U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Ziegler SG, Gahl WA, Ferreira CR. Generalized Arterial Calcification of Infancy. 2014 Nov 13 [Updated 2020 Dec 30]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Generalized Arterial Calcification of Infancy

Synonyms: GACI, Idiopathic Infantile Arterial Calcification (IIAC)

Shira G Ziegler, MD, PhD,[1] William A Gahl, MD, PhD,[2] and Carlos R Ferreira, MD[2]

Created: November 13, 2014; Updated: December 30, 2020.

Summary

Clinical characteristics

Generalized arterial calcification of infancy (GACI) is characterized by infantile onset of widespread arterial calcification and/or narrowing of large and medium-sized vessels resulting in cardiovascular findings (which can include heart failure, respiratory distress, edema, cyanosis, hypertension, and/or cardiomegaly). Additional findings can include typical skin and retinal manifestations of pseudoxanthoma elasticum (PXE), periarticular calcifications, development of rickets after infancy, cervical spine fusion, and hearing loss. While mortality in infancy is high, survival into the third and fourth decades has occurred.

Diagnosis/testing

The diagnosis of GACI is established in a proband with cardiovascular symptoms during infancy associated with widespread arterial calcification on imaging (once secondary causes have been ruled out) and biallelic pathogenic variants in *ENPP1* or *ABCC6* identified on molecular genetic testing.

Management

Treatment of manifestations: It remains unclear whether bisphosphonates (most commonly used is etidronate) increase survival. Standard anti-hypertensive therapy is warranted for hypertension. Aspirin therapy is warranted in those with severe coronary stenosis. Intravitreal VEGF inhibitors for choroidal neovascularization, calcitriol and oral phosphate supplement for hypophosphatemic rickets, and hearing aids (as indicated) are all used in the management of this disorder.

Surveillance: No specific guidelines address the issue of surveillance. The appropriate intervals for monitoring depend on the clinical findings. Low-dose CT scan every 3-4 months is used for the first year of life to monitor arterial calcification; echocardiography and troponin are used at regular intervals to monitor cardiovascular issues. Annual (or more frequent) retinal exam for PXE retinal findings and regular lab testing to assure mineral homeostasis associated with the development of rickets. Due to risk for nephrocalcinosis with treatment for

Author Affiliations: 1 Department of Genetics and Pediatrics Johns Hopkins University School of Medicine Baltimore, Maryland; Email: sgziegler@jhmi.edu. 2 National Human Genome Research Institute National Institutes of Health Bethesda, Maryland; Email: bgahl@helix.nih.gov; Email: ferreiracr@mail.nih.gov.

rickets, urine calcium is monitored to maintain calciuria below 4 mg/kg/d and yearly renal ultrasound is performed. Evaluate for cervical spine fusion prior to elective endotracheal intubation by a lateral cervical spine x-ray.

Agents/circumstances to avoid: Although no clinical studies have been conducted, it seems prudent to avoid the use of warfarin if possible. Similarly, the use of burosumab, an anti-FGF23 monoclonal antibody, remains controversial due to theoretic concerns.

Evaluation of relatives at risk: It is appropriate to evaluate the younger sibs of a proband with GACI in order to identify as early as possible those who would benefit from treatment.

Genetic counseling

GACI is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a GACI-causing pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being heterozygous, and a 25% chance of inheriting neither pathogenic variant. Carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible if the pathogenic variants in the family are known.

Diagnosis

No consensus clinical diagnostic criteria for generalized arterial calcification of infancy (GACI) have been published.

Suggestive Findings

GACI should be suspected in individuals with a combination of the following.

Clinical findings

- Typical cardiovascular findings including heart failure, respiratory distress, edema, cyanosis, hypertension, and/or cardiomegaly
- Characteristic **imaging** findings of widespread arterial calcification and/or narrowing of large and medium-sized vessels
- Appearance of typical clinical and histologic skin findings of pseudoxanthoma elasticum (PXE) and/or angioid streaks on fundoscopy
- Development of hypophosphatemic rickets after infancy

Imaging

- **Computed tomography (CT)** is the preferred imaging modality to assess for calcifications. Multi-detector computed tomography has been reported to detect not only arterial wall calcification but also intimal thickening causing luminal narrowing [Greenberg & Gibson 2005], which appears as a target or bull's eye with a center of high attenuation (the lumen) surrounded by low attenuation (the thickened intima), which is again surrounded by high attenuation (the calcification of the arterial wall).
- **Echocardiogram** can:
  - Detect echobrightness of the arteries near the heart, including the coronary and pulmonary arteries, ascending aorta and aortic arch, and large arteries originating from the aortic arch;
  - Detect the presence of left ventricular hypertrophy and/or pericardial effusion.
- **Ultrasound examination** of the abdomen and head can be used to detect echo-bright vessels.
- **Plain radiographs** can sometimes detect arterial calcifications, but with low sensitivity, and many times arterial calcifications are detected only on reexamination of radiographs after the diagnosis of GACI has been made post mortem [Glatz et al 2006].

- **Magnetic resonance imaging and angiography** are insensitive to detecting arterial wall calcification, but can detect luminal stenosis [Pao et al 1998], especially when performed with breath-hold and cardiac gating techniques [Tran & Boechat 2006].
- **Coronary angiography** can be normal despite the presence of extensive arterial wall calcifications, likely because widespread involvement of all coronary arteries results in diffuse narrowing without the focal areas of stenosis detectable by angiography [Hault et al 2008].

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of GACI is established in a proband with cardiovascular symptoms during infancy associated with widespread arterial calcification on imaging once secondary causes have been ruled out (see Differential Diagnosis), and either biallelic pathogenic variants in *ENPP1* or *ABCC6* on molecular genetic testing (see Table 1) or, if testing is not diagnostic, histologic findings on arterial biopsy [Morton 1978].

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing), depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of GACI has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

A multigene panel that includes some or all of the genes listed in Table 1 and other genes of interest (see Differential Diagnosis) is likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Generalized Arterial Calcification of Infancy (GACI)

Gene [1, 2]	Proportion of GACI Attributed to Pathogenic Variants in Gene [3, 4]	Proportion of Pathogenic Variants [5] Detectable by Method	
		Sequence analysis [6]	Gene-targeted deletion/ duplication analysis [7]
ABCC6	~9%	88% [8]	12% [8]
ENPP1	~67%	96% [8]	4% [8]
Unknown [9]	~24%	NA	

1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. Nitschke et al [2012]
4. While a majority of cases of GACI are caused by biallelic pathogenic variants in *ENPP1,* pathogenic variants in *ABCC6* can cause a clinically indistinguishable phenotype.
5. See Molecular Genetics for information on variants detected in these genes.
6. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
7. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
8. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2017] and personal unpublished data
9. 22 of 92 individuals with GACI reported by Nitschke et al [2012] did not have biallelic pathogenic variants in either *ENPP1* or *ABCC6*; however, two were heterozygous for an *ENPP1* pathogenic variant, and six individuals in five unrelated families were heterozygous for an *ABCC6* pathogenic variant.

