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Clinical Investigations

Idiopathic Arterial Calcification of Infancy

P. J. Van Reempts,[1] K. J. Boven,[1] S. E. Spitaels,[2] A. M. Roodhooft,[1] E. L. J. Vercruyssen,[1] and K. J. Van Acker[1]

Departments of [1]Pediatrics and [2]Cardiology, University Hospital of Antwerp, Wilrijkstraat 10, B-2520 Antwerpen-Edegem, Belgium

Summary. We describe two twin sisters in whom calcification of different arteries was detected in the first weeks of life. Transient renal insufficiency, arterial hypertension, and skeletal abnormalities were also observed. One child had anasarca and heart decompensation at birth. Prenatal infarction of one kidney had occurred in the same infant. A kidney biopsy showed calcium deposits in all the layers of the arteries. Most findings in these patients are compatible with idiopathic arterial calcification of infancy (IACI). Investigation of calcium and phosphorus metabolism revealed spontaneously receding hypercalciuria, increased intraerythrocytic calcium levels, and transient X-ray abnormalities of the long bones. Treatment initially consisted of biphosphonate and later, the calcium antagonist flunarizin. A progressive diminution of the arterial calcification was observed in the course of both treatments.

Key words: Arterial calcification — Calcium transport — Biphosphonate — Flunarizin.

Idiopathic arterial calcification of infancy (IACI) is an ill-defined disorder of young infants characterized essentially by the deposition of calcium salts in different arteries. The pathogenesis of IACI remains unknown and until recently most treatments have remained without result. In this article we describe our experience with two twin sisters with IACI.

Offprint requests to: K. J. Van Acker

Patients and Methods

The patients were homozygotic twins born after a pregnancy of 34 weeks. Pregnancy was complicated by polyhydramnios of one amniotic sac and premature rupture of the other sac. The mother had received a daily dose of 500 IU vitamin D_3 during the entire pregnancy. The family history revealed no particularities: there is one other healthy child.

Patient 1

The first twin was born after cesarean section with anasarca and all the clinical symptoms of heart decompensation. Arterial hypertension and renal insufficiency were also noted. Treatment consisting of fluid restriction, and furosemide was successful but hypertension and high serum creatinine levels persisted. During work-up, at the age of 2 weeks, calcifications in a small left kidney, the abdominal aortic wall, and the left adrenal were found on computed tomography (CT) scan (Fig. 1a). Subsequent sonography revealed calcifications in the thoracic aorta, the mitral and tricuspid valve, and the papillary strings. X-ray of the long bones showed areas of low density in the diaphysis and a dense calcification line at the metaphyseal border (Fig. 2). Surgical biopsy of the left kidney revealed fibrosed glomeruli, atrophic tubuli, and calcium deposits in all the layers of the arteries which occluded the lumina. Some tubular structures also contained calcium salts. The glomerular and tubular lesions were considered to be the consequence of arterial infarction. No intrauterine infections and no disorder known to be associated with arterial calcifications could be demonstrated and the diagnosis of IACI was made. From the age of 2 months, the child was treated with biphosphonate (Didronel) in a daily dose of 10 mg/kg. When elevated intraerythrocytic calcium levels were found,

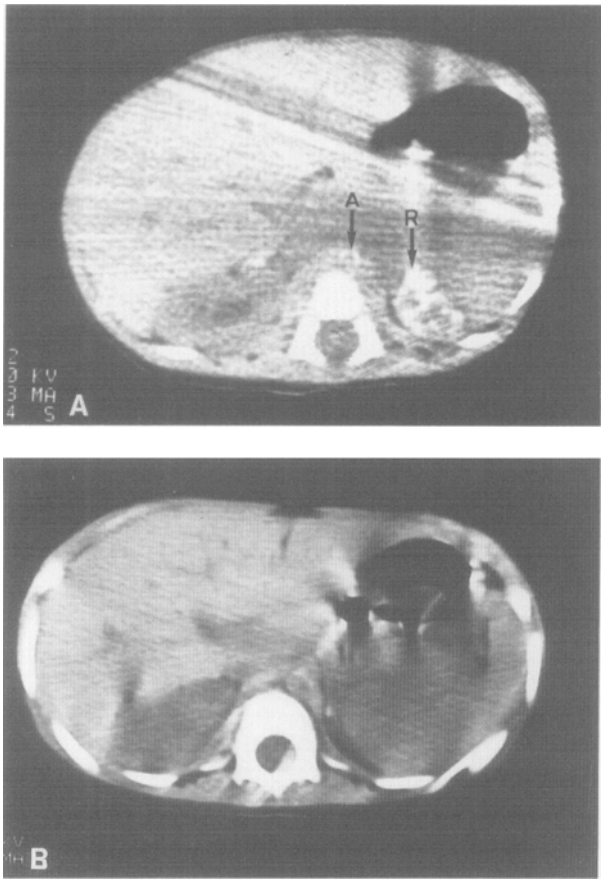

Fig. 1. **(A)** Abdominal CT scan in the first twin at the age of 2 weeks showing aortic (A) and renal (R) calcifications. **(B)** Abdominal CT scan in the same child at the age of 18 months showing the disappearance of the calcifications in aorta and left kidney.

