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ORIGINAL ARTICLE

Longitudinal assessment of vascular calcification in generalized arterial calcification of infancy

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Abstract

Background Generalized arterial calcification of infancy (GACI), also known as idiopathic infantile arterial calcification, is a very uncommon genetic disorder characterized by calcifications and stenoses of large- and medium-size arteries that can lead to end-organ damage.

Objective To describe changes in imaging findings in 10 children with GACI at a single institution from 2010 to 2021.

Materials and methods In this retrospective study we reviewed initial and follow-up body imaging in children with genetic confirmation of GACI at our hospital. All initial images were analyzed for the presence and distribution of arterial calcifications, stenoses and wall thickening/irregularity within the chest, abdomen and pelvis. We compared available follow-up studies to the initial imaging findings. We extracted clinical information including prenatal and postnatal treatment from the children's medical records.

Results We evaluated 10 children (five boys) with a diagnosis of GACI. Median age at first body imaging was 8 days (range: 1 day to 5 years). Six children were identified prenatally and four postnatally. Postnatal presentation included cardiac failure, seizures and hypertension. Images in newborns ($n=8$) most commonly showed diffuse arterial calcifications (6/8; 75%), while stenoses were less common (2/8; 25%) during this period. Two children were diagnosed after the neonatal period — one in infancy and one during childhood. In total, half the children (5/10; 50%) had arterial stenoses — three cases visualized at first imaging and two identified on follow-up images during infancy. Stenoses had completely resolved in one child (1/5; 20%) at last follow-up. Eight children received prenatal or postnatal treatment or both. All children who received both prenatal and postnatal treatment ($n=4$) had completely resolved calcifications at last follow-up.

Conclusion Children with GACI might have characteristic vascular calcifications at birth that raise the suspicion of this disease. Arterial calcifications decrease or disappear spontaneously or after treatment, but arterial stenoses usually persist. Calcifications and arterial stenoses can be easily identified and followed with non-contrast CT and CT angiography.

Keywords Arteries · Calcification · Computed tomography · Computed tomography angiography · Generalized arterial calcification of infancy · Infants · Stenoses · Ultrasound

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Introduction

Generalized arterial calcification of infancy (GACI) is a congenital autosomal-recessive disorder characterized by calcification of medium- and large-size arteries. It is associated with intimal proliferation, leading to arterial stenoses and consequently to refractory heart failure, stroke, hypoperfusion and end-organ damage [1, 2]. Mutations in the gene that encodes for the ectonucleotide pyrophosphatase/phosphodiesterase 1 (*ENPP1*) cause GACI type 1 [3], and mutations in the gene that encodes for the adenosine triphosphate-binding cassette subfamily C member 6 (*ABCC6)* cause GACI type 2 [4–7]. GACI type 1 occurs in 75% of patients and it is associated with autosomal-recessive hypophosphatemic rickets type 2 (ARHR2). This condition can also cause bone deformities, dental problems, calcification of ligaments and short stature. GACI type 2 occurs in 10% of patients and the affected individuals are at risk of developing abnormalities of the elastic tissue of the skin, eye, and cardiovascular and gastrointestinal systems, similar to pseudoxanthoma elasticum. Other forms of GACI without association with *ENPP1* or *ABCC6* genes have been described [8, 9].

Generalized arterial calcification of infancy is an extremely uncommon condition, with an estimated frequency of 1 in 200,000 people and only about 200 cases reported in the literature since it was first described in 1899 [4, 9]. It has a high mortality rate during infancy that ranges from 50% to 85% by 6 months of age [10, 11], but survival into adulthood has also been documented [11–13]. Imaging plays an important role in children with GACI during the prenatal and postnatal periods to identify calcifications and stenoses. Studies have shown that surviving children might have persistent arterial stenoses that can cause significant clinical vascular compromise and ischemic complications [13–16]. US, CT and MRI are the most common modalities for initial imaging evaluation and follow-up.

The goal of early diagnosis and treatment in children with GACI is to promote the regression of arterial calcifications and cessation of the development of arterial stenoses [14, 16–20]. Nonetheless, these calcifications sometimes disappear spontaneously [12, 13, 21, 22].

There is no consensus for the use of imaging to evaluate and monitor children with GACI during or after treatment. Most literature is limited to clinical case reports and clinical reviews [23–26]. To our knowledge, no previous studies described longitudinal imaging findings in children with this condition. Our study describes the initial and follow-up features of 10 children with GACI who were evaluated at our hospital during an 11-year period.

Materials and methods

Patients

This retrospective study complied with the Health Insurance Portability and Accountability Act and was approved by our institutional review board. The requirements for written informed consent were waived. We performed a computer search of our institutional radiology database to include all patients ages 0–18 years with genetic confirmation of GACI mutation (*ENPP1* or *ABCC6*) who presented for imaging evaluation from January 2010 to January 2021. Children with at least one imaging evaluation were included. We retrospectively reviewed clinical information from medical charts to determine the genetic variant of GACI and the clinical presentation of the disease. We also noted prenatal and postnatal treatment and clinical outcomes.

Imaging evaluation and analysis

We included CT, CT angiography, MR angiography and vascular US studies of the neck, chest, abdomen and pelvis for evaluation. We also reviewed available images acquired from referring institutions. At our institution, children with GACI were usually followed with cardiac-gated non-contrast CT followed by CT angiography of the chest, abdomen and pelvis. Because abdomen and pelvis non-contrast and CT angiography images are obtained as a continuation of the chest, the entire acquisition is gated. Since 2014, both phases have been performed with a prospectively electrocardiogram (ECG)-triggered high-pitch spiral acquisition mode (FLASH Spiral Cardio; Siemens Healthcare, Forchheim, Germany), as follows: $2 \times 128 \times 0.6$-mm slice collimation with a z-flying focal spot, 0.28-s gantry rotation time, pitch 3.0. The tube voltage and current were automated according to the child's size. Contrast studies were performed using the nonionic, low-osmolality iodinated contrast agent iohexol (Omnipaque, 350 mg I/mL or 300 mg I/mL; GE Healthcare, Chicago, IL) administered at room temperature using a power injector with a standard dose of 2 mL/kg followed by at least a 10-mL bolus chaser of normal saline. Nonvascular findings were not reviewed for the purposes of this study.

Two pediatric radiologists reviewed all imaging studies in consensus (S.A.C. with 1 year and H.J.O. with 7 years of experience in vascular imaging). They evaluated all studies for the presence of vascular calcifications, stenoses, vessel wall thickening and vessel wall irregularity. All imaging findings were classified as (a) present or absent and (b) progressed, stable or resolved, without grading for severity or measuring length or thickness.