Clinical Characteristics

Clinical Description

Generalized arterial calcification of infancy (GACI) can result either from ENPP1 deficiency (ENPP1-GACI), or from ABCC6 deficiency (ABCC6-GACI) associated with biallelic pathogenic variants in *ENPP1* or *ABCC6* respectively. To date, around 250 individuals have been identified with GACI [Authors, personal observation]. The following description of the phenotypic features associated with this condition is based on these individuals.

Table 2. GACI: Frequency of Select Features

Feature	% of Persons with Feature	Comment
Arterial calcification	88%-95%	Most common sites: aorta, pulmonary, coronary, renal
Extravascular calcification	50%-60%	Most common site: hip; sternoclavicular joint commonly involved
Pseudoxanthoma elasticum findings	~20%	Onset of skin findings in childhood; onset of retinal findings more commonly in adulthood
Hypophosphatemic rickets / osteomalacia	>90% (ENPP1-GACI only)	Mediated by FGF23
Nephrocalcinosis	50% (ENPP1-GACI mainly)	More commonly a complication of rickets/osteomalacia treatment
Cervical spine fusion	~25% (ENPP1-GACI only)	Affects posterior elements
Hearing loss	50%-75% (ENPP1-GACI only)	Variable age of onset

Presentation

A review of published information on 161 individuals with GACI [Chong & Hutchins 2008] identified the following:

- A bimodal age of presentation. 48% had early onset (i.e., in utero or within the first week of life) and 52% had late onset (median age three months).
- In early-onset GACI, the most common initial findings were fetal distress (46%), heart failure (44%), polyhydramnios (38%), hypertension (33%), respiratory distress (30%), hydrops fetalis (28%), edema (24%), "visceral" effusions (20%), cyanosis (22%), cardiomegaly (17%), and ascites (13%).
- In late-onset GACI, the most common presenting findings were respiratory distress (66%), cyanosis (43%), refusal to feed (34%), heart failure (29%), vomiting (24%), irritability (21%), failure to thrive (17%), fever (16%), hypertension (12%), and edema (7%).
- Males and females were affected with similar frequency: 43% of those with early-onset GACI and 48% of late-onset GACI were female.

For individuals with fetal involvement, arterial calcifications are commonly detected at the time of prenatal ultrasound (most commonly in the third trimester, but imaging diagnosis in the second trimester is also possible). For infants with postnatal late-onset GACI, the presenting findings (respiratory distress, cyanosis, refusal to feed, heart failure) lead to imaging studies such as echocardiography and/or CT, and the detection of arterial calcification suggests the diagnosis.

Arterial Calcification

Autopsy studies (reviewed by Chong & Hutchins [2008]) noted that the most commonly calcified arteries in early-onset GACI were hepatic (81%), aorta (80%), pulmonary (67%), coronary (53%), and renal (39%). The most commonly calcified arteries in late-onset GACI were coronary (88%), renal (55%), pulmonary (49%), aorta (36%), adrenal (34%), splenic (31%), pancreatic (28%), and mesenteric (26%).

In a cohort of long-term survivors of GACI, the most common sites of arterial calcification were the aorta (14/16), and renal (11/16), mesenteric (11/16), coronary (10/16), iliac (10/16), and pulmonary (10/16) arteries [Ferreira et al 2021a].

Although generally spared, the cerebral arteries have been involved in several reported individuals [Glatz et al 2006, van der Sluis et al 2006]; presenting manifestations can thus include seizures [Galletti et al 2011], strokes [Van Dyck et al 1989], or recurrent transient ischemic attacks due to cerebrovascular insufficiency [Thomas et al 1990]. Cystic encephalomalacia is rarely reported [Galletti et al 2011, Nitschke et al 2012].

Peripheral arterial calcifications can present with decreased peripheral pulses; in exceptional cases, gangrene has occurred in the distal extremities [Witzleben 1970, Lussier-Lazaroff & Fletcher 1973], likely caused by a combination of vessel luminal narrowing and left ventricular systolic dysfunction.

Pulmonary hypertension refractory to medical therapy is possible [Farquhar et al 2005, Shaireen et al 2013].

Spontaneous resolution of calcification has been reported in several individuals [Sholler et al 1984, Ciana et al 2006]. In those without continued evidence of calcification, arterial stenoses associated with intimal thickening have been observed [Marrott et al 1984, Thiaville et al 1994, Nitschke et al 2012]. Generalized arterial stenoses without prior evidence of arterial calcification are also possible [Nitschke et al 2012, Ferreira et al 2021a].

Arterial calcifications or intimal proliferation may also explain the high frequency of recurrent pregnancy loss (≥4 miscarriages per family in 25% vs in 1%-2% in the general population) and hematochezia (15% vs 2% in the general population) [Ferreira et al 2021a].

Extravascular Calcifications

Periarticular calcifications have been noted in eight of 16 surviving individuals with GACI [Ferreira et al 2021a]. The most common site of involvement is the hip; other commonly affected joints include the wrist, shoulder, elbow, knee, and sternoclavicular joint [Chong & Hutchins 2008, Ferreira et al 2021a].

Other sites of extravascular calcification include the ear lobes [Vera et al 1990, Nitschke et al 2012, Brachet et al 2014], myocardium, and brain parenchyma [Ferreira et al 2021a].

Pseudoxanthoma Elasticum (PXE) Findings

Individuals with GACI can manifest PXE-like changes; these were seen in four of 20 survivors, with onset between ages two and 43 years [Ferreira et al 2021a]. Skin findings typically manifest during childhood, while retinal findings (peau d'orange, angioid streaks, choroidal neovascularization with subsequent retinal hemorrhage) commonly do not appear until adulthood. However, typical retinal findings of PXE were reported in a girl age four years with ENPP1 deficiency [Freychet et al 2014], indicating that earlier onset of ocular complications is possible.

It has been speculated that children with GACI and findings of PXE were not reported until recently because most died before they developed typical signs of PXE, and many features of PXE (e.g., angioid streaks and skin lesions) are frequently overlooked in the clinical examination of individuals with GACI [Nitschke & Rutsch 2012]. See Pseudoxanthoma Elasticum.

Hypophosphatemic Rickets / Osteomalacia

Individuals with GACI caused by pathogenic variants in *ENPP1* who survive the first six months of life (i.e., the critical period) can develop bone deformities, hypophosphatemia, hyperphosphaturia, and elevated alkaline phosphatase, with all the clinical manifestations of autosomal recessive hypophosphatemic rickets type 2 (ARHR2; see Genetically Related Disorders). Conversely, several individuals with ARHR2 have had asymptomatic undiagnosed vascular involvement. Thus, ARHR2 and GACI represent a phenotypic spectrum.

The average age for the development of hypophosphatemia was 1.6 years [Ferreira et al 2021a]. In a cohort of surviving individuals with ENPP1 deficiency (mean age 11.7 years), 11 of 16 (69%) had already developed rickets, with a Kaplan-Meier estimate that almost all individuals would develop rickets/osteomalacia by age 14 years [Ferreira et al 2021a]. This form of rickets/osteomalacia is mediated by FGF23, and can lead to painful calcification of the entheses (insertion sites of ligaments and tendons) in adulthood [Kotwal et al 2020, Ferreira et al 2021a].

