J. Fetal Med. (September 2018) 5:151–154
https://doi.org/10.1007/s40556-018-0176-0

ORIGINAL ARTICLE

Idiopathic Arterial Calcification: Experience from a Single Center in South India

Sylvia M. Colaco[1] · Shanthi Chidambarathanu[2] · Vijayalakshmi Raja[2] · Lata Murlidhar[2] · Sujatha Jagadeesh[2] · Indrani Suresh[3] · Suresh Seshadri[4]

Received: 9 February 2018 / Accepted: 11 May 2018 / Published online: 29 May 2018

Abstract Idiopathic arterial calcification of infancy is a rare autosomal recessive disease, characterized by deposition of calcium along the internal elastic membrane of arteries, accompanied by fibrous thickening of the intima which causes luminal narrowing. We hereby report a series of 20 cases seen over a period of 10 years. Nineteen cases were reported as idiopathic arterial calcification and one was reported as arterial calcification in a twin reversed arterial perfusion sequence. The sites of calcification were mainly aortic valve and root of aorta which was involved in 100% of cases followed by pulmonary artery up to its branches in 18 (90%) cases. There was recurrence in the subsequent pregnancies in three of the cases. Genetic association with ENPP1 was proved in one case. There was no survival in all the cases. Thus, the prognosis of idiopathic arterial calcification is very poor with very few long-term survivors.

Keywords Idiopathic arterial calcification · Fetus · Calcium

✉ Indrani Suresh
drindrani@mediscan.org.in

Sylvia M. Colaco
drsylviac@gmail.com

[1] Little Hearts Clinic, 106, D'almeida Landmark, Near Hanuman Mandir, Vasai Road West, Manickpur, Maharashtra 401202, India

[2] Mediscan Systems, 197, Dr. Natesan Road, Mylapore, Chennai 600 004, India

[3] Fetal Medicine Unit, Mediscan Systems, 197, Dr. Natesan Road, Mylapore, Chennai 600 004, India

[4] Fetal Intervention Unit, Mediscan Systems, 197, Dr. Natesan Road, Mylapore, Chennai 600 004, India

Introduction

Idiopathic arterial calcification (IAC) is a rare autosomal recessive disease characterized by extensive calcification and stenosis of large and medium sized arteries including aorta, coronary and renal arteries. It is a rare condition and was first described by Bryant and White in 1901, and thereafter, around 200 cases have been described in the literature [1]. The diagnosis was mainly established postnatally in the autopsy specimens but due to advancing technology and expertise, around 13 cases have been detected in fetal life so far [2]. We present 20 fetuses with arterial calcification, which is the largest series of cases detected antenatally.

Report of Cases

This is a retrospective descriptive study of cases of fetal arterial calcification seen over a period of 10 years from January 2006 to December 2015. We retrieved 20 cases with evidence of fetal arterial calcification from our database (Sonocare version 6.0). Nineteen cases were reported as idiopathic arterial calcification and one was a case of arterial calcification in a twin reversed arterial perfusion (TRAP) sequence. Maternal and fetal demographic features are summarized in Table 1.

The mean maternal age at diagnosis was 23.85 ± 3.84 years. Parental consanguinity was noted in 14 (70%) cases. There was no history suggestive of infection during the first trimester in any case. Eleven (55%) women were multiparous, whereas 9 (45%) were primiparous. The mean age of diagnosis of the condition was 28.05 ± 5.25 gestational weeks and lowest gestational age at diagnosis was 20 weeks.