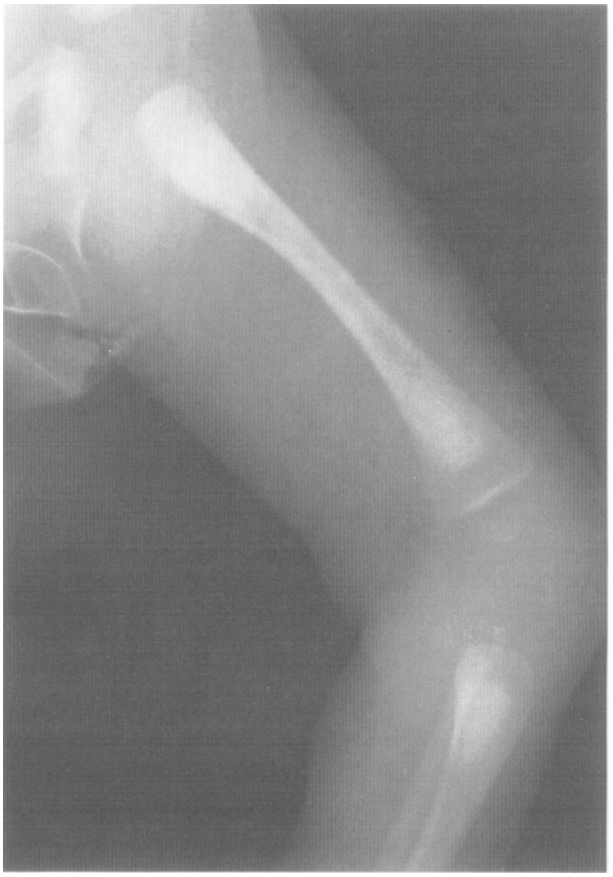

Fig. 2. Skeletal changes in the first child at the age of 2 weeks. In the diaphysis there are areas of low density. A dense calcification line is seen at the metaphyseal border.

the calcium antagonist flunarizin (Sibelium) was added in a daily dose of 1 mg at the age of 7 months. From the age of 11 months, only flunarizin was given. Vitamin D intoxication being highly improbable as a cause of the arterial calcifications, as will be explained later, 1,000 IU vitamin D_3 was administered daily as a prophylactic measure from the second week and during the 18 months of observation. During a follow-up period of 18 months, a progressive diminution of the calcifications was observed on CT scan (Fig. 1b) and sonography. The serum creatinine level normalized at 1.5 months of age. The skeletal abnormalities also disappeared but after biphosphonate had been given for some time, a dense metaphyseal band appeared. Mild hypertension is still present at the age of 18 months.

Patient 2

In the second child, birth and postnatal course were uneventful. After 2 weeks, however, blood pressure became elevated and an increased serum creatinine level was found. Investigations were started at the age of 2 weeks when the calcifications were detected in her twin sister. Ultrasonography of the kidneys remained normal until the age of 1.5 months when echodense formations were noted in both renal cortices. At the age of 8 weeks, calcifications in the papillary strings, mitral valve, and aortic wall were detected by ultrasound (Fig. 3a). CT scans always remained normal. X-rays of the long bones showed the same but less pronounced diaphyseal and metaphyseal abnormalities, as in the other twin. Except for dysplastic tubuli and calcium deposits in some tubular lumina and tubular epithelial cells, kidney biopsy revealed no abnormalities. Intrauterine infections could not be demonstrated. The diagnosis of IACI was made and the same treatment as in the twin sister was started. Biphosphonate (10 mg/kg/day) was given from the age of 2 months to 11 months and flunarizin (1 mg/day) from the age of 7 months. As was given to her sister, a prophylactic treatment of 1,000 IU vitamin D_3 was given daily. During the follow-up period of 18 months, a decrease of the cardiac calcifications was observed on sonography (Fig. 3b). The serum creatinine levels normalized at 1.5 months of age but blood pressure remained mildly elevated.