There are no reports of hypophosphatemia in individuals with GACI caused by pathogenic variants of *ABCC6*, although one individual in the series of Nitschke et al [2012] had GACI with hypophosphatemic rickets and was heterozygous for an *ABCC6* pathogenic variant.

Nephrocalcinosis

Bilateral medullary nephrocalcinosis was seen in five of ten individuals with ENPP1 deficiency who received standard treatment for hypophosphatemic rickets/osteomalacia, while it was not detected in any of seven individuals who were naïve to treatment. Cortical nephrocalcinosis can be seen in the absence of treatment. While medullary nephrocalcinosis is likely a complication from treatment of rickets/osteomalacia (and thus seen only in ENPP1 deficiency), cortical nephrocalcinosis likely represents a consequence of ischemia (and can be seen either with ENPP1 or ABCC6 deficiency) [Ferreira et al 2021b].

Cervical Spine Fusion

Fusion of the posterior elements of the cervical spine (posterior vertebral bodies, articular processes, laminae) was seen in four of 16 individuals with ENPP1 deficiency [Ferreira et al 2021a].

Hearing Loss

In GACI, hearing loss can be conductive, sensorineural, or mixed, and can present as early as in the neonatal period [Brachet et al 2014]. It developed in ten of 16 survivors (63%) with ENPP1-GACI at a median age of 3.7 years, with a Kaplan-Meier estimate of developing hearing loss of 20% by age two years, 50% by four years, and 75% over a lifetime [Ferreira et al 2021a].

Sensorineural hearing loss is presumably due to calcifications of the arteries supplying the inner ear [Lorenz-Depiereux et al 2010], while conductive hearing loss is due to stapedovestibular ankylosis [Nitschke et al 2012, Freychet et al 2014].

Development

Although cognitive development has not been formally assessed in a cohort of individuals with GACI, the majority appear to have normal development. However, the authors are aware of a few individuals with severe global developmental delay in the setting of prior strokes or encephalomalacia. In individuals with periarticular calcifications, motor milestones can be delayed due to pain around the affected joints [Authors, personal observation].

Variability

In one family in which the father and son were homozygous for the same *ENPP1* pathogenic variant, the father presented with hypophosphatemia and rickets and later developed an aortic root dissection at age 28 years, while the son had GACI and hypophosphatemia [Lorenz-Depiereux et al 2010]. Sibs harboring the same pathogenic variants have been reported to have markedly different clinical courses [Ferreira et al 2021a].

Prognosis

In a series of 55 children, the mortality rate at age six months was 30 of 55 (55%) despite intensive therapy [Rutsch et al 2008]. Only one individual died after age six months; thus, the mortality rate was markedly decreased in those who survived the first few months of life. Causes of death were myocardial infarction, congestive heart failure, persistent arterial hypertension, or multiorgan failure.

Long-term survivors, with several in their 20s, include twins age 21 years [Rutsch et al 2008], a woman age 22 years [Marrott et al 1984], individuals age 25 and 26 years at last follow up [Ferreira et al 2021a], and a woman age 37 years [Authors, personal observation]. The oldest individual with ENPP1 deficiency reported to date is a woman age 62 years [Saito et al 2011].

Bisphosphonate treatment was associated with survival beyond infancy in 11 of 17 individuals, while 18 of 26 individuals not treated with bisphosphonates died in infancy [Rutsch et al 2008] (see Treatment of Manifestations). It remains unclear whether bisphosphonate use improves survival [Authors, personal observation].

Genotype-Phenotype Correlations

Marked phenotypic heterogeneity, even among surviving sibs with identical genotypes, argues against a genotype-phenotype correlation in GACI [Ferreira et al 2021a].

Otero et al [2013] (full text; see Supporting Information, Appendix) reported an affected individual with biallelic *ENPP1* pathogenic variants and a heterozygous pathogenic variant in *ABCC6,* which theoretically could have

contributed to the severity of GACI. The individual's healthy mother and brother both were doubly heterozygous for an *ENPP1* pathogenic variant and the *ABCC6* pathogenic variant; thus, it appears that the presence of one heterozygous *ENPP1* pathogenic variant and one *ABCC6* pathogenic variant does not cause GACI.

Nomenclature

In the past, generalized arterial calcification of infancy (GACI) has been variously referred to as idiopathic obliterative arteriopathy, infantile calcifying arteriopathy, occlusive infantile arteriopathy, medial coronary sclerosis of infancy, diffuse arterial calcifying elastopathy of infancy, and arteriopathia calcificans infantum.

Prevalence

GACI shows no ethnic or racial predilection, and has been described throughout the world.

The disease frequency is estimated at one in 200,000 pregnancies, and the carrier frequency at one in 223 individuals [Ferreira et al 2021a].

Genetically Related (Allelic) Disorders

Other phenotypes associated with germline pathogenic variants in *ENPP1* and *ABCC6* are summarized in Table 3.

Table 3. Allelic Disorders

Gene	Disorder	MOI	Clinical Characteristics
ENPP1	Autosomal recessive hypophosphatemic rickets type 2 (ARHR2) (OMIM 613312) [1]	AR	• Short stature, dental caries, & bone deformities • Hypophosphatemia, hyperphosphaturia, & ↑ plasma alkaline phosphatase • Levy-Litan et al [2010] described affected persons diagnosed between ages 2.5 & 16.8 yrs who at dx showed no evidence of GACI. [2] (Whether these persons had had mild features of GACI that were missed during infancy & resolved after development of hypophosphatemia is unknown.)
	Hypophosphatemic rickets / osteomalacia	AD	Fractures, low bone mineral density, hypophosphatemia, hyperphosphaturia, & ↑ FGF23 were reported in persons from 2 unrelated families w/known heterozygous *ENPP1* pathogenic variants [Oheim et al 2020], raising the possibility that certain monoallelic variants in *ENPP1* can lead to osteomalacia.
	Cole disease (OMIM 615522)	AD AR	• Distinctive hypopigmented macules; punctate keratosis on areas of cornification (specifically the palms & soles) • Rare cutaneous calcifications (incl calcinosis cutis & calcific tendinopathy) have been noted. [3]

Table 3. continued from previous page.

Gene	Disorder	MOI	Clinical Characteristics
ABCC6	Pseudoxanthoma elasticum	AR	• Systemic disorder affecting elastic tissue of the skin, eye, & CV & GI systems • Commonly presents w/papules in the skin &/or w/angioid streaks of the retina found on routine eye exam or assoc w/retinal hemorrhage • Rarely, may present w/vascular signs & symptoms, (e.g., GI bleeding, angina, or intermittent claudication) • ↓ vision (from macular hemorrhage & disciform scarring of the macula) is most frequent cause of morbidity & disability. • Normal life span in most persons

AD = autosomal dominant; AR = autosomal recessive; CV = cardiovascular; dx = diagnosis; GACI = generalized arterial calcification of infancy; GI = gastrointestinal; MOI = mode of inheritance

1. Of note, fibroblast growth factor 23 (*FGF23*), a major regulator of phosphorus homeostasis, leads to decreased renal tubular reabsorption of phosphorus. Intact FGF23 (i.e., the active form of FGF23 prior to cleavage into its inactive C terminal) is either elevated or in the upper range of normal in individuals with ARHR2 [Ferreira et al 2021a].

