

## Generalized Arterial Calcification of Infancy

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### Abstract

A 33 weeks' gestation female infant was in significant respiratory distress upon delivery and developed severe hypertension. An echocardiogram revealed biventricular hypertrophy and thickening of the aorta and pulmonary artery. Further imaging demonstrated calcifications in the vessels of the neck, abdomen and extremities and a diagnosis of generalized arterial calcification of infancy was made. She was treated with intravenous pamidronate but continued to deteriorate and died on day-5 of life. The autopsy confirmed heart failure and myocardial infarction as the cause of death. Molecular analysis of the ecto-nucleotide pyrophosphatase/phosphodiesterase 1 gene revealed compound heterozygous mutations, confirming the diagnosis of generalized arterial calcification of infancy.

**Keywords:** Newborn Infant, Generalized Calcification of Infancy, Myocardial Infarction, Heart Failure

### Abbreviations

GACI- generalized arterial calcification of infancy  
 ENPP1- ectonucleotide pyrophosphate/phosphodiesterase 1  
 ABCC6- ATP-binding cassette subfamily C number 6  
 CT- computed tomography

### Introduction

Generalized arterial calcification of infancy (GACI), also known as idiopathic infantile arterial calcification, is a rare inherited autosomal recessive disorder usually diagnosed postnatally or at autopsy. Survival into adulthood has been reported, but most infants succumb to the cardiovascular effects of the disease within the first 6 months of life [1-5]. We highlight the importance of considering GACI in an infant with unexplained heart failure or myocardial infarction and provide molecular confirmation of the diagnosis.

### Case Report

This female 2050g infant was born at 33 weeks gestation via cesarean section for decreased fetal movement and non-reassuring fetal heart tones. She had a grade II/VI systolic murmur and developed moderate respiratory distress. A radiograph was consistent with the respiratory distress syndrome and the cardiac silhouette was prominent. There was no hepatosplenomegaly. She was intubated and given surfactant, evaluated for sepsis and started on ampicillin and gentamicin.

An electrocardiogram showed right atrial enlargement and possible biventricular hypertrophy. An echocardiogram demonstrated a patent ductus arteriosus and mitral and tricuspid regurgitation. There was biventricular hypertrophy with impaired left ventricular

relaxation, a patent foramen ovale, right atrial enlargement, left atrial dilatation, thickening of the aorta and pulmonary artery (Figure 1a) with diminished pulsatility and significant systemic and pulmonary hypertension. The coronary arteries were normal.

She was extubated on day 2 to high flow nasal cannula but was hypertensive with systolic blood pressures of 130-140 mmHg. An abdominal ultrasound revealed a partial thrombus in the right main renal artery and increased echogenicity of the walls of the aorta, renal arteries, common iliac arteries and the superior mesenteric artery consistent with calcification (figure 1b). A cranial ultrasound showed prominent lenticulostriate vasculopathy, compatible with, but not diagnostic of, arterial calcifications.

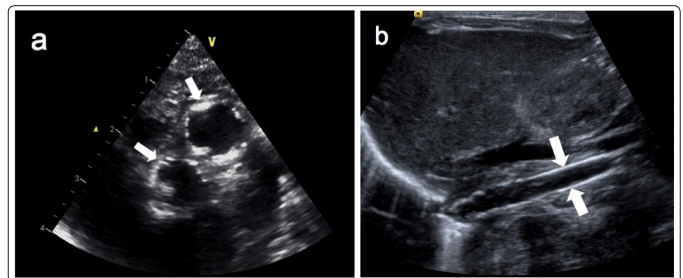
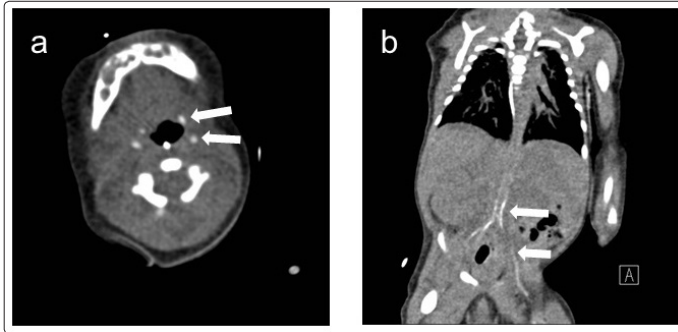


Figure 1

Computerized tomography (CT) of the neck, chest, abdomen and pelvis revealed bilateral vascular wall calcification of the internal and external carotid arteries and their branches, and dense circumferential calcifications in the walls of the abdominal aorta and its branches including the superior mesenteric artery, renal arteries, common and external iliac arteries, left internal iliac artery and the common and superficial femoral arteries (figure 2), confirming the diagnosis of GACI. Her serum calcium, 1, 25- dihydroxy –vitamin D and 25-

hydroxy-vitamin D levels were normal.