Serum calcium was measured by a colorimetric method using methylthymol blue as indicator (Ca-Kit, BioMérieux, France); inorganic phosphorus was measured by an enzymatic method (Boehringer Mannheim GmbH, W. Germany). Alkaline phosphatase was determined enzymatically at 25°C using p-nitrophenylphosphate as substrate (Baker Chemicals BV, Deventer, Holland). $250HD_3$ was measured by a competitive pro-

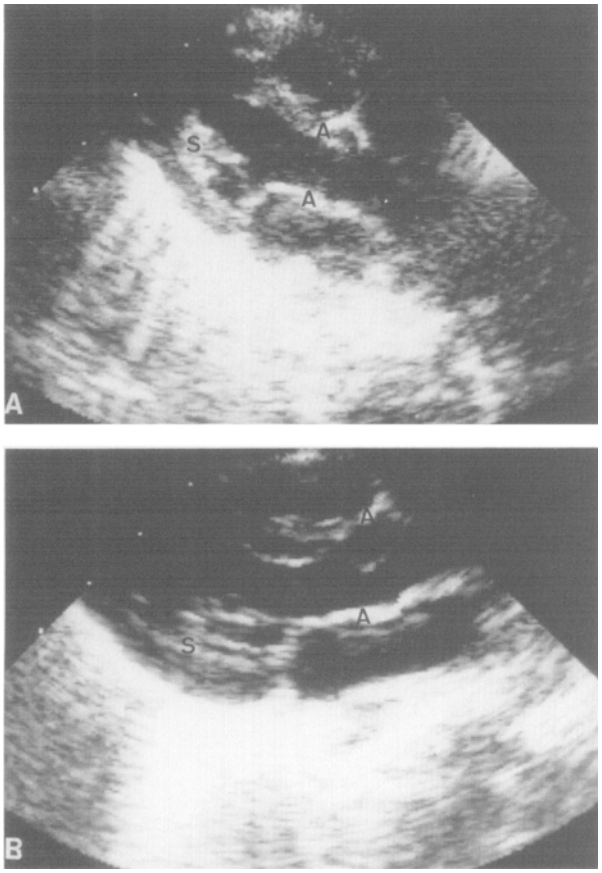

Fig. 3. (A) Cardiac sonography in the second twin at the age of 8 weeks showing calcifications in the aortic wall (A) and the papillary strings (S). (B) Cardiac sonography in the same child at the age of 18 months showing marked diminution of the calcifications in aortic wall (A) and papillary strings (S).

tein-binding assay using rat serum. For the measurement of $1,25(OH)_2D_3$, a radioimmunoassay was used, as described by De Leenheer and Bauwens [1]. Serum calcitonin (iCT) was determined by a radioimmunological method (RIA-mat Calcitonin I, Byk-Mallinckrodt Diagnostica) and parathyroid hormone (iPTH) as intact iPTH by a two-site immunoradiometric assay (Allégro TM Intact PTH, Nichols Institute, CA) as described by Nussbaum et al. [2]. Intraerythrocytic calcium was measured as described by Cameron and Smariga [3]. This method uses atomic absorption spectroscopy in an air-acetylene flame on a 0.5 ml total sample volume containing 0.1–0.2 ml packed erythrocytes. The sample is digested in 1.0 ml of 6% (w/v) trichloracetic acid in a boiling water bath for 30 minutes. The precipitated residue is removed by centrifugation, and 0.5% $LaCl_3$ is added as a releaser to counteract the inhibition of the Ca^{2+} response by phosphate.

Investigation of Calcium and Phosphorus Metabolism (Figs. 4 and 5)

In both children, the serum levels of total calcium and phosphorus were normal for age and remained so during treatment. Alkaline phosphatase levels were normal initially but in patient 1 a slight increase was seen before treatment with biphosphonate was started. In both patients, transient hypercalciuria (up to 25 mg/kg/day and 15 mg/kg/day, respectively) was observed during the second week; treatment with biphosphonate or flunarizin had no influence on the calciuria. In both patients serum values of $25OHD_3$ were mildly elevated initially when they received 1,000 IU vitamin D_3 daily (highest values 109 and 90 nmol/liter, respectively; normal value for this age is 25–75 nmol/liter). The $25OHD_3$ levels increased during therapy with biphosphonate (up to 144 and 108 nmol/liter, respectively). The serum levels of $1,25(OH)_2D_3$ were determined only during biphosphonate and simultaneous vitamin D_3 treatment: an elevation was seen in one instance in both patients (213 and 231 pg/ml; normal value for this age is 165 ± 62 pg/ml). iCT, measured before any treatment was given, was normal in both patients (0.3 and 0.2 pg/ml; normal value <0.5 pg/ml). iPTH values were always within normal limits (between 30 and 58 pg/ml; normal values for this age are 20–75 pg/ml) and were not influenced by any treatment.