2. That is, no vascular or periarticular calcifications on imaging studies.

3. Eytan et al [2013]

Differential Diagnosis

Disorders with Vascular Calcification

Singleton-Merten syndrome (OMIM 182250 and 616298) is an autosomal dominant disorder caused by pathogenic variants in *IFIH1* or *DDX58*.

- Severe aortic calcification, dental anomalies (delayed eruption and early loss of permanent teeth, alveolar bone erosion), osteopenia, and acroosteolysis are salient features of the disease [Feigenbaum et al 2013].
- Unlike generalized arterial calcification of infancy (GACI), aortic calcification in Singleton-Merten syndrome starts later in life (age range at diagnosis: 6-39 years).

Metastatic calcification due to hypervitaminosis D, hyperparathyroidism, or end-stage renal disease

- Diffuse arterial calcification tends to affect the media of the vessels, and extensive extravascular calcification involves the renal tubules, bronchial walls, and basal mucosa and muscularis mucosae of the stomach.
- Compared with GACI, metastatic calcification exhibits a different distribution of extravascular calcification, and the microscopic vascular changes occur in the media with little intimal proliferation.

Twin-twin transfusion syndrome (TTTS) and twin reversed arterial perfusion (TRAP) sequence

- Increased echogenicity due to calcification has been described in the wall of the pulmonary trunk, proximal branch pulmonary arteries [Saxena & Soni 2003, Bassil Eter et al 2009], and ascending aorta in the recipient twin of TTTS [Saxena & Soni 2003]. Pulmonary artery calcification has also been described in pump twins in TRAP sequence [Royston & Geoghegan 1983, Popek et al 1993]. Since this always occurs in the volume-overloaded fetus (recipient twin in TTTS and pump twin in TRAP sequence), it presumably results from increased cardiac output in utero [Popek et al 1993].
- Histologically, calcium is deposited primarily in the media [Popek et al 1993], whereas in GACI it is deposited along the internal elastic lamina. Additionally, in TTTS and TRAP sequence calcification does not occur elsewhere in the body [Saxena & Soni 2003].

Disorders with Occlusive Arteriopathy

Pediatric fibromuscular dysplasia (FMD). This noninflammatory arteriopathy can be unifocal or multifocal, is associated with hypertension, and commonly affects the renal and mesenteric arteries and the abdominal aorta [Green et al 2016, Louis et al 2018], all common sites of stenosis in GACI. In fact, a child with a clinical diagnosis of pediatric FMD was eventually found to have ENPP1 deficiency [Ferreira et al 2021a]; thus, other individuals with pediatric FMD could benefit from molecular genetic testing of *ENPP1*.

Grange syndrome (OMIM 602531) is an autosomal recessive disorder caused by pathogenic variants in *YY1AP1*. This extremely rare syndrome is characterized by diffuse vascular stenoses with intimal thickening [Weymann et al 2001] in a distribution pattern resembling fibromuscular dysplasia, brachysyndactyly, and osteopenia with increased bone fragility [Grange et al 1998, Volonghi et al 2012].

Chronic arsenic poisoning. Diffuse thickening of the intima of medium- and small-sized arteries (without calcification) has been described in chronic arsenic poisoning, leading to death by myocardial infarction in children as young as age two years [Rosenberg 1974].

Management

No clinical practice guidelines for GACI have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with generalized arterial calcification of infancy (GACI), the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with GACI

System/Concern	Evaluation	Comment
Cardiovascular	Referral to a pediatric cardiologist	Incl: • EKG & echocardiogram • Assessment of blood pressure [1] & peripheral pulses
	CT of chest, abdomen, & pelvis	To evaluate extent & distribution of vascular calcification
	Serum levels of cardiac-specific troponin T or troponin I	Assess for evidence of myocardial ischemia.
Skeletal	Skeletal radiographs	As needed to assess for periarticular calcification or cervical spine fusion
Mineral metabolism	Metabolic workup incl: • Serum creatinine • Serum phosphorus • Urine phosphorus • Urine creatinine • Alkaline phosphatase • Serum calcium • Serum PTH	To evaluate for evidence of hypophosphatemic rickets by measuring: • Tubular reabsorption of phosphate • Ratio of renal tubular maximum reabsorption rate of phosphate to GFR
Hearing loss	Audiology assessment	Evaluate for conductive or sensorineural hearing loss.
Genetic counseling	By genetics professionals [2]	To inform patients & families re nature, MOI, & implications of GACI in order to facilitate medical & personal decision making

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Family support/ resources	Assess: • Use of community or online resources such as Parent to Parent; • Need for social work involvement for parental support; • Need for home nursing referral.	

GFR = glomerular filtration rate; MOI = mode of inheritance; PTH = parathyroid hormone
1. Referral to a pediatric nephrologist is indicated in the setting of refractory hypertension
2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with GACI

Manifestation/ Concern	Treatment	Considerations/Other
Arterial calcification	Bisphosphonate therapy [1] using one of the following: • Etidronate (20 mg/kg/d PO) • Pamidronate (0.25 mg/kg on day 1, then 0.5 mg/kg/d on days 2 & 3 for 1st cycle, then 0.5 mg/kg/d x3 days IV per cycle; cycles rptd every 2 mos) • Risedronate (1mg/kg/wk PO)	• After initiation of therapy, vascular calcifications have been reported to disappear as early as 2.5 wks (as assessed by radiographs) and as late as 2 yrs [van der Sluis et al 2006, Meradji et al 1978] • Vascular calcifications do not reappear after discontinuation of treatment even after 10 yrs [van der Sluis et al 2006] • Prolonged etidronate use in persons w/GACI has been assoc w/severe skeletal toxicity, incl radiographic findings resembling hypophosphatasia [2] or osteopetrosis [3] [Otero et al 2013]. Thus, some authors recommend close monitoring for resolution of arterial calcifications during treatment so that use of bisphosphonates can be discontinued as soon as possible [Otero et al 2013].
Hypertension	Standard therapy	Since hypertension in GACI is likely caused by renal artery stenosis, it may be beneficial to use ACE inhibitors or angiotensin II type 1 receptor blockers.
Severe coronary stenosis	Aspirin therapy if coronary stenosis is present	
PXE retinal changes	Intravitreal VEGF inhibitors for choroidal neovascularization	
Hypophosphatemic rickets	Calcitriol (15-25 ng/kg/d) & oral phosphate supplement (25-50 mg/kg/d in 3-5 daily doses)	Doses adjusted based on alkaline phosphatase, PTH, & calciuria levels
	Orthopedics eval if bone deformities develop	Surgical interventions may be necessary.
Hearing loss	Hearing aids as indicated	

ACE = angiotensin-converting enzyme; PTH = parathyroid hormone; VEGF = vascular endothelial growth factor
1. It remains unclear whether bisphosphonates (etidronate in particular) are associated with improved survival.
2. Radiographic findings resembling hypophosphatasia include pan craniosynostosis, bowing of long bones, metaphyseal cupping and fraying, and radiolucent tongues.
3. Radiographic findings resembling osteopetrosis include osteosclerosis and femoral Erlenmeyer flask deformity.