Table 1 Demographics and clinical information

Patient	Gender	Age at diagnosis	Diagnostic test	Genetic mutation	Affected siblings	Clinical presentation	Age at first imaging	Age at last imaging	Treatment		Deceased
									Prenatal	Postnatal	
1[a]	F	6 d	Postnatal US	*ABCC6*	Yes	Poor feeding, decreased cardiac contractility, respiratory failure, HIE, cardiac shock Older sibling diagnosed with GACI	6 d	9 y	None	Biphosphonate[c]	No
2	M	Prenatal	Prenatal US	*ENPP1*	No	Died at 2 months of age of heart and respiratory failure	1 d	-	None	Biphosphonate[c]	Yes
3	F	Prenatal	Prenatal US	*ENPP1*	No	Calcifications on prenatal US	15 d	1 y	Biphosphonate[c]	Biphosphonate[c]	No
4	M	Prenatal	Prenatal US	*ENPP1*	No	Calcifications on prenatal US	3 d	1 y	Biphosphonate[c]	Sodium thiosulfate	No
5	F	Prenatal	Prenatal US, genetic testing	*ENPP1*	No	Calcifications on prenatal US Two older siblings (twins) died during infancy diagnosed with GACI	8 d	3 y	Biphosphonate[c]	Sodium thiosulfate	No
6	M	1 d	Postnatal US	*ABCC6*	No	Cardiac and respiratory failure at birth; first clinical suspicion on prenatal US, no confirmatory test or treatment was established	10 d	1 y	None	Sodium thiosulfate	No
7[b]	F	Prenatal	Prenatal genetic testing	*ABCC6*	Yes	Perinatal ischemic event; older sibling with GACI died at birth and other sibling diagnosed with GACI	7 d	-	None	None	No
8	F	Prenatal	Prenatal US	*ABCC6*	No	Calcifications on prenatal US	6 d	5 y	Biphosphonate[c]	Sodium thiosulfate	No
9[a]	M	Postnatal[d]	Head CT and postnatal US	*ABCC6*	Yes	Renal failure, cardiac failure and hypertension, extensive cerebral calcifications, mid-aortic syndrome, cardiomegaly; younger sibling diagnosed with GACI	9 m	14 y	None	Biphosphonate[c]	No

Table 1 (continued)

Patient	Gender	Age at diagnosis	Diagnostic test	Genetic mutation	Affected siblings	Clinical presentation	Age at first imaging	Age at last imaging	Treatment		Deceased
									Prenatal	Postnatal	
10[b]	M	Postnatal[d]	Postnatal genetic testing	*ABCC6*	Yes	Seizures at 18 months of age, suspected stroke in utero; older sibling with GACI died at birth and other sibling diagnosed with GACI	5 y	8 y	None	None	No

d days old, *F* female, *GACI* generalized arterial calcification of infancy, *HIE* hypoxic–ischemic encephalopathy, *m* months old, *M* male, *US* ultrasound, *y* years old

[a, b] Children are siblings

[c] Most common bisphosphonate used was etidronate

[d] Age at diagnosis not specified in the medical chart

For longitudinal assessment, we grouped imaging studies for each child into one of three categories according to age at imaging: 0–1 months of age (newborn), 1 month to 2 years, or older than 2 years. Next we describe a summary of findings using available imaging and noting any improvement, progression or stability of vascular findings.

Results

Study population

Our final sample included 10 children with a known diagnosis of GACI by genetic testing who underwent body imaging evaluation. Four children had GACI type 1 (*ENPP1* mutation) and six had GACI type 2 (*ABCC6* mutation). Our cohort included five boys and five girls, and among them two pairs of siblings. Median age at first imaging was 9 days (range: 1 day to 8 years) and at last imaging follow-up, 5 years (range: 1–11 years). Six children were identified prenatally, five by fetal US given the presence of calcifications in multiple vascular beds with genetic confirmation after birth and one by prenatal genetic testing. The remaining four children were diagnosed postnatally. The diagnosis of GACI was suspected in older children with less severe or nonspecific clinical manifestations who had a known affected sibling or family history. In postnatally diagnosed children, clinical presentations included seizures ($n = 1$), hypertension and mid-aortic syndrome ($n = 1$) and cardiac and respiratory failure ($n = 1$). A 2-month-old boy with diffuse arterial calcifications, diagnosed by prenatal US but who did not receive prenatal treatment, died of respiratory and heart failure. The remaining children were alive at last follow-up (median age at last follow-up: 4 years; range: 1–11 years). Demographic and clinical information is summarized in Table 1.

Eight children underwent body imaging during the neonatal period (0–28 days of age), one child was diagnosed in infancy (> 28 days to 2 years of age) and one child was diagnosed during childhood (2 years to 11 years of age). Follow-up studies were performed in eight children. Treatments and imaging findings are summarized in Table 2.

Imaging findings

Calcifications

Primary findings in newborns demonstrated diffuse arterial calcifications (6/8; 75%) that tended to be circumferential and contiguously involve the length of the vessel, visualized as hyperechogenicity of the vessel wall on US (Fig. 1) or hyperattenuation on CT (Figs. 2 and 3).

Table 2 Imaging findings at first body imaging and progressive calcifications and stenoses at last follow-up in 10 children with generalized arterial calcification of infancy (GACI)

Children with GACI ($n=10$)	Prenatal treatment	First body imaging		Postnatal treatment	Last follow-up	
		Calcifications	Stenoses		Calcifications	Stenoses
Neonates ($n=8$)	No	Diffuse arterial calcifications	Renal artery stenosis	Yes	Calcifications resolved	Renal artery stenosis persisted
	No	Diffuse arterial calcifications	No stenosis	Yes	Died at 2 months old	
	Yes		No stenosis	Yes	Calcifications resolved	No stenoses were seen
	Yes		No stenosis	Yes	Calcifications resolved	No stenoses were seen
	Yes		No stenosis	Yes	Calcifications resolved	Stenoses of the celiac artery, renal arteries, iliac arteries
	No		No stenosis	Yes	Calcifications improved	Stenoses of the descending aorta, renal arteries, pulmonary arteries
	No	No calcifications	No stenosis	No	Punctate arterial calcifications of carotid arteries	No stenoses were seen
	Yes	Punctate arterial calcifications in the pulmonary artery	Stenosis in the pulmonary artery	Yes	Calcifications resolved	No stenoses
Infants ($n=1$)	No	No calcifications	Right renal artery and infrarenal aortic stenoses	Yes	No calcifications	Stenosis and post-stenotic dilation resolved
Children ($n=1$)	No	Normal imaging		No	No follow-up	Persistent supravalvular aortic stenosis with post-stenotic aortic dilation and infrarenal aortic stenosis; progression of right renal artery stenosis

Most calcifications resolved over time. For example, the first imaging in a newborn demonstrated punctate arterial calcifications of the pulmonary artery that resolved at 5 years of age (Fig. 4). Conversely, punctate calcifications of carotid arteries appeared in a 4-year-old girl with a known affected sibling (Fig. 5) after a previous normal chest and abdomen CT angiography during the neonatal period. Arterial calcifications seen at first imaging had either resolved or decreased in five of the seven children at last follow-up (71%).

