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BRIEF COMMUNICATION

Prenatal Diagnosis of Idiopathic Infantile Arterial Calcification

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Abstract Idiopathic infantile arterial calcification is a rare disorder which is generally fatal and characterized by extensive calcification of large- and medium-sized arteries. The diagnosis is usually made at autopsy or in the neonatal period, when there is cardiac failure. Prenatal diagnosis is possible in the latter half of pregnancy when there are hyperechoic vessel walls, hypertrophied ventricular musculature, and nonimmune fetal hydrops. There are only few cases reported to have been diagnosed antenatally. The inheritance is autosomal recessive and most of the affected individuals have mutations in ENPP1 and ABCC6 genes. Molecular genetic tests and genetic counseling should be offered to provide early prenatal diagnosis in subsequent pregnancies.

Keywords Idiopathic infantile arterial calcification · Generalized arterial calcification of infancy · Arterial calcification · Fetal hydrops · Cardiac failure

Introduction

Generalized arterial calcification of infancy (GACI), also known as idiopathic infantile arterial calcification (IIAC) is a rare disease with about 180 reported cases [1]. Prenatal diagnosis has been reported in fewer than ten cases and represents a severe form with worse prognosis [2]. The case reported here presented with cardiomegaly and pericardial effusion at 36 weeks of gestation. The hyperechogenicity of large vessels may be missed if one is not aware of the condition. As the disease is heritable in an autosomal recessive manner, it is important to make the diagnosis in the proband. Parents should be offered genetic counseling, molecular genetic tests of proband, and prenatal diagnosis in subsequent pregnancies. Prenatal diagnosis by ultrasound is often made in the third trimester and the condition is usually not evident in early pregnancy. Prenatal diagnosis by molecular genetic test is possible early in gestation.

Report of Case

A multigravida with previous two normal issues was referred at 36 weeks of gestation, as the screening ultrasound revealed cardiomegaly. The patient had received regular antenatal care and an anomaly scan done at 19 weeks of gestation was reported to be normal. There was history of second degree consanguinity. Targeted ultrasonography revealed moderate cardiomegaly and pericardial effusion in the fetus (Fig. 1). There was no structural abnormality of the heart on fetal echocardiography. The origin of great vessels, the interventricular and interatrial septae and the valves were normal. The venous connections to the atrial chambers were normal. The fetus was noted to have abnormally echogenic walls of great arteries and on closer look, the aortic and pulmonary vessel walls appeared calcified with narrowing of abdominal aorta. The iliac arteries were almost obliterated at their origin (Fig. 2). The coronaries were also calcified. A diagnosis of idiopathic arterial calcification was made and the patient was recalled the next day.

The woman presented with intrauterine demise of the fetus a day after the diagnosis, and delivered a fresh

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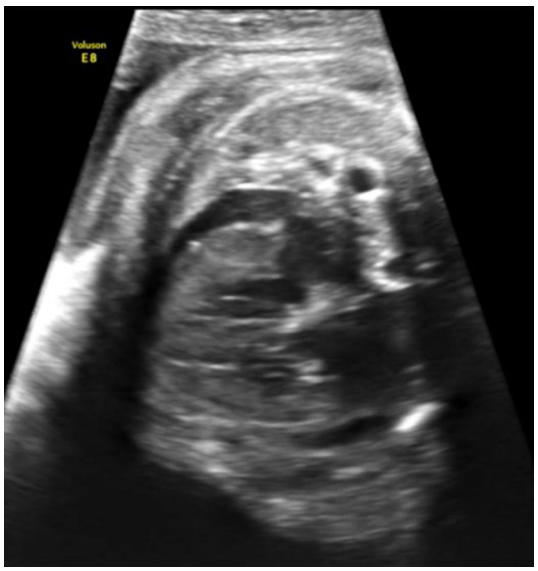

Fig. 1 Cardiomegaly, hypertrophied ventricles, and pericardial effusion

stillborn male baby weighing 3000 g. There were no associated malformations on external examination of the baby. The parents declined fetal autopsy and further genetic tests as they were not planning another pregnancy.

