 μmol/l)) but other investigations including blood film; thyroid function tests; serum immunoglobulins; autoantibodies; TORCH (toxoplasma, rubella, cytomegalovirus, and herpes virus) screen; serum parathormone; plasma calcium, phosphate and magnesium; serum alkaline phosphatase; plasma cholesterol and triglycerides; liver function tests; urine aminoacids, mucopolysaccharides, and excretion of calcium and hydroxyproline were all normal. Over the next 48 hours the infant required an exchange transfusion for haemolytic jaundice though there was no evidence of blood group incompatibility or sepsis. After this, treatment with chlorothiazide and spironolactone was started and her cardiac failure and hepatosplenomegaly gradually regressed. Then treatment with disodium etidronate (20 mg three times a day) was started, and by four weeks of age her hepatosplenomegaly had resolved and she was gaining weight. At six weeks the dose of disodium etidronate was reduced to 11 mg three times a day and treatment with diuretics was stopped.

At 11 weeks she presented with screaming episodes (probably angina pectoris) and acute heart failure with electrocardiographic evidence of inferolateral myocardial ischaemia. Shortly after admission she suffered a cardiac arrest and resuscitation was unsuccessful. At necropsy the coronary arteries were grossly narrowed by widespread endarteritis and there was extensive calcium deposition between the muscular and subintimal layers.

PATIENT 2
Five years later the mother again became pregnant. Serial fetal echocardiography showed the development of a pericardial effusion and calcification of the great vessels by 33 weeks' gestation (fig 1). In view of the developing calcification and hydramnios, labour was induced at 35 weeks. When fetal distress developed an emergency caesarean section was carried out and a male infant (2580 g) was delivered. On examination both radial pulses were absent and the child was tachypnoeic. Chest and abdominal x rays

Department of Paediatric Cardiology, Freeman Hospital, Newcastle upon Tyne
G Stuart C Wren H Bain

Correspondence to Dr Graham Stuart, Department of Paediatric Cardiology, Freeman Hospital, Newcastle upon Tyne NE7 7DN.
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Figure 1  Fetal echocardiograms in patient 2 showing (A) calcification (Ca) of the ascending aorta and a pericardial effusion (PE). LV, left ventricle. (B) There was calcification of the aortic arch, descending aorta (Desc aorta), and right pulmonary artery (RPA).

Figure 2  Echocardiogram at one day of age in patient 2 showing (A) calcification (Ca) of the aorta and right pulmonary artery (RPA) with a pericardial effusion (PE). LV, left ventricle. (B) There was prominent calcification of the aortic arch, right pulmonary artery (RPA), innominate artery (IA), left carotid artery (LCA), and left subclavian artery (LSA).
confirmed the presence of widespread arterial calcification. Cross sectional echocardiography showed that the heart was structurally normal but prominent calcification of the aorta and proximal pulmonary arteries was evident (fig 2). Further investigations including cranial ultrasound, plasma calcium and phosphate, serum alkaline phosphatase, serum creatinine, plasma electrolytes, serum albumin, and urine calcium and phosphate were normal. Treatment with disodium etidronate (20 mg three times a day), spironolactone, chlorothiazide, and digoxin was started. A thoracic computerised tomographic scan at three weeks showed calcification in both the thoracic and descending aorta. Five weeks later the child was readmitted in cardiac failure with clinical angina. There was electrocardiographic evidence of left ventricular hypertrophy with anterolateral ischaemia and despite treatment with glyceryl trinitrate and morphine his condition deteriorated. He died five days later. Permission for necropsy was refused.

Discussion

Idiopathic infantile arterial calcification is very rare. Its incidence is unknown but over 100 cases have been reported. Symptoms usually develop in the first few months of life although a few cases present in childhood or adolescence.12 The sexes are equally represented and though it is not uncommon for siblings to be affected14 the karyotype is usually normal. An autosomal recessive inheritance has been postulated.15 Presentation in preterm infants is associated with a higher incidence of aortic calcification and a more severe form of the disease.6-10 Our patients presented with the typical non-specific features of poor feeding, cyanosis, heart failure, lethargy, and respiratory distress. Clinical examination is often not helpful and the diagnosis is usually made by the recognition of arterial calcification on chest and abdominal x rays.7 Soft tissue calcification (especially periarticular) is often an associated feature.78 Peripheral pulses may be normal, absent, or weak and hypertension may be present.6-10 The electrocardiogram is often normal but may show signs of left ventricular hypertrophy or myocardial ischaemia.11 At cardiac catheterisation evidence of stiffness in the pulmonary and systemic artery walls, a low diastolic pressure, and a wide pulse pressure have been reported.12 Aortography may show coronary artery occlusion or stenosis.13 In many cases, however, the diagnosis is not made until after death.1416 The histopathological features include intimal fibrous proliferation in elastic and muscular arteries with elastic tissue degeneration and secondary calcification.15 This intimal proliferation is thought to be the fundamental pathological change and Witzleben has suggested that "occlusive infantile arteriopathy" is a more appropriate term for the condition.15

Biochemical investigations are usually normal and there is no identifiable abnormality

of calcium metabolism. In patient 1 the plasma concentration of pyrophosphate was lower than the normal adult range. Pyrophosphate is a potent inhibitor of calcification and it is possible that idiopathic infantile calcification is due to a deficiency of pyrophosphate. An alternative explanation is that the low pyrophosphate concentration is a secondary event related to calcium deposition. Others suggested that the underlying defect may be dystrophic calcification occurring in a previously injured arterial wall,1 a disorder of iron metabolism,3 or an inherited disorder of elastin structure.8

Antenatal diagnosis by fetal echocardiography has not been reported though Rosenbaum and Blumhagen noted striking acoustic shadowing of the aorta on abdominal ultrasound in a preterm infant.17 In our second patient calcification was first detected at 33 weeks' gestation. If this is typical then diagnosis by fetal echocardiography may allow elective preterm delivery before the onset of cardiac failure but it will be too late for termination of pregnancy.

Although spontaneous regression and survival to adult life have been reported,1216 85% of patients with idiopathic infantile arterial calcification die in the first six months of life.13 Corticosteroids18 and a combination of corticosteroids, thyroid hormone, and oestrogen1 have been used to treat this condition with no convincing evidence of efficacy. Meradji et al used disodium etidronate and reported regression of calcification within a few weeks and complete and permanent disappearance by two years.9 This compound is a diphasonate used to treat metastatic calcification.10 We used this compound in both our patients in a dose that is known rapidly to suppress bone turnover in adults. Despite this there was no objective improvement in the radiological and echocardiographic appearances and both children died. The patient described by Meradji had only mild coronary involvement and no signs of cardiac failure and may have had a milder variant of the condition. There has been no subsequent report of the successful use of diphasonate in this condition.

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In this issue:

- The 6th Einthoven Symposium will be held on 19 October 1990 in Leiden. The Symposium, co-sponsored by the Netherlands Heart Foundation and the European Society for Cardiology, will be on electricity and the heart. Information from Mrs J Rust, Phia Bergbouitaan 21, 2343 PM Oegstgeest, The Netherlands. Telephone (+31) 71-17.35.53.