Surveillance

No specific guidelines address the issue of surveillance. The appropriate intervals for monitoring depend on clinical findings and need to be more frequent in those with a more severe presentation.

Table 6. Recommended Surveillance for Individuals with GACI

System/Concern	Evaluation	Frequency
Arterial calcification	Low-dose CT scan	Every 3-4 mos in 1st yr of life
Cardiovascular issues	• Echocardiography • Troponin	At regular intervals depending on degree of severity (as per cardiologist)
PXE retinal findings	Exam by retinal specialist	Annually, or more frequently as per specialist
Mineral homeostasis	Serum phosphate, creatinine, alkaline phosphatase, calcium, PTH; urine phosphate & creatinine	Annually before development of rickets; quarterly while on rickets treatment; after 2 wks of dosage modification
Hypercalciuria assoc w/treatment of hypophosphatemic rickets	Urine calcium	Maintain calciuria <4 mg/kg/d.
Nephrocalcinosis assoc w/treatment of hypophosphatemic rickets	Renal ultrasound	Annually
Cervical spine fusion	Lateral cervical spine radiograph	Prior to elective endotracheal intubation / surgery

PTH = parathyroid hormone

Agents/Circumstances to Avoid

Although no clinical studies have been conducted, it seems prudent to avoid the use of warfarin if possible. The matrix Gla protein (MGP), a potent anti-mineralization factor, needs to be activated by a vitamin K-dependent enzyme, and warfarin interferes with the vitamin K cycle. Warfarin has also been shown to accelerate ectopic mineralization in *Abcc6* knockout mice [Li et al 2013].

One question is whether burosumab, an anti-FGF23 monoclonal antibody approved by the FDA for the treatment of X-linked hypophosphatemia and tumor-induced osteomalacia, could also treat the hypophosphatemic rickets of ENPP1 deficiency. This approach, however, remains controversial due to theoretic concerns that it could worsen ectopic calcification by lowering pyrophosphate concentrations. However, one individual with ENPP1-related rickets, who was initially thought to have X-linked hypophosphatemia, received burosumab for months without developing any vascular calcification [Boyce et al 2020].

Evaluation of Relatives at Risk

It is appropriate to evaluate the younger sibs of a proband with GACI in order to identify as early as possible those who would benefit from institution of treatment and preventive measures. Evaluations can include:

- Molecular genetic testing if the GACI-causing pathogenic variants in the family are known;
- Imaging studies if the pathogenic variants in the family are not known.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Enzyme replacement therapy. The administration of a recombinant form of ENPP1 prevents calcification and mortality [Albright et al 2015], improves hypertension and cardiac function [Khan et al 2018], and prevents intimal proliferation [Nitschke et al 2018] in mouse models of ENPP1 deficiency. It also prevented the osteomalacia, increased bone density, and markedly improved bone strength in mutant mice, while preventing the development of nephrocalcinosis [Ferreira et al 2021b].

Magnesium. In a mouse model of ENPP1 deficiency, increased dietary magnesium during pregnancy and continued postnatally was shown to prevent ectopic mineralization, likely by competing with calcium for phosphate binding [Kingman et al 2017].

One infant who did not initially respond to etidronate administration eventually showed improvement with a combination of etidronate, magnesium, and calcium carbonate [Dursun et al 2019]; however, it is impossible to know whether this child would have shown spontaneous regression of calcification even in the absence of magnesium administration.

Sodium thiosulfate. A combination of etidronate and sodium thiosulfate was administered in a child with GACI, with no improvement of calcification and demise after one month [Hollwey et al 2019]. The administration of intravenous sodium thiosulfate led to improvement of calcific stenosis of celiac and mesenteric arteries in a child with a complex genotype [Omarjee et al 2020]. Thus, the use of sodium thiosulfate has not been associated with consistent improvement, and its benefits remain unclear.

Cardiac transplantation. One individual who received a heart transplant did well, with no recurrence of disease over two years of follow-up post transplant [Giovannoni et al 2014]. Another individual continues to do well several years post transplant [Authors, personal observation].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Generalized arterial calcification of infancy (GACI) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are typically heterozygous for an *ENPP1* or *ABCC6* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that each parent is heterozygous for a GACI-causing pathogenic variant and to allow reliable recurrence risk assessment.
    - In rare families, only one parent of a proband with an autosomal recessive disorder is heterozygous and the proband is affected as the result of either: (1) one pathogenic variant inherited from the heterozygous parent and a second pathogenic variant that occurred *de novo* in the proband (*de novo*

variants are known to occur at a low but appreciable rate in autosomal recessive disorders such as GACI [Authors, personal observation]); (2) uniparental isodisomy and consequent homozygosity for the pathogenic variant transmitted by a heterozygous parent.
    - Note: In a consanguineous family, both the father and the proband were homozygous for the same *ENPP1* pathogenic variants. (The father of the proband had autosomal recessive hypophosphatemic rickets type 2 while the proband was affected with GACI [Lorenz-Depiereux et al 2010]; see Genetically Related Disorders).
- Most heterozygotes are asymptomatic and are not at risk of developing the disorder. However, adult individuals with heterozygous *ENPP1* pathogenic variants from two unrelated families were reported with fractures, low bone mineral density, hypophosphatemia, hyperphosphaturia, and elevated FGF23 [Oheim et al 2020]; thus, it appears that certain heterozygous variants in *ENPP1* could lead to osteomalacia.

Sibs of a proband

- If both parents are known to be heterozygous for a GACI-causing pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being heterozygous, and a 25% chance of inheriting neither pathogenic variant.
- A sib who inherits biallelic pathogenic variants may have a clinical course markedly different from that of the proband (see Clinical Description, Variability).
- Most heterozygotes are asymptomatic and are not at risk of developing the disorder, although it is possible that certain heterozygous pathogenic variants in *ENPP1* could lead to osteomalacia in adulthood [Oheim et al 2020].

Offspring of a proband

- Because mortality in infancy is high, no individuals with GACI have been reported to have children to date.
- It is entirely possible that affected individuals who survive into adulthood will be able to conceive. For these individuals, offspring will be obligate heterozygotes for a pathogenic variant in *ENPP1* or *ABCC6* provided their reproductive partner is not affected or heterozygous (see Prevalence).

Other family members. Each sib of the proband's parents is at a 50% risk of being heterozygous for a GACI-causing pathogenic variant.

Carrier (Heterozygote) Detection

Carrier testing for at-risk relatives requires prior identification of the *ENPP1* or *ABCC6* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative genetic alteration/s are unknown).