Discussion

Infantile arterial calcification was first described in 1901 by Bryant and White [3]. It is a rare disease characterized by extensive calcification of medium and large arteries. There is calcium hydroxyapatite deposition in the internal elastic lamina, disruption of elastic fibers, and extensive intimal fibrous proliferation [4]. It is mostly diagnosed in the neonatal period or early infancy and presents with rapidly progressive heart failure and refractory hypertension. The condition is nearly always fatal. Prenatal diagnosis is mostly made at the beginning of third trimester. The fetus may have nonimmune hydrops fetalis, polyhydramnios, hypertrophic cardiomyopathy, pericardial effusion, and highly echogenic great vessel walls with narrowing of aorta at its bifurcation into common iliac arteries.

Clinical Presentation

The spectrum of disease varies from fetal demise in later pregnancy to refractory hypertension and rapidly progressive ischemic heart failure within few months of birth. Coronary arteries are almost always involved and 85 % of affected infants die within 6 months due to myocardial ischemia/infarction [4]. Other less common clinical presentations are joint swelling with periarticular calcification, gangrene of extremities, visceral infarction, seizures, progressive hepatic failure, and cerebral atrophy [5, 6]. More severe cases of nonimmune hydrops fetalis result from hypertension, ventricular hypertrophy, and cardiac failure due to dystrophic calcification [2, 7]. A case series by Nasrallah et al. described three fetuses with GACI, one of which was diagnosed by 23 weeks. All three cases had an echogenic intracardiac focus at 20 weeks' gestation. The presence of echogenic intracardiac focus was suggested to be an early sign of GACI in patients with family history. There are other reports of prenatally detected cases of GACI. The condition may also present as in utero meconium peritonitis due to mesenteric ischemia. Wax et al. [8] reported a case that presented with hepatic vascular calcification at 18th weeks of gestation [9].

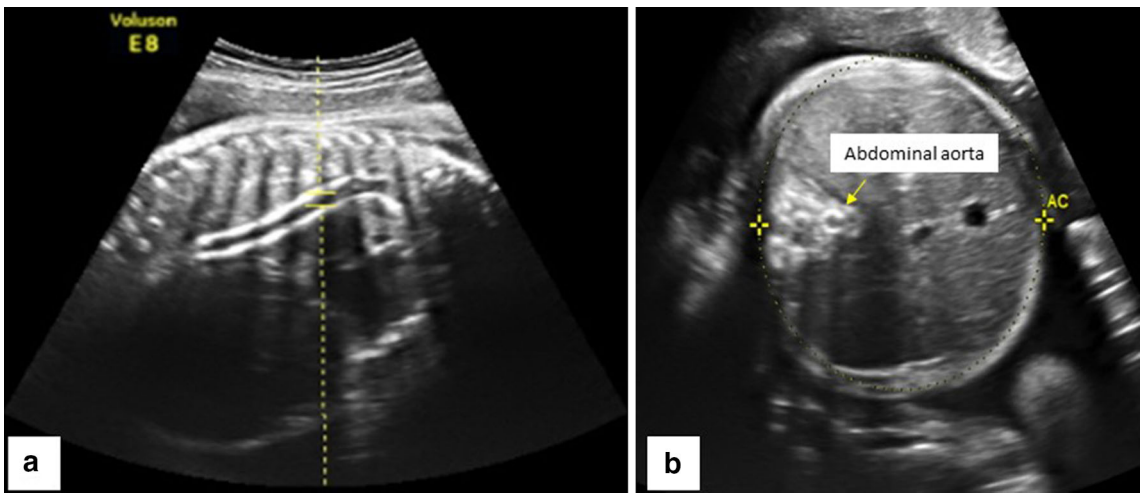

Fig. 2 **a** Hyperechogenic walls of descending aorta which tapers with obliteration of iliac vessels. **b** Transverse section of abdominal aorta, which matches the echogenicity of vertebral bone

