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Case Report

Prenatal Diagnosis of Idiopathic Infantile Arterial Calcinosis – a Case Report on a Rare Fatal Condition

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Abstract:

During the menopausal transition, which begins 4 to 6 years prior to stopping menstruation, women at this stage experience progressive changes in ovarian activity and physiological impairment of hypothalamic-pituitary-ovarian axis function associated with fluctuations in levels. hormonal; where they can suffer symptoms related to menopause such as vasomotor symptoms, sleep disorders, mood changes, memory problems and genitourinary syndrome of menopause. Neurological symptoms such as sleep disturbance and mood swings are the most important discomfort in the transition to menopause, which impacts quality of life, productivity and physical health. A review of the associations between menopause and/or hormone levels with sleep problems, mood and reduced cognitive performance is performed. During the transition to menopause, women experience dramatic fluctuations in the levels of sex hormones such as estradiol, progesterone, and androgens, responsible for changes in behavior, cognition, mood, and sleep.

Keywords: idiopathic infantile arterial calcinosis; enpp1; calcifications

Introduction

Idiopathic infantile arterial calcinosis also known as Generalised arterial calcinosis of infancy (GACI) is a rare genetic disorder causing extensive premature calcification of major vessels. About 200 cases have been reported till date as per literature [1] and only less than 10 cases have been reported to be diagnosed during prenatal period by ultrasound [6]. Hyperechogenicity of large vessels in the antenatal ultrasound helps in the prenatal diagnosis of this disease. Patient with positive history of IIAC in index pregnancy, unexplained death during neonatal or early infancy period can undergo molecular testing for diagnosis in early gestation. Genetic counselling and pre-implantation genetic diagnosis can be offered to these parents for their future pregnancies.

Case Presentation

A 31 year old Gravida 3, Para 2, living 1 and abortion 1 presented at 17 weeks of gestation with her chorionic villous sampling report showing mutation in ENPP1 gene at exon 9 in homozygous condition. She is a known case of hypothyroidism and her NT scan was normal. She had previous one intrauterine death at 34 weeks of gestation and the autopsy showed mutation in ENPP1 gene following which both the parents went for genetic counselling and underwent karyotyping. Both the parents had mutation in ENPP1 gene at exon 9 on chromosome 6q in heterozygous state. Hence chorionic villous sampling was done for this current pregnancy. It was reported as mutation in the similar variant in homozygous state. Patient was advised for medical termination of pregnancy. Inspite of explaining the poor prognosis and very fewer evidence of success with bisphosphonate therapy, both the parents want to continue the pregnancy. Anomaly scan showed multiple echogenic lesions in the left ventricle.

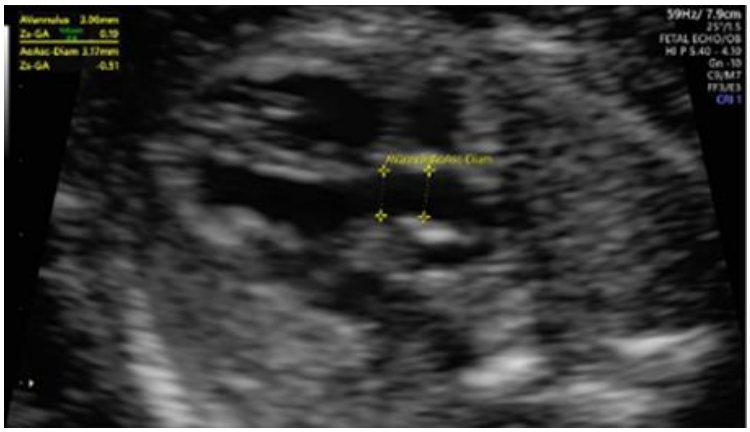

Figure 1: Hyperechogenicity of the vessel walls seen in the anomaly scan

Fetal echocardiography showed diffuse calcification in papillary muscle tip, TV annulus, Left ventricle, crux, descending aorta, abdominal aorta extending upto its bifurcation.