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the GACI-causing pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Fetal ultrasound examination. The earliest detected prenatal manifestation of the disease was at 14 weeks' gestation, in the form of echogenic foci in the mitral valve [Ciana et al 2006]. Hepatic vascular calcification has been detected as early as 18 weeks' gestation [Wax et al 2001]. However, such early ultrasound findings are not typical, and other cases present with a normal anatomy ultrasound even later in pregnancy; thus, serial scans are important [Nasrallah et al 2009].

The detection of an echogenic intracardiac focus as early as 20 weeks' gestation has been proposed as an early marker of the disease in individuals with a family history of GACI [Nasrallah et al 2009]. Of note, the absence of identification of vessel echo brightness on fetal ultrasound in a fetus at term does not rule out GACI, since faint calcifications can be missed in utero but detected postnatally [Cheng et al 2005].

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **GACI Global**
  PO Box 123
  Argyle TX 76226
  Email: info@gaciglobal.org
  www.gaciglobal.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Generalized Arterial Calcification of Infancy: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ABCC6	16p13.11	ATP-binding cassette sub-family C member 6	ABCC6 @ LOVD	ABCC6	ABCC6

Table A. continued from previous page.

ENPP1	6q23.2	Ectonucleotide pyrophosphatase/ phosphodiesterase family member 1	ENPP1 database	ENPP1	ENPP1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Generalized Arterial Calcification of Infancy (View All in OMIM)

173335	ECTONUCLEOTIDE PYROPHOSPHATASE/PHOSPHODIESTERASE 1; ENPP1
208000	ARTERIAL CALCIFICATION, GENERALIZED, OF INFANCY, 1; GACI1
603234	ATP-BINDING CASSETTE, SUBFAMILY C, MEMBER 6; ABCC6
614473	ARTERIAL CALCIFICATION, GENERALIZED, OF INFANCY, 2; GACI2

Molecular Pathogenesis

ENPP1 breaks the phosphodiester bonds of extracellular nucleotides. Its most important substrate is ATP, cleaved into AMP and inorganic pyrophosphate. A deficiency of ENPP1 activity thus leads to a deficiency of both AMP and inorganic pyrophosphate. Pyrophosphate is the main inhibitor of hydroxyapatite deposition, so its deficiency leads to ectopic calcification, while the deficiency of AMP (or downstream adenosine) leads to intimal proliferation and consequently arterial narrowing. *ABCC6* encodes a plasma membrane transporter, the substrate of which is unknown, although ATP remains a candidate.

Mechanism of disease causation. The disease is caused by pathogenic variants in *ENPP1* or *ABCC6* leading to deficient enzymatic or transport activity, respectively.

Gene-specific laboratory technical considerations: *ABCC6*. Presence of two pseudogenes

Chapter Notes

Acknowledgments

This work was supported in part by the Intramural Research Program of the National Human Genome Research Institute.

Revision History

- 30 December 2020 (ha) Comprehensive update posted live
- 13 November 2014 (me) Review posted live
- 25 June 2014 (cf) Original submission

References

Literature Cited

Albright RA, Stabach P, Cao W, Kavanagh D, Mullen I, Braddock AA, Covo MS, Tehan M, Yang G, Cheng Z, Bouchard K, Yu ZX, Thorn S, Wang X, Folta-Stogniew EJ, Negrete A, Sinusas AJ, Shiloach J, Zubal G, Madri JA, De La Cruz EM, Braddock DT. ENPP1-Fc prevents mortality and vascular calcifications in rodent model of generalized arterial calcification of infancy. Nat Commun. 2015;6:10006. PubMed PMID: 26624227.

Bassil Eter R, Dulac Y, Acar P. Pulmonary diffuse arterial calcifications: a very rare complication in the recipient of a twin-to-twin transfusion syndrome. Cardiol Young. 2009;19:410–2. PubMed PMID: 19450382.

Boyce AM, Gafni RI, Ferreira CR. Generalized arterial calcification of infancy: new insights, controversies, and approach to management. Curr Osteoporos Rep. 2020;18:232–41. PubMed PMID: 32172442.

Brachet C, Mansbach AL, Clerckx A, Deltenre P, Heinrichs C. Hearing loss is part of the clinical picture of ENPP1 loss of function mutation. Horm Res Paediatr. 2014;81:63–6. PubMed PMID: 24216977.

Cheng K-S, Chen M-R, Ruf N, Lin S-P, Rutsch F. Generalized arterial calcification of infancy: different clinical courses in two affected siblings. Am J Med Genet A. 2005;136:210–3. PubMed PMID: 15940697.

Chong CR, Hutchins GM. Idiopathic infantile arterial calcification: the spectrum of clinical presentations. Pediatr Dev Pathol. 2008;11:405–15. PubMed PMID: 17990935.

Ciana G, Trappan A, Bembi B, Benettoni A, Maso G, Zennaro F, Ruf N, Schnabel D, Rutsch F. Generalized arterial calcification of infancy: two siblings with prolonged survival. Eur J Pediatr. 2006;165:258–63. PubMed PMID: 16315058.

Dursun F, Atasoy Öztürk T, Güven S, Kırmızıbekmez H, Seymen Karabulut G, Kalın S, Sözeri B. Magnesium and anti-phosphate treatment with bisphosphonates for generalised arterial calcification of infancy: A case report. J Clin Res Pediatr Endocrinol. 2019;11:311–8. PubMed PMID: 30525344.

Eytan O, Morice-Picard F, Sarig O, Ezzedine K, Isakov O, Li Q, Ishida-Yamamoto A, Shomron N, Goldsmith T, Fuchs-Telem D, Adir N, Uitto J, Orlow SJ, Taieb A, Sprecher E. Cole disease results from mutations in ENPP1. Am J Hum Genet. 2013;93:752–7. PubMed PMID: 24075184.

Farquhar J, Makhseed N, Sargent M, Taylor G, Osiovich H. Idiopathic infantile arterial calcification and persistent pulmonary hypertension. Am J Perinatol. 2005;22:121–5. PubMed PMID: 15838744.

Feigenbaum A, Müller C, Yale C, Kleinheinz J, Jezewski P, Kehl HG, MacDougall M, Rutsch F, Hennekam RC. Singleton-Merten syndrome: an autosomal dominant disorder with variable expression. Am J Med Genet A. 2013;161A:360–70. PubMed PMID: 23322711.

Ferreira CR, Hackbarth ME, Ziegler SG, Pan KS, Roberts MS, Rosing DR, Whelpley MS, Bryant JC, Macnamara EF, Wang S, Müller K, Hartley IR, Chew EY, Corden TE, Jacobsen CM, Holm IA, Rutsch F, Dikoglu E, Chen MY, Mughal MZ, Levine MA, Gafni RI, Gahl WA. Prospective phenotyping of long-term survivors of generalized arterial calcification of infancy (GACI). Genet Med. 2021a;23:396–407. PubMed PMID: 33005041.