Stenoses

Two neonates had stenoses at first imaging (2/8, 25%), one of the left pulmonary artery (Fig. 4), which ultimately resolved by 5 years of age, and the other of the right renal artery, which persisted at last follow-up (Fig. 6). Two neonates without stenoses at first imaging developed stenoses in infancy at the site of previously seen calcifications. One child with a family history of GACI, diagnosed at 9 months of age, had right renal artery stenosis present at first imaging, which persisted at last follow-up, and also a supravalvular aortic stenosis with an ascending aortic dilation identified at last imaging (Fig. 7).

In one child, stenoses in the descending aorta and pulmonary arteries progressed. Another child, who had diffuse arterial calcifications at first imaging, had developed stenoses of the celiac and superior mesenteric arteries at last follow-up (Fig. 8).

Vessel wall irregularities

Two children developed vessel wall irregularities on follow-up images that were not seen in the neonatal period. Circumferential wall thickening was not identified in this cohort.

Treatment

Eight children (8/10) received prenatal or postnatal treatment or both (Table 1). Four children received experimental bisphosphonate (etidronate) treatment prenatally, via oral administration to the mother during the third trimester. These four children received further treatment,

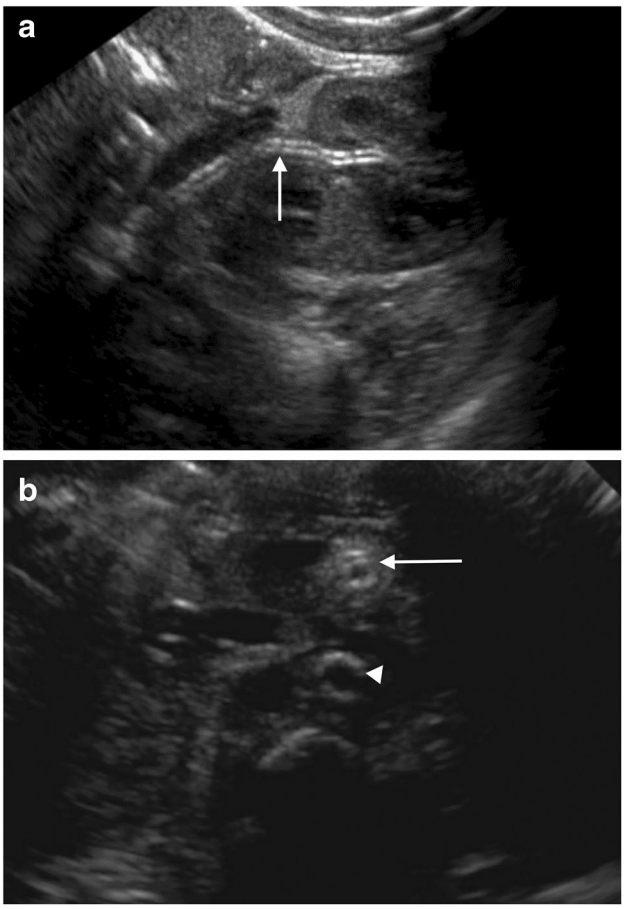

Fig. 1 Generalized arterial calcification of infancy type 1 in a 1-day-old boy. **a** Transverse gray-scale US image of the left kidney shows parallel linear vascular calcifications along the left renal artery (*arrow*). **b** Transverse midline US image shows circumferential calcification of the aorta (*arrowhead*) and superior mesenteric artery (*arrow*)

three with a calcium mobilizing agent, sodium thiosulfate, for 12 months intravenously, and one with postnatal biphosphonates. All of these children had complete resolution of calcifications at last follow-up (Fig. 9).

Three children received only postnatal treatment. Two received biphosphonates and one received sodium thiosulfate. One child in this group developed stenoses of the descending aorta, renal arteries and pulmonary arteries at the site of previous calcifications (Figs. 2 and 3).

Of the two children diagnosed after the neonatal period, one received bisphosphonates and had stenoses of the ascending aorta, infrarenal aorta and right renal artery that had progressed at last follow-up (Fig. 7); the other child diagnosed later in childhood, via genetic testing, did not receive therapy and had normal imaging.

Discussion

We report changes in vascular findings over time in 10 children with GACI. The two main findings in all imaging modalities were diffuse arterial calcifications at birth and arterial stenoses in older children. Arterial calcifications usually regressed over time, whereas stenoses, which appeared in the same vessels as the calcifications, either remained or progressed in most children. Previous literature reported that affected individuals with GACI most commonly presented prenatally with fetal distress, heart failure and polyhydramnios [4, 9, 27–29]. However, in our sample children diagnosed prenatally by the presence of calcifications received prenatal treatment and were asymptomatic during the neonatal period. Given the rarity of the disease, it is difficult to reach a significant number to determine (1) whether increased diagnosis is the result of improved awareness or better and more widely available prenatal US and (2) whether improved outcomes are a result of genetic testing or timely treatment. Similarly, the small numbers and the systemic nature of the disease prevent us from generating the evidence necessary to prove whether the imaging findings of the number of vascular beds involved or the degree of calcification correlate with long-term outcomes, even if multi-institutional registry-type studies were to be reported. In this small cohort, we report a mortality rate of 10%, with one death in a 2-month-old after respiratory and heart failure; this rate is much lower than previously reported.