Table 1 Demographic variables of patient profile

No	Age (years)	Marriage	Pregnancy	Gest age (weeks)[a]	Calcification site	Hydrops
1.	25	III CSM	Multi	29	AO, AA, AB, IA	Yes
2.	21	NCSM	Primi	36	AO, AA, AB, IA, PA, BPA	Yes
3.	20	III CSM	Multi	35	AO, AA, AB, IA, PA, BPA, valves	Yes
4.	25	III CSM	Primi	30	AO, AA, AB, IA, PA, BPA, valves	Yes
5.	27	III CSM	Multi	20	TV	No
				28	AO, PA, valves	Yes
6.	34	NCSM	Multi	29	AO, AA, AB, IA, PA, BPA, valves	Yes
7.	27	III CSM	Multi	29	AO, AA, AB, IA, PA, BPA, valves	Yes
8.	18	II CSM	Primi	35	AO, PA, valves	Yes
9.	25	IV CSM	Primi	30	AO, AA, AB, IA, PA, BPA, valves	Yes
10.	27	III CSM	Primi	32	AO, AA, AB, IA, PA, BPA, valves	No
11.	23	II CSM	Multi	30	AO, AA, AB, IA, PA, BPA, valves, RA	Yes
12	27	II CSM	Multi	27	AO, AA, AB, IA, PA, BPA, valves	Yes
13	18	NSCM	Primi	30	AO, AA, AB, IA, PA, BPA, valves	No
14[b]	20	II CSM	Primi	20	AO, PA	Yes
15	21	III CSM	Multi	29	AO, AA, AB, IA, PA, BPA, valves	Yes
16	23	III CSM	Multi	20	TV	No
				28	AO, AA, AB, IA, PA, BPA, valves	Yes
17	21	III CSM	Primi	25	Valves, AO, PA	No
18	24	III CSM	Multi	33	AO, AA, AB, IA, PA, BPA, valves, RA	Yes
19	27	NSCM	Primi	20	PA, BPA, AO	Yes
20	24	NCSM	Primi	22	AO, AA, AB, IA, PA, BPA	Yes

Primi primigravida, *Multi* multigravida, *CSM* consanguineous marriage, *NCSM* non-consanguineous marriage, *II CSM* second degree consanguineous marriage, *III CSM* third degree consanguineous marriage, *IV CSM* fourth degree consanguineous marriage, *AO* aorta, *AA* ascending aorta, *AB* abdominal aorta, *IA* iliac arteries, *PA* pulmonary artery, *BPA* branch pulmonary artery, *RA* renal arteries

[a]Completed weeks

[b]Genetic testing done for this case

The sites of calcification were mainly aortic valve and root of aorta, which was involved in 100% of cases, followed by pulmonary artery up to its branches in 18 (90%) cases (Figs. 1, 2). The involvement of cardiac valves, ascending aorta, abdominal aorta, iliac and renal arteries were seen in 15 (75%), 14 (70%), 14 (70%), 14 (70%) and 2 (10%) cases respectively. Hydrops was present in 16 (80%) cases, whereas features of poor cardiac contractility were