Intraerythrocytic calcium levels were determined when both children were on biphosphonate treatment. Values of, respectively, 121 and 128 nmol/ml packed erythrocytes were found, which is significantly higher than the mean value of 37 ± 14 nmol/ml packed erythrocytes found in the same laboratory in 52 infants from the same age group. Twenty weeks of biphosphonate treatment had no influence on these levels. When flunarizin was added, a decrease of between 54 and 60% was observed after 2 weeks which was not reversed when biphosphonate was stopped and only flunarizin was given. With continuing flunarizin treatment, a progressive increase of the intraerythrocytic calcium levels to around 70% of the original value was observed.

In the mother, normal values for $25OHD_3$ (50 nmol/liter), iPTH (30 pg/ml), and iCT (<0.5 pg/ml) were obtained during the first week after delivery.

Discussion

In the neonate, arterial calcifications may be caused by a number of disorders in the mother or/and the child [4]. None of these disorders could be demonstrated in the present cases and common intrauterine infections were excluded. Vitamin D intoxication in the mother and the children is highly improbable: not only did the mother receive low doses of vitamin D, but the serum $25OHD_3$ level shortly after parturition was normal in the mother and was only

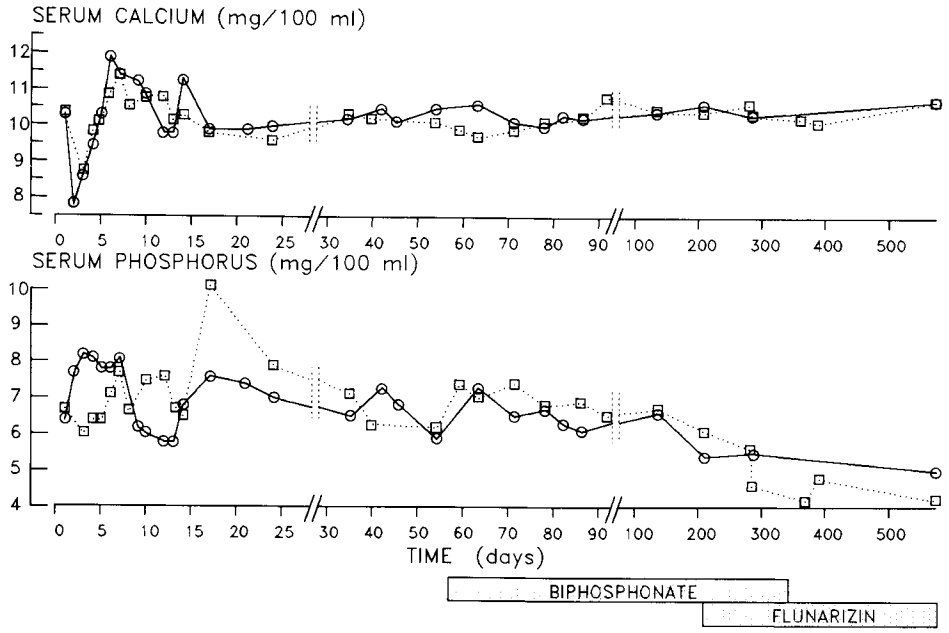

Fig. 4. Evolution of serum calcium and phosphorus in both children (dotted line = patient 1, full line = patient 2).