**Figure 2**

She received intravenous pamidronate and tolerated it well [2, 3]. The hypertension was treated with hydralazine with mild improvement in her blood pressure. She then developed tonic-clonic movements of her extremities and received lorazepam. She became agitated and her respiratory distress increased. Cardiac ischemia was considered and a troponin level was 1.49 ng/mL (normal range 0 - 0.05 ng/ml). She continued to deteriorate and, after consultation with her parents, comfort care was provided and she died on day 5.

### Autopsy findings

The heart was markedly enlarged and the aorta and pulmonary arteries thickened. Microscopically there were calcifications in the left main and circumflex coronary arteries, aorta, pulmonary arteries, and renal vessels, ranging from fine linear stranding to larger disruptive masses. Fibrointimal proliferation was seen in the pulmonary arteries. The right and left ventricular walls were hypertrophied, measuring 0.7 cm and 0.9 cm respectively. There were foci of acute myocardial infarction in the interventricular septum and the left ventricular papillary muscle. The liver showed bridging and geographic centrilobular necrosis, typical of congestive heart failure [5]. The kidneys were remarkable for multiple small parenchymal and glomerular calcifications with features of thrombotic microangiopathy and glomerular infarcts in the left kidney. Scattered calcifications were noted in the adrenal parenchyma and in the superficial cortex of the ovaries. Histologic examination of the placenta was normal.

These autopsy findings were consistent with the clinical and radiologic findings and confirmed the diagnosis of GACI. Post-mortem karyotyping was normal, but molecular analysis revealed compound heterozygous mutations in the ecto-nucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) gene.

### Discussion

GACI is characterized by diffuse calcification of the medium and large arteries with deposition of hydroxyapatite in the internal elastic lamina. In addition, there is proliferation of fibroblasts and inflammatory cells within the tunica intima, which further decreases the elasticity of the arteries [4, 5]. Although there is a broad spectrum of clinical presentations of GACI, the most common include heart failure, hypertension and respiratory failure [6, 7]. Patients usually succumb to complications of myocardial infarction and heart failure and [5], as there is no known cure for this disorder, the prognosis is usually poor. Bisphosphonate therapy has had limited benefit in some patients [2, 3].

Although rarely diagnosed prenatally, GACI can be diagnosed by obstetrical ultrasound and fetal echocardiogram and there is some evidence in a mouse model that supplemental magnesium provided to the mother and the pups can reduce ectopic mineralization in the offspring [8]. GACI follows an autosomal recessive pattern of inheritance and molecular analysis of the ENPP1 and ATP-binding cassette subfamily C number 6 (ABCC6) genes can provide a prenatal diagnosis or confirm the diagnosis postnatally [1,9,10]. Compound heterozygous or homozygous mutations in the ENPP1 gene have been found in approximately 75% of cases of GACI. The ENPP1 gene is important for production of ecto-nucleotide pyrophosphatase/phosphodiesterase 1, an enzyme that produces inorganic pyrophosphate. Inorganic pyrophosphate prevents hydroxyapatite deposition [1]. The exact function of ABCC6 is unknown. ABCC6 mutations were initially believed to cause pseudoxanthoma elasticum, another disorder involving pathologic calcification of the arteries. However, Rutsch and colleagues have recently shown that GACI can be caused by abnormalities in either the ENPP1 or ABCC6 genes [10]. This has led to speculation that GACI and pseudoxanthoma elasticum are part of a disease spectrum with GACI representing the severe end of the spectrum. Although the clinical, radiographic and autopsy findings in our patient were typical of GACI, compound heterozygous mutations in the ENPP1 gene confirmed the diagnosis.

GACI should be considered in infants with signs of myocardial ischemia but an echocardiogram that shows normal coronary artery origins [3]. While echocardiography is useful, it may not provide a definitive diagnosis and additional imaging is usually necessary. Routine radiography in our infant revealed a calcific density projecting over the left lower cervical spine and such calcifications have been reported in infants with GACI [11]. The calcifications may be noted in joints, soft tissues and vascular structures on plain films [11, 12]. Imaging techniques such as CT better define the calcification of the soft tissue and vascular structures and ultrasound may also be useful.

### Conclusion

We present a case of GACI diagnosed by clinical presentation, imaging and autopsy findings consistent with other reported cases. We confirmed the diagnosis with post-mortem molecular analysis. GACI is a rare, often fatal disease, although more favorable outcomes and some mitigation of symptoms may be possible with earlier recognition and diagnosis. The diagnosis of GACI should be considered in a newborn who presents with hypertension, myocardial infarction and heart failure. As this condition follows an autosomal recessive pattern of inheritance, prenatal genetic counseling is required for appropriate family planning.

**Conflicting Interests:** The authors have no conflicts of interests to disclose.

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