Diagnosis

Most cases of IIAC are diagnosed at autopsy or during the first few months of infancy [1]. Prenatal diagnosis is extremely rare with about ten reported cases [2, 7, 10]. In cases presenting postnatally, ultrasound examination of the abdomen and head are often used to detect the echo-bright vessels. CT scan is the preferred imaging modality to demonstrate the arterial hyper-echogenicity. Standard radiographs can sometimes detect arterial calcifications, but have low sensitivity, and many times, arterial calcifications are detected only on review of radiographs after the diagnosis of GACI has been made [11]. In the past, the diagnosis of GACI was usually made at autopsy. The diagnostic gold standard was biopsy of a medium-sized artery, typically the temporal artery to look for typical histologic changes consistent with GACI [3]. Recently, however, such an invasive procedure has been considered unnecessary for the diagnosis. The diagnosis can be confidently made when no secondary cause for arterial calcification is evident [12]. Prenatal diagnosis is carried out by sonographic examination. The walls of large vessels appear hyperechoic, ventricles are dilated and there may be hydrops fetalis [3]. As the vascular calcification may not be visible until late gestation or postnatally, the diagnosis cannot be easily made in early pregnancy.

Genetic Basis

GACI is reported to be caused by mutations in ENPP1 gene and ABCC6 gene. ENPP1 gene is located on chromosome 6q23.2 and codes for the enzyme pyrophosphatase/phosphodiesterase 1. Pyrophosphatase/phosphodiesterase 1 is involved in generation of the inorganic pyrophosphate which is a physiologic inhibitor of calcium deposition [13]. Rutsch et al. [14] identified 40 different homozygous or compound heterozygous mutations in 75 % of patients with GACI. Nitschke et al. [15] identified 13 different mutations in ABCC6 gene in 28 GACI patients.

IIAC is inherited as an autosomal recessive disorder with a 25 % recurrence risk in future pregnancies. Genetic counseling is very important and molecular analysis of ENPP1 and ABCC6 genes should be offered to the family. If disease-causing mutations have been identified in the index case, early prenatal diagnosis by mutation analysis is possible [16].

Differential Diagnosis

Vascular calcification can occur due to hypervitaminosis D, hyperparathyroidism, and end-stage renal disease. Compared with GACI, these metastatic calcifications are usually diffuse vascular and extravascular calcifications and exhibit a different distribution of extravascular calcification involving the renal tubules, bronchial walls, and stomach. Syphilitic aortitis can be distinguished from GACI in that calcifications are confined to the proximal aorta, presents later in life (rarely before age 19 years), and it is accompanied by other signs of congenital syphilis, such as Hutchinson teeth, interstitial keratitis, sabre tibiae, or saddle-shaped nose.

Autosomal recessive hypophosphatemic rickets type 2 is caused by biallelic pathogenic variants in ENPP1 gene. The age of presentation is usually between 3 and 16 years and shows no evidence of GACI at the time of diagnosis. The child presents with short stature, dental caries, and bone deformities. There will be hypophosphatemia, hyperphosphaturia, and elevated plasma alkaline phosphatase on biochemical investigation. Biallelic pathogenic variants in ABCC6 cause pseudoxanthoma elasticum (PXE), an autosomal recessive disorder. Individuals most commonly present with papules in the skin and/or with angioid streaks of the retina/retinal hemorrhage and rarely, with gastrointestinal bleeding, angina, or intermittent claudication. Patients with GACI can have additional findings of pseudoxanthoma elasticum (PXE) involving skin and retina. There is a close relationship between GACI and PXE.

Treatment

GACI is generally lethal and various treatment modalities such as estrogens, steroids, and bisphosphonates have been described [1]. There are few reports of response to treatment with bisphosphonates. As pyrophosphate derivatives, bisphosphonates may prevent or reverse abnormal calcium deposition in patients with abnormal serum calcium levels. However, the side effects and doubtful efficacy outweigh its benefits as therapy for this condition. The role of intrauterine administration of biphosphonate is also not clear. Medical treatment of cardiovascular complications is usually unsuccessful [17]. Spontaneous resolution of calcification has occasionally been reported but the long-term prognosis in survivors is not described [5].

Conclusion

GACI is a rare, fatal disease of extensive arterial calcification usually diagnosed in later pregnancy or postnatal period. The disease can present as fetal hydrops during pregnancy or with cardiac failure postnatally. When there is a family history, serial sonographic examination for signs of calcification may allow early diagnosis. Genetic counseling and molecular analysis should be offered in index cases to provide early prenatal diagnosis in subsequent conceptions. The disease is generally lethal and the role of medical therapy needs to be explored.

Compliance with Ethical Standards

Conflict of interest None.

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