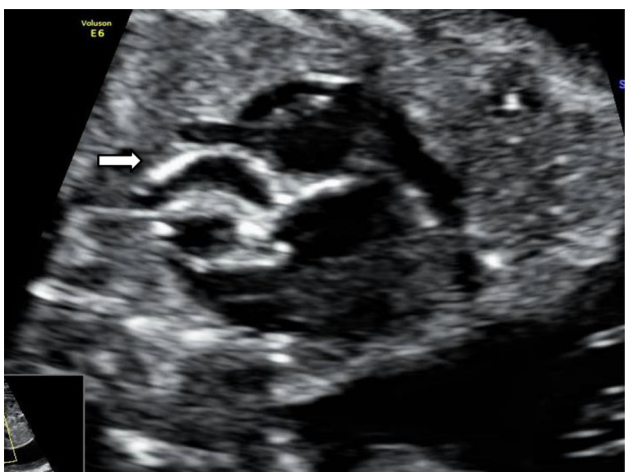

Fig. 1 Calcification in the aortic valve and ascending aorta

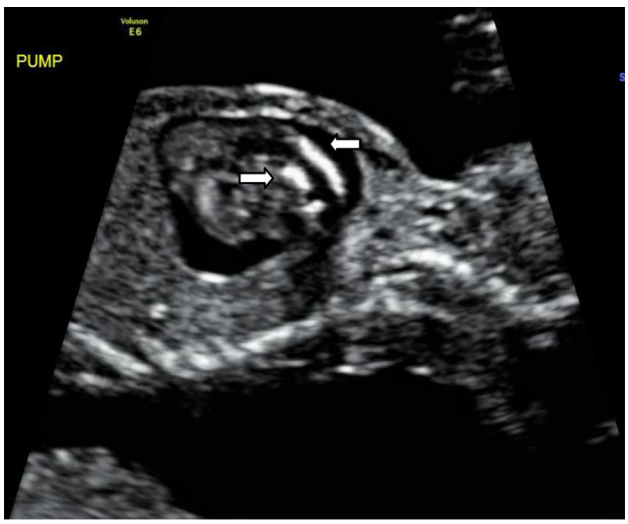

Fig. 2 Calcification in the pulmonary artery with pericardial effusion

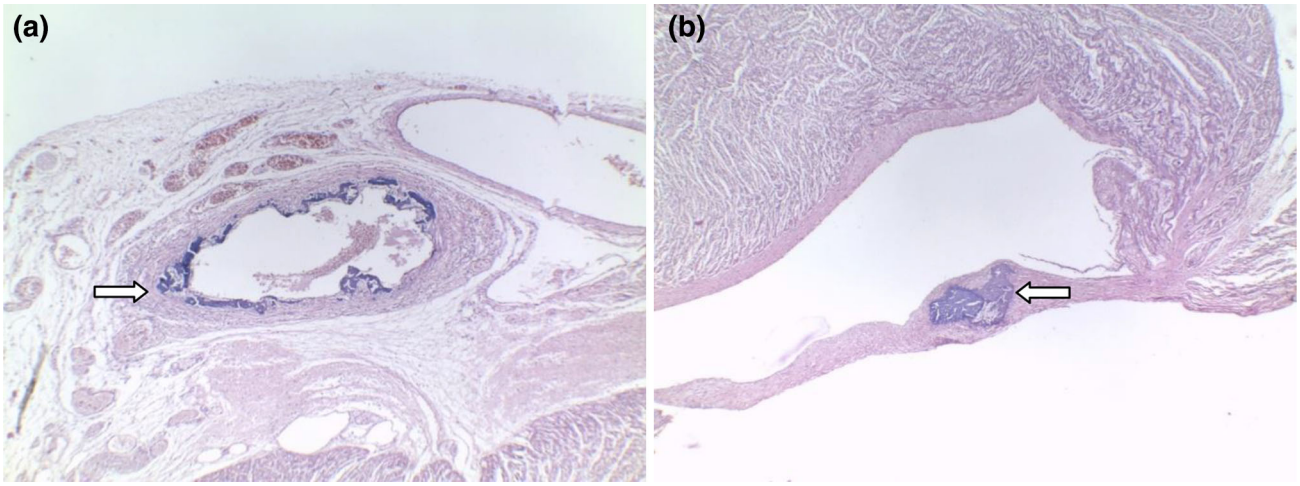

Fig. 3 Histopathological examination of the coronary artery and the tricuspid valve with Prussian blue stain showed uniform calcium deposits

seen in 2 (10%), and in the latter, extensive involvement up to the renal vasculature was noted. There were two cases where calcification of the tricuspid valve alone was seen as early as 20 weeks and it evolved into a full blown picture of IAC by 28 weeks of gestation. Autopsy report was available in only two cases and histopathological examination of the valves and arteries with Prussian blue stain showed uniform calcium deposition in the aorta, pulmonary artery, tricuspid valve and coronary artery (Fig. 3a, b).