The imaging features of GACI are easy to recognize prenatally on US and postnatally on US or CT when there is diffuse calcification of major vessels. Previous literature has recommended CT as the preferred imaging modality [9]. At our institution, we have more recently adopted cardiac-gated high-pitch low-dose CT without contrast agent, followed by CT angiography of the chest, abdomen and pelvis at birth or time of diagnosis. In our experience, imaging at birth is fundamental to determine the baseline of the disease. Follow-up images at 1 month of treatment and then every 6 months are obtained for these children's assessment until calcifications disappear. After calcifications have regressed, the non-contrast imaging phase can be omitted because there have been no reports of recurring calcifications. The addition of a contrast-enhanced phase could be used to evaluate the evolution and development of arterial stenoses [23]. The prevalence of arterial stenoses after infancy in our study highlights the importance of CT angiographic imaging. Identifying areas of stenosis offers prognostic information for children at risk of end-organ damage. Follow-up images after resolution of calcifications can be dictated by patient symptoms or initial CT angiography findings. However, vascular US remains a very useful imaging modality and is the first imaging obtained in a number of neonates in whom

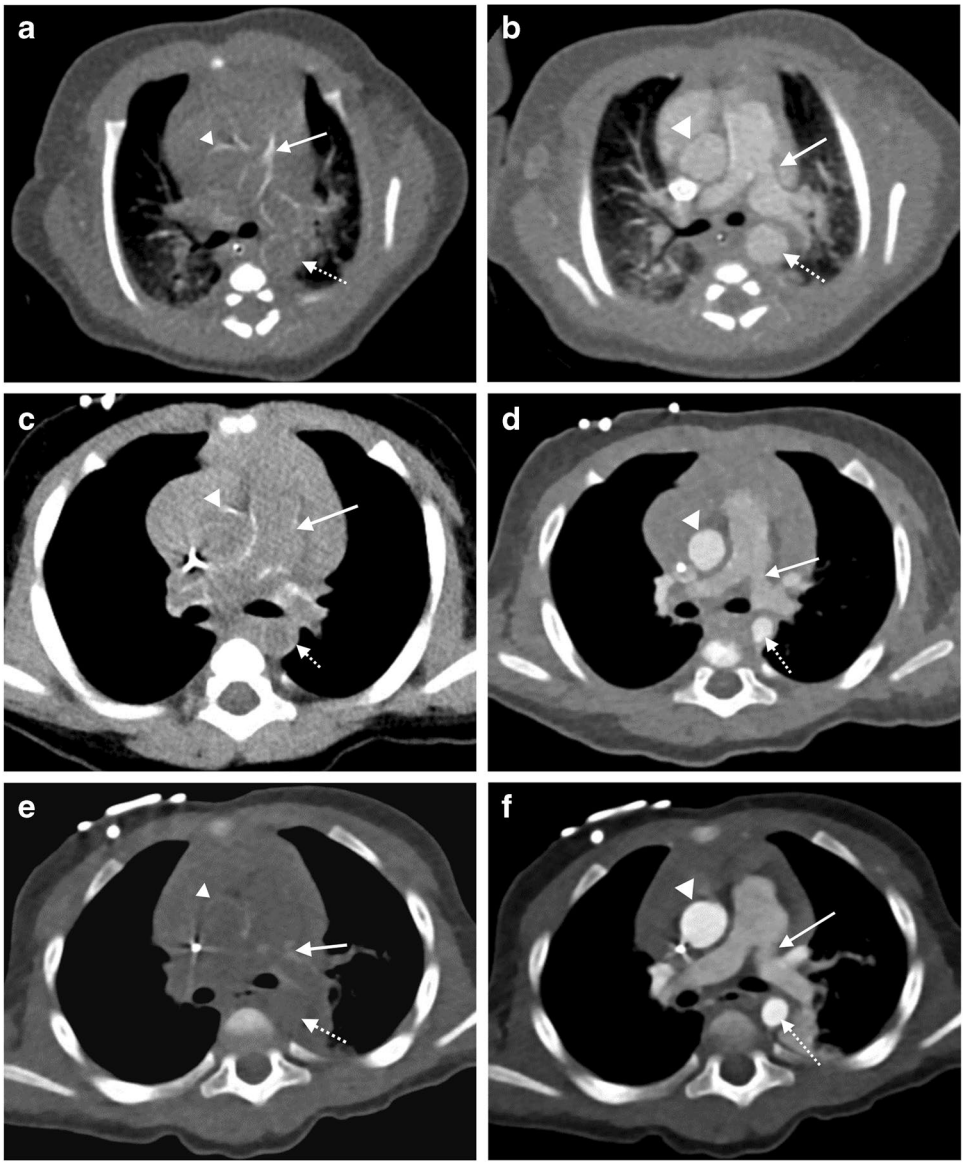

Fig. 2 Generalized arterial calcification of infancy type 2 in an infant boy. **a, b** Axial nonenhanced CT (**a**) and axial CT angiography (**b**) of the chest at 10 days old show calcifications of the ascending aorta (*arrowhead*), descending aorta (*dashed arrow*) and pulmonary arteries (*solid arrow*) with normal caliber. **c, d** Axial nonenhanced CT (**c**) and axial CT angiography (**d**) of the chest at 6 months old show calcifications diminished. **e, f** Axial nonenhanced CT (**e**) and axial CT angiography (**f**) of the chest at 12 months old show stenosis of the left pulmonary artery (*solid arrow*) and descending aorta (*dashed arrow*). *Arrowheads* indicate ascending aorta

bedside imaging is deemed more appropriate, for example in children who are unstable and unable to be transported to the radiology department. Findings of circumferential arterial calcification in multiple medium and large vessels with or without arterial stenoses can suggest the diagnosis. While localized punctate calcifications were seen in two children in our cohort, this is not a common presentation of the disease. Calcifications in infancy tend to be diffuse and locations of the stenoses are variable, including pulmonary arteries, thoracic and abdominal aorta, mesenteric arteries and, most frequently, renal arteries. While circumferential wall and intimal thickening have been reported [23], they were not identified in our patients.

Although arterial stenoses are common in GACI, it is not clear that the underlying intimal hyperplasia is related to vascular calcification [30]. Nevertheless, postnatal treatment of GACI focuses on changing calcium metabolism, thereby preventing new calcifications and reversing existing lesions. GACI is commonly associated with mutations in either of two genes — *ENPP1* or *ABCC6* — that regulate calcification and mineralization processes through the generation of inorganic pyrophosphate, a strong inhibitor of mineralization [9, 31]. These genes are also related to other diseases of mineralization such as autosomal-recessive hypophosphatemic rickets type 2 (ARHR2) and pseudoxanthoma elasticum, respectively [31, 32]. The effects of calcium-dissolving treatment on the development of arterial stenoses is controversial, and the causative relationship between vascular stenoses and previous presence of vascular calcifications is unknown [30, 31, 33, 34].

