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Idiopathic infantile arterial calcification: clinical presentation, therapy and long-term follow-up

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Abstract Idiopathic infantile arterial calcification (IIAC) is a rare disease characterised by extensive depositions of hydroxyapatite in the internal elastic lamina of medium-sized and large arteries, frequently accompanied by periarticular calcifications. We report on three patients with various presenting signs and symptoms. Diagnostic imaging techniques and therapy with bisphosphonates will be discussed. For the first time long-term follow-up of up to 25 years will be reported.

Keywords Idiopathic infantile arterial calcification · Bisphosphonates · Therapy · Diagnostics · Long-term follow-up

Introduction

Idiopathic infantile arterial calcification (IIAC) is a rare disease characterised by extensive depositions of hydroxyapatite in the internal elastic lamina of medium-sized and large arteries with stenosis due to myointimal proliferation. Patients are diagnosed prenatally or in early infancy. Unfortunately, most patients are diagnosed at autopsy. The

disease is often lethal in infancy, because of ischaemic cardiomyopathy and other complications of obstructive arteriopathy [2, 3, 6, 11, 14, 15].

We report on two families with three IIAC patients. One patient died at 6 weeks of age, and two were treated with bisphosphonates. We describe clinical presentation, therapy and long-term follow-up of etidronate therapy of up to 25 years.

Patient 1

The patient was the second child of consanguineous Turkish parents. Seven years earlier a healthy brother had been born; in between, two miscarriages at 12 weeks of gestation had occurred. During the last 3 days of the pregnancy diminished foetal movement was noticed by the mother. After a gestational age of 36 weeks a caesarian section was performed because of foetal distress. A 3,240 g boy was born. Apgar scores after 1 min and 5 min were 2 and 3, respectively. Umbilical cord blood gas analysis showed pH 6.98 and base excess -16 mmol/l. The baby was intubated and ventilated. No dysmorphic features were found. Femoral pulsations were palpable. Soon after birth convulsions were seen, and phenobarbital was administered.

A chest roentgenogram showed an enlarged heart with signs of congestive heart failure. Cranial ultrasound showed hyperechogenic white matter and striatal arteries (Fig. 1). Ischaemic areas in the cortex were found on magnetic resonance imaging. Echocardiography revealed a structurally normal heart with myocardial hypertrophy and poor ventricular function.

During the next days hypertension with a mean arterial pressure of 80 mmHg to 90 mmHg was noticed, and nifedipine administration was started. To exclude a (vascular) renal cause of the hypertension an ultrasound of the renal arteries and kidneys was performed, which showed a hyperechogenic renal artery wall with diminished flow on both sides (Fig. 2). Further investigation revealed extensive hyperechogenic foci in the aortic wall and hepatic arteries. Total-body computed tomography showed calcifications in

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Fig. 1 Cerebral ultrasound on the first day indicated hyperechoic striatal arteries (*white arrow*)

the aorta, kidney, liver, carotid and coronary arteries and periarticular calcifications in the hip. The large and medium-sized cerebral arteries appeared to be unaffected, but increased whitening around the striatum and calcifications in putamen and nucleus caudatus were found. Re-evaluation of the conventional radiographs of the first day, together with the new knowledge, revealed clear calcification of the abdominal aorta and the ligaments of the left hip. The diagnosis of idiopathic infantile arterial calcification was made.

Computed tomography and microscopic evaluation of the placenta showed multiple calcifications in the vessels. However, the umbilical vessels were normal.

Electrocardiography revealed no ischaemia. Electroencephalography showed epileptic activity on day 2. Blood biochemistry showed normal values for calcium, phosphate, alkaline phosphatase, parathormone and 25-hydroxyvitamin D. Plasma level of renin was elevated (415 mU/l, reference value 11–148 mU/l), confirming reno-vascular hypertension.

After 1 week hypertension was refractory to nifedipine and labetalol was added successfully. Therapy with orally administered etidronate at a dose of 18 mg/kg body weight

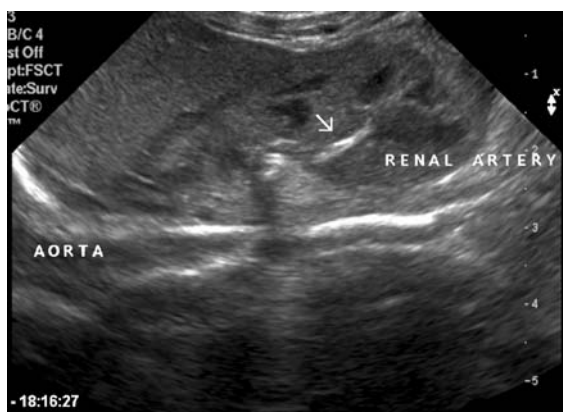


Fig. 2 Abdominal ultrasound shows hyperechoic renal artery and abdominal aorta, interpreted as calcifications

was started when the child was 13 days old. Two weeks after treatment with bisphosphonates had been initiated the effect was evaluated by ultrasound. No significant decrease in intracranial, intra-abdominal and periarticular calcifications was seen. However, after 3.5 months, significant reduction in calcifications was seen. No calcifications of the renal, carotid and liver arteries and aorta were found on ultrasound. Cerebral ultrasound showed decreased striatal calcifications, but also a large supratentorial watershed lesion on the left side.