Among the 19 cases of IAC, there were three cases in which there had been a recurrence in the subsequent pregnancies. In one family (Case no. 14 of Table 1) we could confirm the disease by molecular confirmation and offer prenatal testing. They were a IV degree consanguineous couple. First pregnancy was an intrauterine demise. In the II pregnancy, they came to the center at 32–33 weeks and the fetus was found to have idiopathic arterial calcification. Hence, they were advised postnatal evaluation. The child lived for one day and DNA of the child was sent to Department of Paediatrics Muenster University Childrens Hospital, Germany. A homozygous mutation was detected in ENPP 1 gene. This mutation was in Exon 21 (c.2212G > A; p.G738R) in homozygous form. Parents were found to be heterozygous for the same mutation. In subsequent pregnancy, chorionic villus sampling (CVS) was done, DNA was extracted, maternal contamination was ruled out and sent to same lab for testing. Fetus was reported to be affected as mutation was homozygous and pregnancy was terminated.

Discussion

A previous review stated that almost 48% of patients presented at birth or in utero, while 52% cases were identified during infancy [3]. We have detected 20 cases antenatal based on ultrasound with features suggestive of hyperechogenicity in cardiac valves and the walls of major arteries. The actual incidence of pre and postnatal cases of IAC is unknown as there is no published data available.

Clinical manifestations are related to vasoocclusive disease of multiple organs. This disease has varied presentation from fetal demise in the second trimester to onset of symptoms in early infancy. The most common fetal complications include cardiomegaly, cardiac arrhythmias, heart failure, hydrops fetalis and fetal demise often early in pregnancy. Postnatally, a previously healthy neonate may present with nonspecific symptoms, especially vomiting and refusal to feed which may worsen to respiratory distress with cyanosis. Death is usually attributed to acute cardiac failure or myocardial ischemia, due to changes in the coronary arteries.

The most described pathogenesis in 80% of cases is a homozygous missense or compound heterozygous nonsense mutation that leads to an inactivation of ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) gene on chromosome 6q [4]. ENPP1 is expressed on fibroblasts, osteoblasts and hepatocytes. ENPP1 gene has nucleotide pyrophosphohydrolase activity and produces inorganic pyrophosphate (PPi). PPi prevents deposition of calcium hydroxyapatite crystal in the arteries [5]. The mutation of ENPP1 gene results in variable degrees of calcification and intimal fibrosis of medium and large arteries of cardiac and renal vascular system. There are other known (*ABCC6*, NT5E and SLC20A2) and unknown gene mutations, associated with arterial calcification [6]. It is difficult to carry out molecular studies in all cases as genetic diagnosis is an expensive test. In the present study, molecular diagnosis was established in only one case where there was a family history of IAC in the previous baby.

Histologic changes typically include fragmentation and calcium deposition in the internal elastic lamina and fibrointimal hyperplasia causing luminal narrowing. This results from the deposition of calcium hydroxyapatite in the internal elastic lamina layer [7]. The material laid down in the internal elastic lamina stains positively with Prussian blue, and can be very well seen in the histopathological slides [8].

The TRAP twin fetus in this series was not classified as IAC in view of presence of volume overload. Similar cases with increased echogenicity due to calcification has been described in the wall of the pulmonary trunk, proximal branch pulmonary arteries and ascending aorta in the recipient twin of TTTS and TRAP sequence. 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. Histologically, calcium is deposited primarily in the media, whereas in IAC it is deposited along the internal elastic lamina [10]. Additionally, in TTTS and TRAP sequence, calcification does not occur elsewhere in the body. In fact, one recipient twin of a TTTS with isolated calcification of the proximal aorta and central pulmonary arteries was reported as a case of IAC, while in all likelihood, it was denied by another author [11]. In another report of pulmonary arterial and intracranial calcification in the recipient twin of a TTTS, the authors surmised that IAC was the likely cause [12]. Even though there are few case reports on occurrence of arterial calcification in TTTS, many maybe under-reported due to early in utero loss of the recipient fetus.

In the past years, the diagnosis was established by arterial biopsy which remains the gold standard of diagnosis but now diagnosis can be established with noninvasive imaging techniques. Though only in two cases IAC could be proven by autopsy, the sonographic features were similar in the remaining cases, which means prenatal sonographic imaging maybe sufficient for early detection. Majority of the cases were diagnosed at later second half of pregnancy, late second or third trimester except a few which showed specks of calcification in some unusual sites in early gestation. The follow-up data is insufficient hence further evolution of the cases was not known.