Bisphosphonates are non-hydrolyzable inorganic pyrophosphate analogs with osteoclastic effects. The low biological

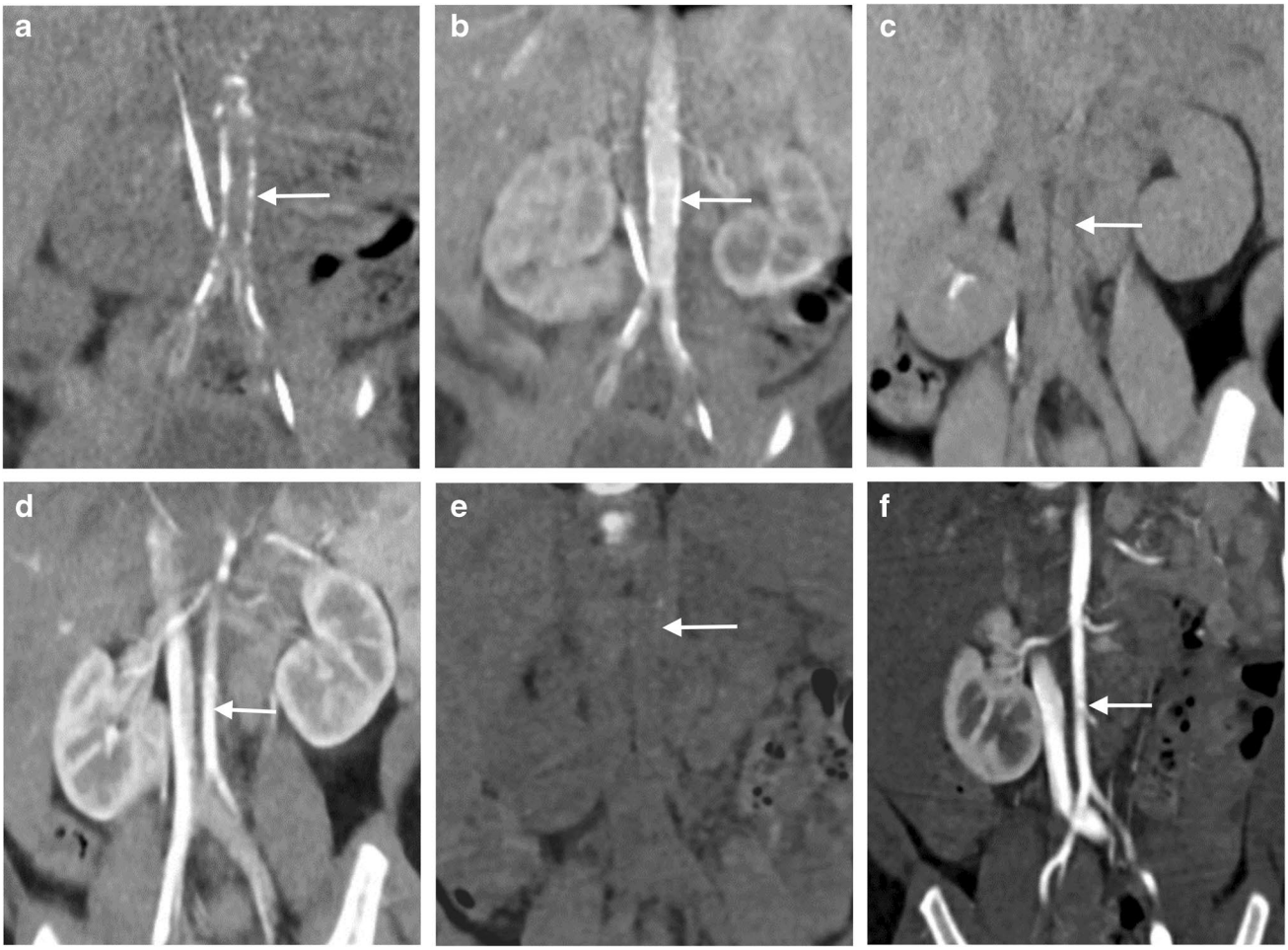

Fig. 3 Generalized arterial calcification of infancy type 2 in an infant boy (same boy as in Fig. 2). **a, b** Coronal nonenhanced CT (**a**) and CT angiography (**b**) of the abdomen and pelvis at 10 days old show calcifications of the aorta (*arrow*) and iliac vessels with normal caliber. **c, d** Coronal nonenhanced CT (**c**) and CT angiography (**d**) at 6 months old show aortic and iliac calcifications resolved (*arrow*). **e, f** Coronal nonenhanced CT (**e**) and CT angiography (**f**) at 12 months old show development of infrarenal aortic stenosis (*arrow*)

potency of etidronate, a first-generation bisphosphonate, requires administration of relatively large doses of the drug to elicit the desired therapeutic effect of inhibition of osteoclastic bone resorption in children with Paget disease and osteoporosis. In some patients, excessive treatment over protracted periods of time led to pathological inhibition of normal bone mineralization and to the speculation that high-dose etidronate could be used as a form of inorganic pyrophosphate replacement therapy to treat ectopic calcification in GACI [35]. While bisphosphonates can prevent calcification in animal models with GACI, there is no evidence that these agents can reverse existing calcifications [36] or improve survival in humans with GACI [4].

Although the second- and third-generation bisphosphonates have become popular replacements for etidronate for osteoporosis because of their greater potency, use of these newer agents for GACI is counterintuitive. These advanced bisphosphates are far more potent biological inhibitors of osteoclast activity than etidronate, which allows them to be administered in small doses that deliver too few moles of inorganic pyrophosphate analog to inhibit mineralization, an undesirable effect of etidronate for children with metabolic bone disease. Studies in murine models of GACI showed that etidronate can prevent the development of vascular calcification, but they showed no evidence that treatment reverses existing calcifications [36, 37]. As our analyses show, new vascular calcifications rarely develop after birth and existing calcifications often regress spontaneously over time, so there seems to be little justification for administering bisphosphonates postnatally in children with GACI, particularly given that these agents have the potential to cause severe bone toxicity when used for prolonged periods [38, 39]. By contrast, recent preclinical studies of recombinant ENPP-1 as enzyme replacement therapy