Abdominal computed tomography (CT) and X-ray showed a clear reduction in periarticular calcification of the hip, and arterial calcifications had disappeared completely (Fig. 3). At the same time rickets-like lesions with metaphyseal widening of the ulna and diminished mineralisation developed, with a moderate increase in serum alkaline phosphatase levels. Phosphate, calcium, parathyroid hormone (PTH) and 25-dihydroxyvitamin D levels were normal. The etidronate dose was reduced and was stopped after 1 year.

Echocardiography repeated after 8 months showed normal ventricular function and mild myocardial hypertrophy. Electroencephalography showed no epileptic ac-

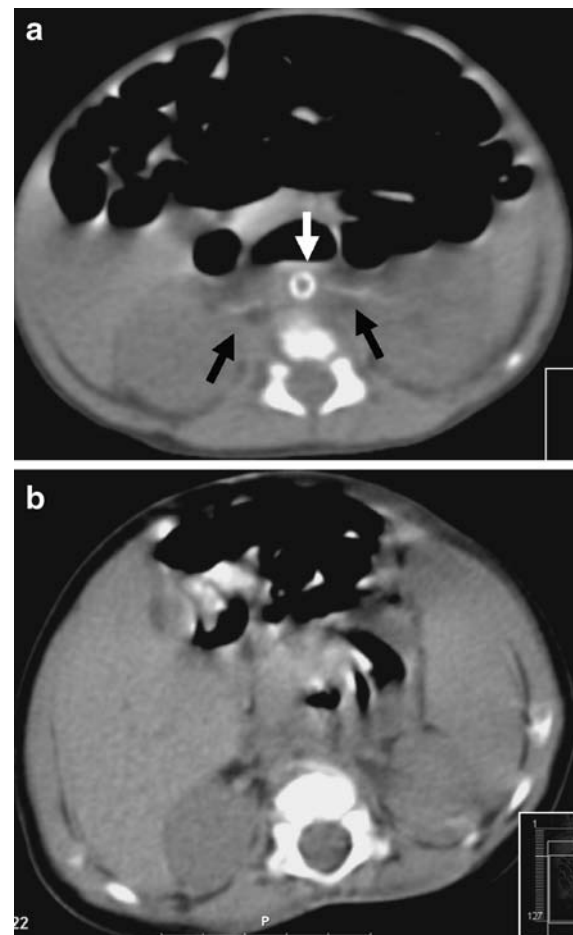


Fig. 3 Computed tomography scan before (a) and 3.5 months after (b) etidronate treatment. a Clear calcification of the abdominal aorta (*white arrow*) and renal arteries (*black arrows*) are shown. b No calcifications

tivity after day 7. Follow-up at 2 years of age showed an axial hypotonia and a right-sided hemiparesis. The child speaks a few words and still needs anti-hypertensive treatment. Ultrasound revealed no calcifications. Results of DNA analysis for IIAC were negative.

Patient 2

A 6-week-old boy of non-consanguineous parents, with a history of refusal to feed and sudden dyspnoea, was admitted in shock. Peripheral pulsations were not palpable, and he was hypotensive. Shock was refractory to digitalis, dopamine and hypovolaemic treatment. Two days later he died. Postmortem examination revealed thrombosis of the coronary artery, myocardial infarction and extensive arterial calcification, confirming the diagnosis IIAC.

Patient 3

Two years later a brother was born at term after a normal pregnancy and delivery. Because of the history of his sibling he was admitted in our hospital for diagnostic reasons. Physical examination showed no abnormalities; especially, he had normal blood pressure and peripheral pulsations. X-rays revealed calcification of the carotid, radial, femoral and dorsal pedis arteries and abdominal aorta and ligamentous calcifications of the shoulder. An electrocardiogram (ECG) was normal. Aortography showed no arterial abnormalities. Examination of the umbilical vessels revealed extensive calcifications in the wall around the vessels outside the intima.