As the condition has a genetic etiology, genetic counseling of the family is of the utmost importance. Once the diagnosis is confirmed, the family should be counseled about the nature and inheritance pattern of the disease and implications of genetic findings. Molecular diagnosis for determination of the mutant gene by testing the parents and index case can be offered which may help them to decide about present and future pregnancies.

No standard treatment approach exists for individuals affected by IAC. Spontaneous resolution of calcification was reported in a few cases. There are isolated case reports in the literature stating reduction in calcium deposition after bisphosphonate therapy [9] but the mechanism by which bisphosphonates affects IAC remains unclear.

In conclusion, increased echogenicity of the fetal vasculature should alert the fetal imaging specialist about fetal arterial calcification. As prognosis for patients with IAC remains very poor with very few long-term survivors, early diagnosis and appropriate genetic workup is likely to guide the families involved.

Acknowledgements Dr. Prof Dr. Frank Rutsch and his team of scientists, Department of Paediatrics, Muenster University Childrens Hospital Germany.

References

1. Amine M, Faten H, Rim H, Nidhal HS, Njim L, Moussa A, Zakhama A. A rare cause of death in infancy: idiopathic infantile arterial calcification. Pathologica. 2015;107(1):29–31.
2. Agrawal G, Chintala K. Antenatal diagnosis of idiopathic arterial calcification with hydrops fetalis. Eur Heart J Cardiovasc Imaging. 2015;16(7):816.
3. Chong CR, Hutchins GM. Idiopathic infantile arterial calcification: the spectrum of clinical presentations. Pediatr Dev Pathol. 2008;11(5):405–15.
4. Rutsch F, Ruf N, Vaingankar S, Toliat MR, Suk A, Höhne W, Schauer G, Lehmann M, Roscioli T, Schnabel D, Epplen JT. Mutations in ENPP1 are associated with 'idiopathic' infantile arterial calcification. Nat Genet. 2003;34(4):379.
5. Rutsch F, Vaingankar S, Johnson K, Goldfine I, Maddux B, Schauerte P, Kalhoff H, Sano K, Boisvert WA, Superti-Furga A, Terkeltaub R. PC-1 nucleoside triphosphate pyrophosphohydrolase deficiency in idiopathic infantile arterial calcification. Am J Pathol. 2001;158(2):543–54.
6. Numakura C, Yamada M, Ariyasu D, Maesaka A, Kobayashi H, Nishimura G, Ikeda M, Hasegawa Y. Genetic and enzymatic analysis for two Japanese patients with idiopathic infantile arterial calcification. J Bone Miner Metab. 2006;24(1):48–52.
7. Glatz AC, Pawel BR, Hsu DT, Weinberg P, Chrisant MR. Idiopathic infantile arterial calcification: two case reports, a review of the literature and a role for cardiac transplantation. Pediatr Transplant. 2006;10(2):225–33.
8. Rao U, Rani H, Rao R, Dinesh U, Ramamurthy B. Idiopathic infantile arterial calcification with thrombotic microangiopathy—a unique case. Fetal Pediatric Pathol. 2010;29(6):413–8.
9. 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(1):107.
10. Royston D, Geoghegan F. Disseminated arterial calcification associated with acardius acephalus. Arch Dis Child. 1983;58(8):641–3.
11. Stella J, Buers I, de Wetering K, Höhne W, Rutsch F, Nitschke Y. Effects of different variants in the ENPP1 gene on the functional properties of ectonucleotide pyrophosphatase/phosphodiesterase family member 1. Hum Mutat. 2016;37(11):1190–201.
12. Kei OC, Duncan WJ, Human DG. Pulmonary arterial and intracranial calcification in the recipient of a twin–twin transfusion. Cardiol Young. 2002;12(5):488–90.