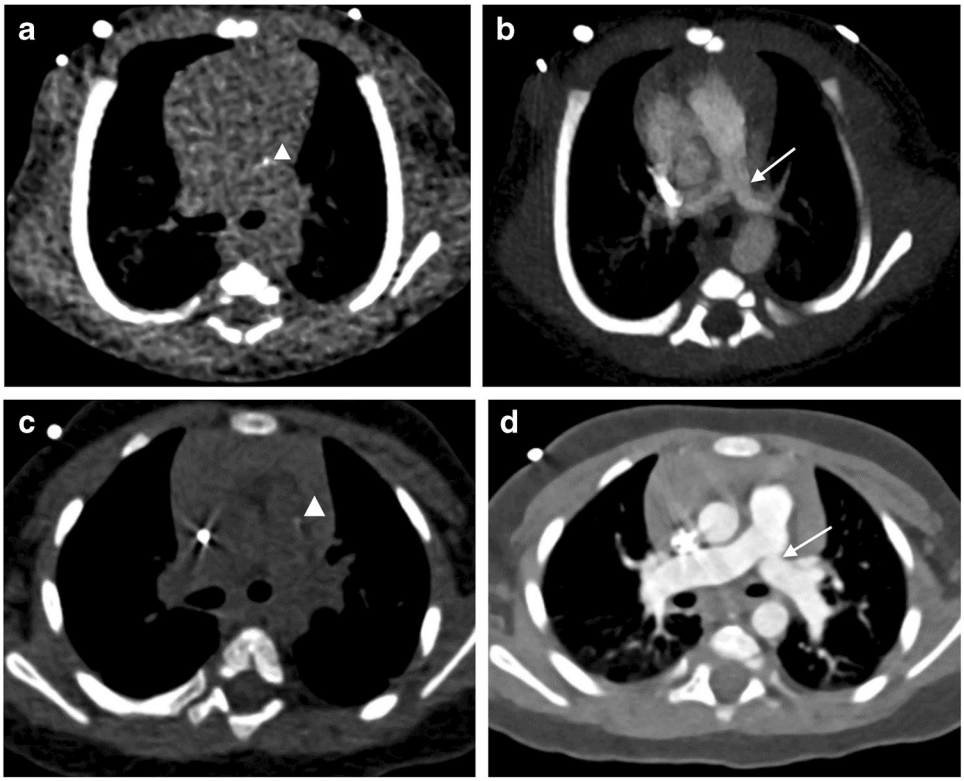

Fig. 4 Generalized arterial calcification of infancy type 2 in an infant girl. **a, b** Six days old. Axial CT image of the chest without contrast agent (**a**) shows punctate calcifications of the left pulmonary artery (*arrowhead*). Axial CT angiography of the chest (**b**) shows smooth contour without definitive stenosis of the left pulmonary artery (*arrow*). **c, d** Ten months old. Axial CT image of the chest without contrast (**c**) shows decreased calcification (*arrowhead*). Axial CT angiography image of the chest (**d**) shows proximal left pulmonary artery stenosis (*arrow*), with development of post-stenotic dilation. At 5 years of age, there was no residual calcification or stenosis (not shown)

for murine models of GACI offer far greater promise as a treatment that can inhibit both vascular calcification and intimal proliferation [30, 40–42].

Sodium thiosulfate increases the solubility of calcium and has been used to treat ectopic calcifications caused by renal failure, dermatomyositis and hyperphosphatemic tumoral calcinosis [40, 43]. A case report described experimental treatment with intravenous sodium thiosulfate as a viable therapeutic option in a severe case of pseudoxanthoma elasticum, opening the door to future studies using this treatment in related conditions [2]. Sodium thiosulfate efficacy is attributed to the chelation of calcium to soluble calcium thiosulfate complexes and its strong antioxidant properties [2]. Our limited preliminary observations suggest similar benefits regarding calcifications but no effects on arterial stenoses in GACI. Four children from our cohort received sodium thiosulfate postnatally, and all of them had resolution or decreases in arterial calcifications at the last follow-up. Stenoses completely resolved in one child treated with sodium thiosulfate but progressed in two other children with the same treatment. Regression of stenoses might be related to the history of prenatal treatment; however, we saw very variable progression of findings with prenatal and postnatal treatment.

Our study has several limitations. First, this is a retrospective study with a small heterogeneous sample. Some children were diagnosed and treated prenatally with

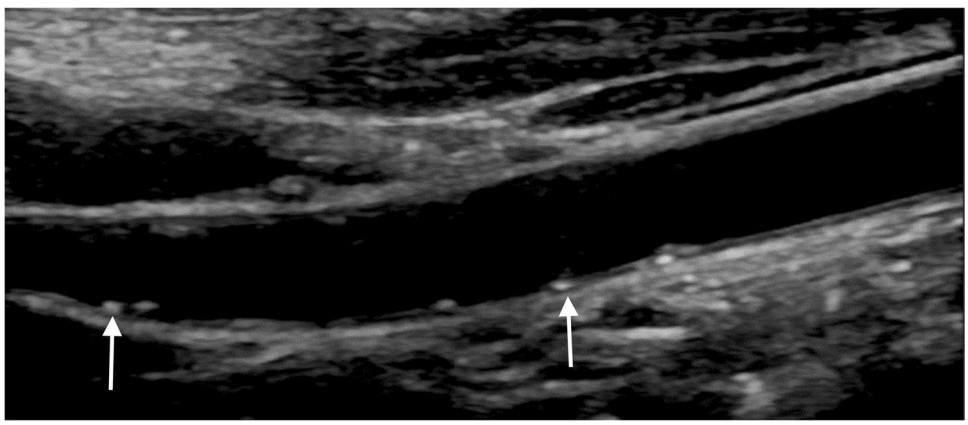

Fig. 5 Generalized arterial calcifications of infancy type 2 in a 4-year-old girl. Longitudinal gray-scale US image of the carotid artery shows punctate echogenic foci (*arrows*) along the arterial walls without evidence of stenosis. CT angiography of the chest, abdomen and pelvis was normal (not shown)