On the 5th day, therapy with etidronate (20 mg/kg per day) was started. After 2.5 weeks all calcifications had disappeared on X-ray. In the 2nd year the etidronate dose was tapered off and stopped. The child showed normal growth and development. At the last follow-up he was a healthy 25-year-old adult, normotensive and without neurological or cardiac symptoms. His ECG was normal. CT and ultrasound showed only very small residual calcifications in the aortic arch and carotid arteries, but no calcifications in other arteries and ligaments.

Discussion

IIAC is a rare condition characterised by calcification of the internal elastic lamina of muscular arteries and stenosis due to myointimal proliferation [3, 13]. Patients may present with failure to thrive, hypertension, myocardial infarctions and convulsions. Cerebral vascular insufficiency may cause cerebral infarctions [5, 12, 13]. Periarticular calcifications are a well-known feature in IIAC [1, 7]; these appear to be localised in the ligaments [6, 14].

The gold standard for diagnosis is arterial biopsy. This rather invasive technique may be replaced by combining radiographic techniques as conventional radiographs, computed tomography, and ultrasound. Prenatal diagnosis

is possible with ultrasound and reveals dilated cardiac ventricles, hydrops fetalis and hyperechogenic large vessels [2].

Today, bisphosphonates are primarily known for their use in osteoporosis, where they inhibit osteoclastic activity and thereby inhibit bone resorption [9]. Bisphosphonates are also successfully used in Paget's disease and have been tried in fibrodysplasia ossificans progressiva (FOP). The latter condition is characterised by progressive heterotopic ossification of tendons, ligaments, fascia and skeletal muscle [4]. FOP shows some resemblance to IIAC, and this led to the use of bisphosphonates in IIAC. Unlike etidronate, the newer (amino)bisphosphonates have no appreciable effect in inhibiting mineralisation but are far more potent than etidronate in inhibiting bone resorption. Therefore, one should not use the more potent new bisphosphonates in IIAC because they are less effective for this condition. Rickets is a well-known adverse effect of etidronate, but signs will disappear after cessation of therapy [11, 13]. Etidronate had no adverse effect on growth in our patients.

In physiological conditions the process of extracellular matrix calcification is tightly controlled and limited to bones, teeth, and non-articular cartilage. In IIAC ectonucleotide pyrophosphate/phosphodiesterase 1 (ENPP1) activity is diminished [8]. ENPP1 is a cell surface enzyme generating PPI, which regulates cell differentiation and inhibits calcification in the form of hydroxyapatite. Rutsch et al. [7] found mutations on chromosome 6q that inactivated ENPP1. These loss-of-function mutations were found in eight of 11 kindreds with IIAC but could not be found in our patient 1.

Survival beyond infancy is exceptional in IIAC, but the prognosis varies widely. Many patients will die prenatally, presenting with hydrops because of heart failure. The oldest patient reported was 22 years old [5]. She had been diagnosed at the age of 3 months and treated only with digitalis. She had had three myocardial infarctions and a grand mal seizure. Stuart et al. [10] described two siblings who had died, despite etidronate treatment, as a result of cardiac complications. Successful treatment with bisphosphonates has been reported in a few cases [6, 14], but long-term follow-up has never been reported before. In general, calcifications disappear between 4 months and 2 years of therapy. Our third patient demonstrates that calcifications do not reappear after bisphosphonate treatment has been stopped, suggesting that ENPP1 deficiency has less effect on calcifications postnatally. However, the arterial wall could remain damaged after removal of calcium, with histology resembling arterial fibromuscular dysplasia [5]. This might cause persisting hypertension despite the disappearance of calcifications in patient 1. Moreover, his large watershed lesion resulted in irreversible cerebral damage. Previously, Meradji et al. [6] reported on the 5-year follow-up of a girl with IIAC who was successfully treated with etidronate therapy (20 mg/kg) for 3 years. Prolonged follow-up showed that 10 years after cessation of treatment no reappearance of calcifications was found.

She always had normal blood pressure. Growth was normal, and she attended a regular school.

In conclusion, IIAC is a rare disease characterised by depositions of hydroxyapatite in the internal elastic lamina of muscular arteries and myointimal proliferation. Recent research has revealed a loss-of-function mutation of ENPP1 as a cause of the disorder. As a consequence, the term 'idiopathic' might be less appropriate. Foetal echo (cardio)graphy is recommended in future pregnancies of affected families. In the future, prenatal DNA analysis might be possible. Insight into the pathogenesis might lead to new therapeutic targets. Until then, medication for the palliative treatment of hypertension, cardiac failure and convulsions should be started. Early diagnosis and start of treatment with bisphosphonates may dissolve arterial calcifications and may prevent further ischaemic damage.

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