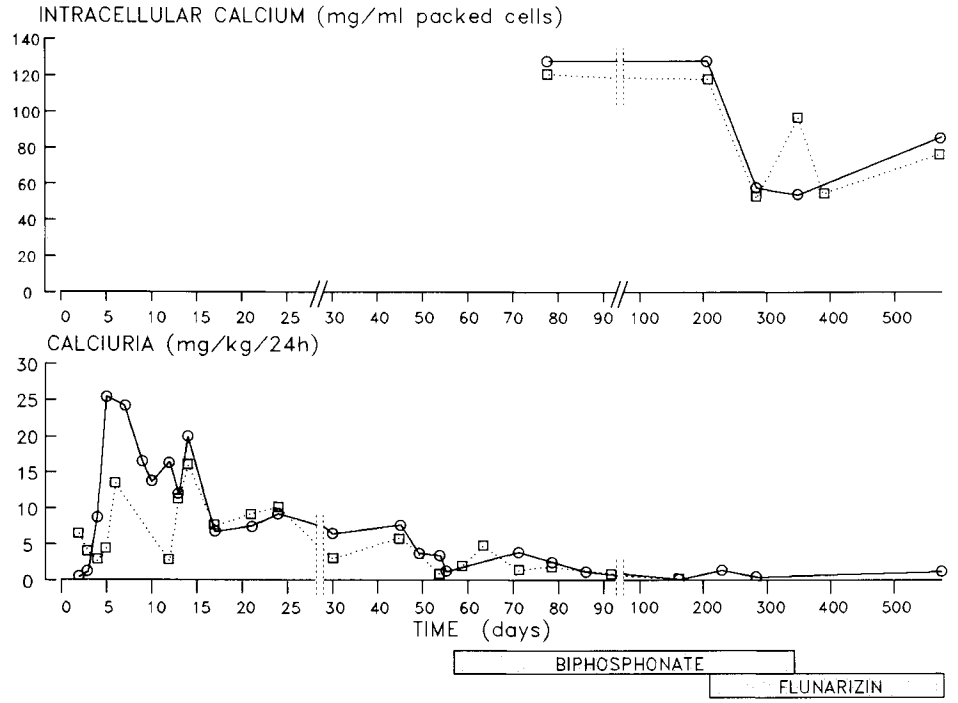

Fig. 5. Evolution of intraerythrocytic calcium and calciuria in both patients (dotted line = patient 1, full line = patient 2).

slightly elevated in the children despite prophylactic treatment with 1,000 IU of vitamin D. Furthermore, calciuria was only temporarily increased and renal function normalized despite continuing vitamin D treatment. Hyperparathyroidism in mother or children was excluded on the basis of the normal serum iPTH levels.

Most findings in our patients are compatible with IACI, a syndrome that has been reported in approximately 90 cases [5–26]. From the clinical point of view, polyhydramnios and cardiac failure at birth, as seen in patient 1, are commonly observed in this syndrome. The pattern of calcification involving mainly the aorta and the heart valves also suggests

IACI although the arteries of most tissues may be involved. Prenatal infarction of the kidney, as observed in patient 1, has been described in IACI [6, 18]. Kidney biopsy in patient 1 showed involvement of all three layers of the arterial wall, as is seen in advanced cases [20]: the initial deposition of calcium salts, probably calcium phosphate [6, 9, 21], occurs along the elastic membrane of the arteries. Transient renal insufficiency was described in one other patient with IACI [18].

The pathogenesis of IACI remains unknown. There are no indications for an excessive intake of vitamin D by the pregnant mothers or a hypersensitivity to vitamin D [20]. There are also no arguments available for arteritis due to intrauterine infection. A number of hypotheses such as an abnormality of the elastic tissue [7, 8, 22, 23, 25] or injury to the intercellular substance in the media of the arteries [24] have been proposed but have never been substantiated.

We investigated the calcium-phosphorus metabolism in our patients, an aspect that has been neglected in IACI. Abnormal findings were a transient hypercalciuria, transient X-ray abnormalities of the long bones, and elevated intraerythrocytic calcium levels on several occasions. None of these abnormalities have been described previously and their relation with IACI remains uncertain. Prematurity [29] and furosemide treatment may have contributed to the hypercalciuria in the second week. Although it is tempting to extrapolate the high calcium levels in the erythrocytes to other cells such as the arterial wall cells, we have not investigated this and the extracellular calcifications observed in these patients remain difficult to explain.

In view of the high intraerythrocytic calcium levels, the use of a calcium antagonist was a logical step. Flunarizin was preferred to other calcium antagonists because of its greater effect on erythrocytic calcium and its sparing effect on myocardium and autonomous blood flow regulation in the brain [27, 28]. Flunarizin treatment caused a marked decrease of the intraerythrocytic calcium in both children but after some time, a leveling off towards 70% of the original value was observed. The role of this treatment in the disappearance of the calcifications is difficult to assess. Biphosphonate treatment has been claimed to be successful in IACI [9, 10]. A calcium antagonist, in conjunction with biphosphonate, was used in one other case in whom the arterial calcifications disappeared [18]. Spontaneous cure has, however, also been described [25]. The possibility of an underlying calcium transport disturbance and the therapeutic use of biphosphonate and calcium antagonists therefore need further investigation. The appearance in our patients of a dense fibrous metaphyseal zone is a well-known effect of biphosphonate treatment. The elevated $1,25(OH)_2D_3$ levels may reflect a homeostatic response to the mineralization defect usually associated with biphosphonate treatment [30].

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