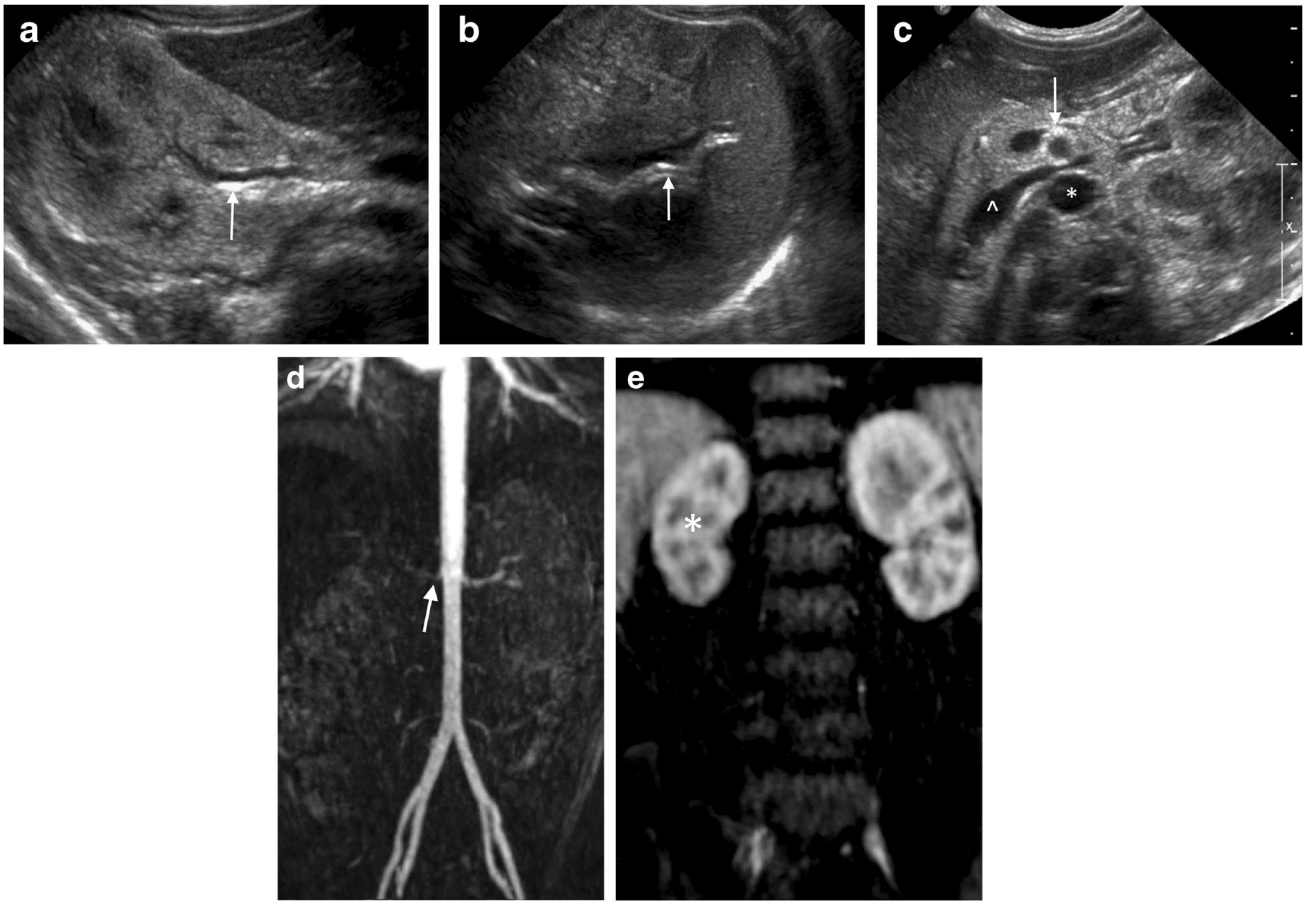

Fig. 6 Generalized arterial calcifications of infancy type 2 in a 6-day-old girl. **a** Transverse gray-scale US shows diffuse arterial calcification of the right renal artery (*arrow*). **b** Transverse gray-scale US shows diffuse arterial calcification of the splenic artery (*arrow*). **c** Transverse gray-scale US shows diffuse arterial calcification of the superior mesenteric artery (*arrow*) and aorta (*) as the left renal vein crosses between them and joins the inferior vena cava (^). Follow-up CT of the chest, abdomen and pelvis at 5 years of age showed complete resolution of calcifications (not shown). **d, e** Contrast-enhanced coronal MR angiography images of the abdomen (**d**) and pelvis (**e**) at 9 years of age show residual right renal artery stenosis (*arrow*) resulting in asymmetrically smaller (*) right kidney

biphosphonates, while others received other treatments postnatally that included sodium thiosulfate. Second, our patients underwent imaging with several modalities with variable intervals, which limits the comparison of findings among them. Third, some children did not have imaging after infancy, which might have led to underestimation of the final findings by preventing the visualization of notable changes that similarly occurred in other children later in childhood. Fourth, only descriptive statistics were possible because of the low statistical power. Finally, a lack of protocol in imaging of these children might be reflected in the heterogeneous findings and imaging modalities that were used. An imaging protocol should be established to objectively compare and review vascular findings in children with GACI.

Conclusion

Children with GACI have characteristic vascular calcifications that can be identified prenatally, during the neonatal period, or at any point after birth. Early clinical manifestations during infancy or childhood might raise the suspicion of this disease. Arterial calcifications sometimes decrease or disappear spontaneously with time or after treatment, but arterial stenoses usually persist and sometimes progress with time. Imaging plays an important role in follow-up because it can provide prognostic information and help guide treatment decisions. The evolution of calcifications and development of arterial stenoses can be easily identified and followed with non-contrast CT and CT angiographic imaging. Given the rarity of the disease, a multicenter registry trial might be needed to evaluate a larger number of children, imaging findings and outcomes.

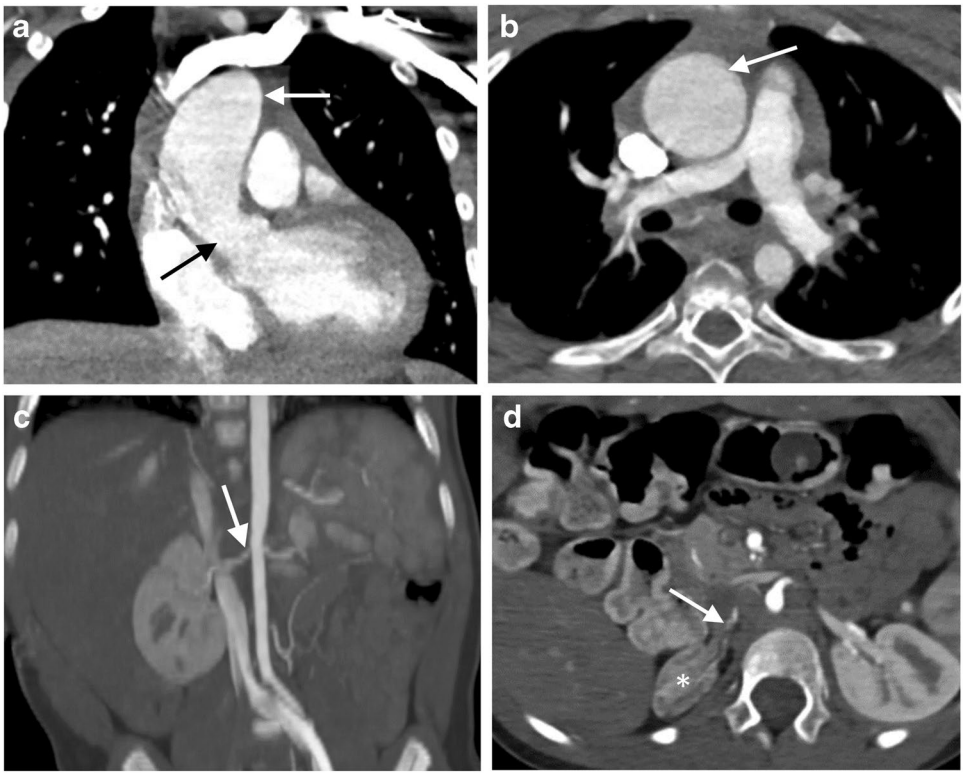

Fig. 7 Generalized arterial calcifications of infancy type 2 in a 11-year-old boy. **a, b** Coronal (**a**) and axial (**b**) CT angiography images of the chest show supravalvular aortic stenosis (*black arrow*) with an ascending aortic dilation (*white arrow*); no calcifications were visualized. **c** Coronal oblique maximum-intensity projection CT angiography shows right renal artery stenosis (*arrow*). **d** Axial CT angiography of the abdomen from the same study shows diffuse right renal artery stenosis (*arrow*). Note atrophic right kidney (*)