Ferreira CR, Kavanagh D, Oheim R, et al. Response of the ENPP1-deficient skeletal phenotype to oral phosphate supplementation and/or enzyme replacement therapy: Comparative studies in humans and mice. J Bone Miner Res. 2021b;36:942–55. PubMed PMID: 33465815.

Freychet C, Gay C, Lavocat MP, Teyssier G, Patural H, Bacchetta J, Cottalorda J, Meunier BB, Linglart A, Baujat G, Stephan JL. GACI syndrome: a case report with a neonatal beginning. Arch Pediatr. 2014;21:632–6. PubMed PMID: 24768072.

Galletti S, Nitschke Y, Malavolti AM, Aquilano G, Faldella G, Corvaglia L, Rutsch F. Generalized arterial calcification of infancy: fatal clinical course associated with a novel mutation in ENPP1. JIMD Rep. 2011;1:23–7. PubMed PMID: 23430823.

Giovannoni I, Callea F, Travaglini L, Amodeo A, Cogo P, Secinaro A, Bizzarri C, Cutrera R, El Hachem M, Francalanci P. Heart transplant and 2-year follow up in a child with generalized arterial calcification of infancy. Eur J Pediatr. 2014;173:1735–40. PubMed PMID: 25367056.

Glatz AC, Pawel BR, Hsu DT, Weinberg P, Chrisant MRK. Idiopathic infantile arterial calcification: two case reports, a review of the literature and a role for cardiac transplantation. Pediatr Transplant. 2006;10:225–33. PubMed PMID: 16573612.

Grange DK, Balfour IC, Chen SC, Wood EG. Familial syndrome of progressive arterial occlusive disease consistent with fibromuscular dysplasia, hypertension, congenital cardiac defects, bone fragility, brachysyndactyly, and learning disabilities. Am J Med Genet. 1998;75:469–80. PubMed PMID: 9489789.

Green R, Gu X, Kline-Rogers E, Froehlich J, Mace P, Gray B, Katzen B, Olin J, Gornik HL, Cahill AM, Meyers KE. Differences between the pediatric and adult presentation of fibromuscular dysplasia: results from the US Registry. Pediatr Nephrol. 2016;31:641–50. PubMed PMID: 26525198.

Greenberg SB, Gibson J. New findings in idiopathic arterial calcification of infancy detected by MDCT. AJR Am J Roentgenol. 2005;185:530–2. PubMed PMID: 16037532.

Hault K, Sebire NJ, Ho SY, Sheppard MN. The difficulty in diagnosing idiopathic arterial calcification of infancy, its variation in presentation, and the importance of autopsy. Cardiol Young. 2008;18:624–7. PubMed PMID: 18842162.

Hollwey A, Forster C, Mushtaq T. P031 Use of disodium etidronate and sodium thiosulfate in a premature neonate with generalised arterial calcification of infancy. Arch Dis Child. 2019;104:e2.

Khan T, Sinkevicius KW, Vong S, Avakian A, Leavitt MC, Malanson H, Marozsan A, Askew KL. ENPP1 enzyme replacement therapy improves blood pressure and cardiovascular function in a mouse model of generalized arterial calcification of infancy. Dis Model Mech. 2018;11:dmm035691. PubMed PMID: 30158213.

Kingman J, Uitto J, Li Q. Elevated dietary magnesium during pregnancy and postnatal life prevents ectopic mineralization in Enpp1asj mice, a model for generalized arterial calcification of infancy. Oncotarget. 2017;8:38152–60. PubMed PMID: 28402956.

Kotwal A, Ferrer A, Kumar R, Singh RJ, Murthy V, Schultz-Rogers L, Zimmermann M, Lanpher B, Zimmerman K, Stabach PR, Klee E, Braddock DT, Wermers RA. Clinical and biochemical phenotypes in a family with ENPP1 mutations. J Bone Miner Res. 2020;35:662–70. PubMed PMID: 31826312.

Levy-Litan V, Hershkovitz E, Avizov L, Leventhal N, Bercovich D, Chalifa-Caspi V, Manor E, Buriakovsky S, Hadad Y, Goding J, Parvari R. Autosomal-recessive hypophosphatemic rickets is associated with an inactivation mutation in the ENPP1 gene. Am J Hum Genet. 2010;86:273–8. PubMed PMID: 20137772.

Li Q, Guo H, Chou DW, Harrington DJ, Schurgers LJ, Terry SF, Uitto J. Warfarin accelerates ectopic mineralization in Abcc6(-/-) mice: clinical relevance to pseudoxanthoma elasticum. Am J Pathol. 2013;182:1139–50. PubMed PMID: 23415960.

Lorenz-Depiereux B, Schnabel D, Tiosano D, Häusler G, Strom TM. Loss-of-function ENPP1 mutations cause both generalized arterial calcification of infancy and autosomal-recessive hypophosphatemic rickets. Am J Hum Genet. 2010;86:267–72. PubMed PMID: 20137773.

Louis R, Levy-Erez D, Cahill AM, Meyers KE. Imaging studies in pediatric fibromuscular dysplasia (FMD): a single-center experience. Pediatr Nephrol. 2018;33:1593–9. PubMed PMID: 29869115.

Lussier-Lazaroff J, Fletcher BD. Idiopathic infantile arterial calcification: roentgen diagnosis of a rare cause of coronary artery occlusion. Pediatr Radiol. 1973;1:224–8. PubMed PMID: 4779072.

Marrott PK, Newcombe KD, Becroft DM, Friedlander DH. Idiopathic infantile arterial calcification with survival to adult life. Pediatr Cardiol. 1984;5:119–22. PubMed PMID: 6473121.

Meradji M, de Villeneuve VH, Huber J, de Bruijn WC, Pearse RG. Idiopathic infantile arterial calcification in siblings: radiologic diagnosis and successful treatment. J Pediatr. 1978;92:401–5. PubMed PMID: 416189.

Morton R. Idiopathic arterial calcification in infancy. Histopathology. 1978;2:423–32. PubMed PMID: 730123.

Nasrallah FK, Baho H, Sallout A, Qurashi M. Prenatal diagnosis of idiopathic infantile arterial calcification with hydrops fetalis. Ultrasound Obstet Gynecol. 2009;34:601–4. PubMed PMID: 19813208.

Nitschke Y, Baujat G, Botschen U, Wittkampf T, du Moulin M, Stella J, Le Merrer M, Guest G, Lambot K, Tazarourte-Pinturier MF, Chassaing N, Roche O, Feenstra I, Loechner K, Deshpande C, Garber SJ, Chikarmane R, Steinmann B, Shahinyan T, Martorell L, Davies J, Smith WE, Kahler SG, McCulloch M, Wraige E, Loidi L, Höhne W, Martin L, Hadj-Rabia S, Terkeltaub R, Rutsch F. Generalized arterial calcification of infancy and pseudoxanthoma elasticum can be caused by mutations in either ENPP1 or ABCC6. Am J Hum Genet. 2012;90:25–39. PubMed PMID: 22209248.

Nitschke Y, Rutsch F. Generalized arterial calcification of infancy and pseudoxanthoma elasticum: two sides of the same coin. Front Genet. 2012;3:302. PubMed PMID: 23269929.