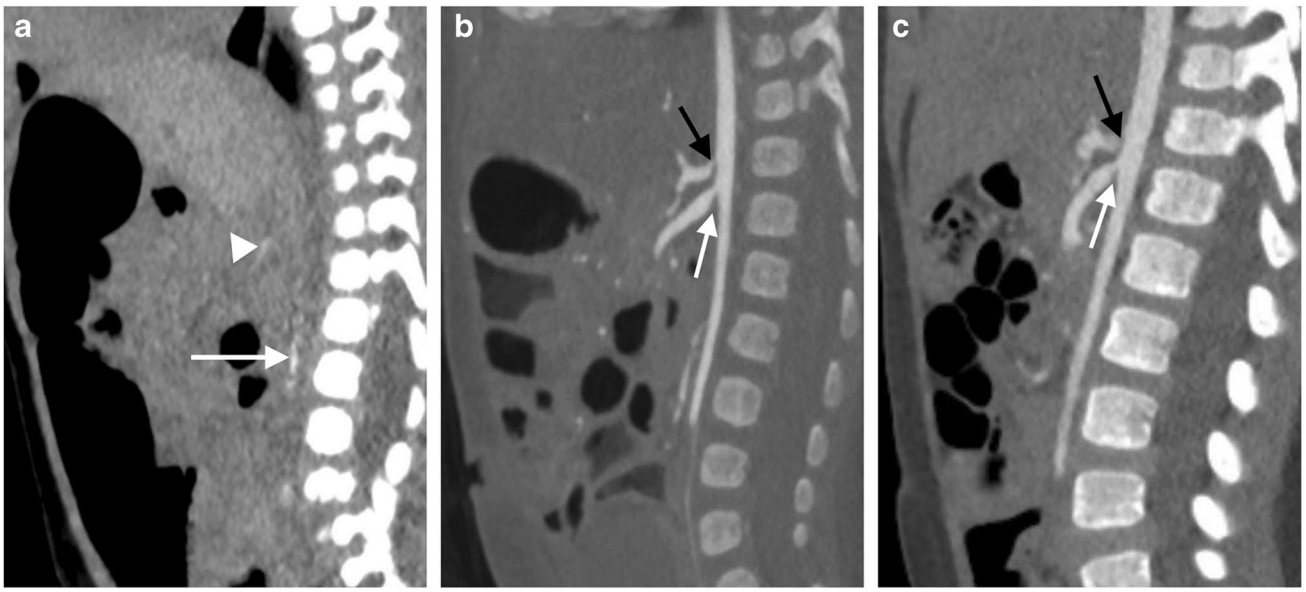

Fig. 8 Generalized arterial calcifications of infancy type 1 in a girl during infancy. **a** Sagittal CT image of the abdomen and pelvis at 5 weeks old shows calcifications of the infrarenal aorta (*arrow*) and superior mesenteric artery (*arrowhead*). Calcifications were also present in the renal arteries, iliac arteries, thoracic aorta and coronary arteries (not shown). **b** Follow-up sagittal CT angiography of the abdomen and pelvis at 8 months old shows resolution of calcifications with stenosis of the celiac trunk (*black arrow*) and superior mesenteric artery (*white arrow*). **c** Follow-up sagittal CT angiography image of the abdomen and pelvis at 3 years old shows resolution of calcifications with progressive stenosis of the celiac trunk (*black arrow*) and superior mesenteric artery (*white arrow*). Stenoses were also present in the renal arteries, descending aorta and iliac arteries (not shown)

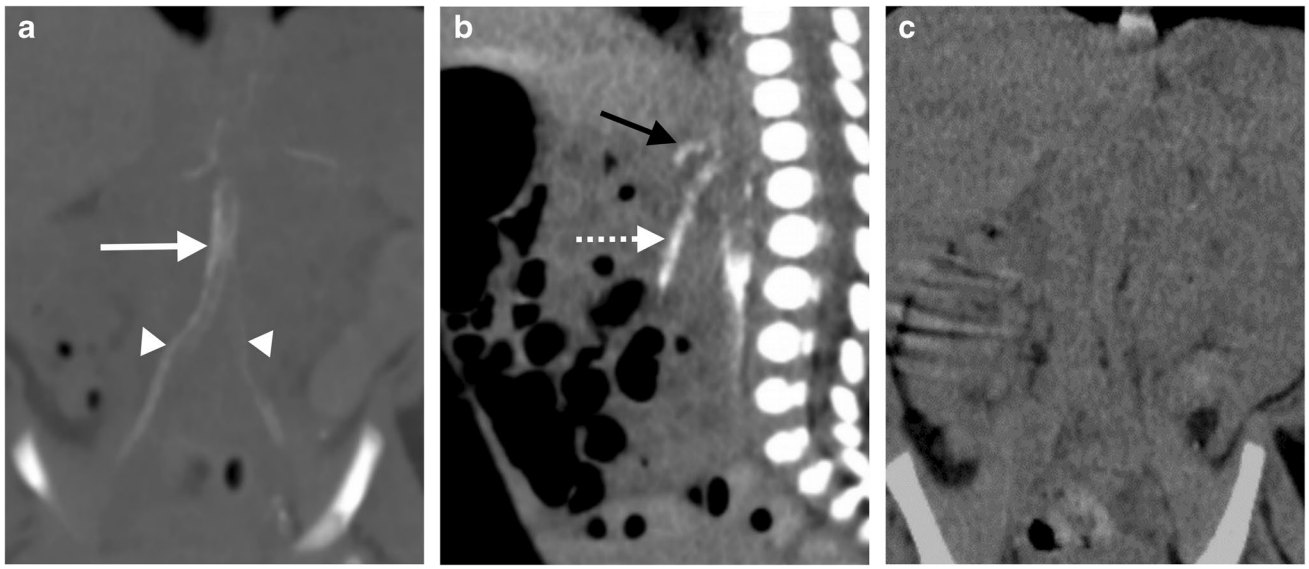

Fig. 9 Generalized arterial calcifications of infancy type 2 in a 3-day old boy. **a** Coronal CT image without contrast agent shows extensive calcifications of the aorta (*arrow*) and common iliac arteries (*arrowheads*). **b** Sagittal CT image shows calcifications of the celiac trunk (*solid arrow*), superior mesenteric artery (*dotted arrow*) and renal arteries (not shown). **c** Follow-up coronal CT image without contrast agent at 8 months old shows calcifications resolved

Declarations

Conflicts of interest None

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