Nitschke Y, Yan Y, Buers I, Kintziger K, Askew K, Rutsch F. ENPP1-Fc prevents neointima formation in generalized arterial calcification of infancy through the generation of AMP. Exp Mol Med. 2018;50:1–12. PubMed PMID: 30369595.

Oheim R, Zimmerman K, Maulding ND, Stürznickel J, von Kroge S, Kavanagh D, Stabach PR, Kornak U, Tommasini SM, Horowitz MC, Amling M, Thompson D, Schinke T, Busse B, Carpenter TO, Braddock DT. Human heterozygous ENPP1 deficiency is associated with early onset osteoporosis, a phenotype recapitulated in a mouse model of Enpp1 deficiency. J Bone Miner Res. 2020;35:528–39. PubMed PMID: 31805212.

Omarjee L, Nitschke Y, Verschuere S, Bourrat E, Vignon MD, Navasiolava N, Leftheriotis G, Kauffenstein G, Rutsch F, Vanakker OM, Martin L. Severe early-onset manifestations of pseudoxanthoma elasticum resulting from the cumulative effects of several deleterious mutations in ENPP1, ABCC6 and HBB: transient improvement in ectopic calcification with sodium thiosulfate. Br J Dermatol. 2020;183:367–72. PubMed PMID: 31646622.

Otero JE, Gottesman GS, McAlister WH, Mumm S, Madson KL, Kiffer-Moreira T, Sheen C, Millán JL, Ericson KL, Whyte MP. Severe skeletal toxicity from protracted etidronate therapy for generalized arterial calcification of infancy. J Bone Miner Res. 2013;28:419–30. PubMed PMID: 22972716.

Pao DG, DeAngelis GA, Lovell MA, McIlhenny J, Hagspiel KD. Idiopathic arterial calcification of infancy: sonographic and magnetic resonance findings with pathologic correlation. Pediatr Radiol. 1998;28:256–9. PubMed PMID: 9545482.

Popek EJ, Strain JD, Neumann A, Wilson H. In utero development of pulmonary artery calcification in monochorionic twins: a report of three cases and discussion of the possible etiology. Pediatr Pathol. 1993;13:597–611. PubMed PMID: 8247958.

Rosenberg HG. Systemic arterial disease and chronic arsenicism in infants. Arch Pathol. 1974;97:360–5. PubMed PMID: 4825098.

Royston D, Geoghegan F. Disseminated arterial calcification associated with acardius acephalus. Arch Dis Child. 1983;58:641–3. PubMed PMID: 6684415.

Rutsch F, Böyer P, Nitschke Y, Ruf N, Lorenz-Depierieux B, Wittkampf T, Weissen-Plenz G, Fischer RJ, Mughal Z, Gregory JW, Davies JH, Loirat C, Strom TM, Schnabel D, Nürnberg P, Terkeltaub R, et al. Hypophosphatemia, hyperphosphaturia, and bisphosphonate treatment are associated with survival beyond infancy in generalized arterial calcification of infancy. Circ Cardiovasc Genet. 2008;1:133–40. PubMed PMID: 20016754.

Saito T, Shimizu Y, Hori M, Taguchi M, Igarashi T, Fukumoto S, Fujitab T. A patient with hypophosphatemic rickets and ossification of posterior longitudinal ligament caused by a novel homozygous mutation in ENPP1 gene. Bone. 2011;49:913–6. PubMed PMID: 21745613.

Saxena A, Soni NR. Pulmonary artery calcification in recipient twins of twin to twin transfusion syndrome: a report of three cases. Pediatr Cardiol. 2003;24:80–3. PubMed PMID: 12574984.

Shaireen H, Howlett A, Amin H, Yusuf K, Kamaluddeen M, Lodha A. The mystery of persistent pulmonary hypertension: an idiopathic infantile arterial calcification. BMC Pediatr. 2013;13:107. PubMed PMID: 23855924.

Sholler GF, Yu JS, Bale PM, Hawker RE, Celermajer JM, Kozlowski K. Generalized arterial calcification of infancy: three case reports, including spontaneous regression with long-term survival. J Pediatr. 1984;105:257–60. PubMed PMID: 6747757.

Stenson PD, Mort M, Ball EV, Evans K, Hayden M, Heywood S, Hussain M, Phillips AD, Cooper DN. The Human Gene Mutation Database: towards a comprehensive repository of inherited mutation data for medical research, genetic diagnosis and next-generation sequencing studies. Hum Genet. 2017;136:665–77. PubMed PMID: 28349240.

Thiaville A, Smets A, Clercx A, Perlmutter N. Idiopathic infantile arterial calcification: a surviving patient with renal artery stenosis. Pediatr Radiol. 1994;24:506–8. PubMed PMID: 7885787.

Thomas P, Chandra M, Kahn E, McVicar M, Naidich J, LaCorte M. Idiopathic arterial calcification of infancy: a case with prolonged survival. Pediatr Nephrol. 1990;4:233–5. PubMed PMID: 2400650.

Tran KH, Boechat MI. Idiopathic infantile arterial calcification: imaging evaluation and the usefulness of MR angiography. Pediatr Radiol. 2006;36:247–53. PubMed PMID: 16429273.

van der Sluis IM, Boot AM, Vernooij M, Meradji M, Kroon AA. Idiopathic infantile arterial calcification: clinical presentation, therapy and long-term follow-up. Eur J Pediatr. 2006;165:590–3. PubMed PMID: 16649023.

Van Dyck M, Proesmans W, Van Hollebeke E, Marchal G, Moerman P. Idiopathic infantile arterial calcification with cardiac, renal and central nervous system involvement. Eur J Pediatr. 1989;148:374–7. PubMed PMID: 2707283.

Vera J, Lucaya J, Garcia Conesa JA, Aso C, Balaguer A. Idiopathic infantile arterial calcification: unusual features. Pediatr Radiol. 1990;20:585–7. PubMed PMID: 2251001.

Volonghi I, Frigerio M, Mardighian D, Gasparotti R, Del Zotto E, Giossi A, Costa P, Poli L, Jeannin G, Gregorini GA, Padovani A, Pezzini A. Grange syndrome: an identifiable cause of stroke in young adults. Am J Med Genet A. 2012;158A:2894–8. PubMed PMID: 22987684.

Wax JR, Blackstone J, Pinette MG, Cartin A. Hepatic vascular calcification: an early second trimester sonographic feature of idiopathic infantile arterial calcinosis. Am J Obstet Gynecol. 2001;185:1267–8. PubMed PMID: 11717671.

Weymann S, Yonekawa Y, Khan N, Martin E, Heppner FL, Schinzel A, Kotzot D. Severe arterial occlusive disorder and brachysyndactyly in a boy: a further case of Grange syndrome? Am J Med Genet. 2001;99:190–5. PubMed PMID: 11241488.

Witzleben CL. Idiopathic infantile arterial calcification--a misnomer? Am J Cardiol. 1970;26:305–9. PubMed PMID: 4196111.

License