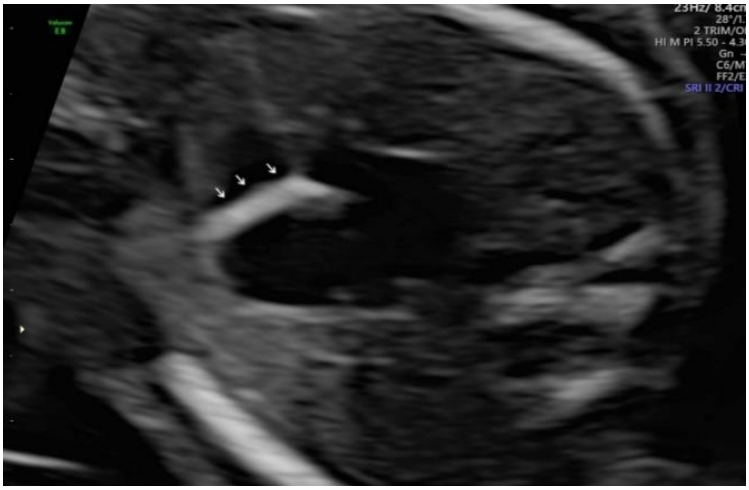

Figure 2: Calcifications seen in the descending aorta extending upto abdominal aorta

After fetal medicine expert and neonatologist opinion, patient opted for medical termination of pregnancy.

Discussion

Idiopathic infantile arterial calcinosis is an autosomal recessive disorder with fatal outcome. It was first described by Bryant and white in 1901 [1, 2]. Approximately 85% of cases are caused by loss of function mutation in ectonucleotide pyrophosphatase/ phosphodiesterase -1 (ENPP1) gene in chromosome 6q23 and causes death within the first 6 months of life [1,5]. The association between IIAC and ENPP1 has been explained by Rutsch et al in 2003 [2]. ENPP1 is expressed on fibroblasts, osteoblasts and hepatocytes and is responsible for pyrophosphohydrolase activity. It produces inorganic pyrophosphatase (Ppi) which prevents the deposition of calcium hydroxyapatite crystals in the arteries [7]. The mutation of this gene leads to deposition of calcium along the internal elastic membrane of medium and large arteries of cardiac and renal system, accompanied by fibrous thickening of the intima which causes luminal narrowing.

Diagnosis:

Most of the diagnosis is made during autopsy [8]. Prenatal diagnosis can be made if risk factors like consanguinity, positive family history or history of IIAC in the index pregnancy along with serial fetal echocardiogram. Few cases have reported association of polyhydramios and fetal hydrops with IIAC [5, 7]. Even though arterial biopsy is the gold standard for diagnosis of IIAC, DNA analysis for ENPP1 is a good antenatal screening test. IIAC should be suspected in patient with risk factors like consanguinity, positive family history, previous IIAC in the index pregnancy, unexplained early neonatal death and hyperechogenicity of the vessel wall [5]. Once the suspicion is made, serial ultrasound examinations and amniotic fluid testing to detect DNA mutation should be advised.

Treatment:

Very few studies have reported successful treatment with bisphosphonate therapy, an analogue of PPi [2, 8]. It alters the calcium balance by interfering with hydroxyapatite crystal formation and inhibits the calcium deposition in the vessels. Postnatal treatment with bisphosphonate has poor prognosis and the most common side effect of prolonged use of bisphosphonates leads to severe skeletal dysplasia similar to rickets [4]. More studies should be done to study the outcome of medical therapy with bisphosphonates. Therefore, once the diagnosis of IIAC is made, couples should be offered genetic counselling and preimplantation genetic diagnosis should be advised.

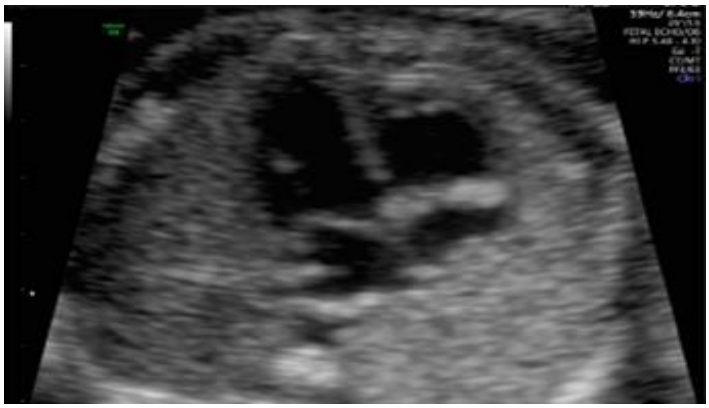

Figure 3: Diffuse calcifications of the left ventricle seen in the fetal echocardiography

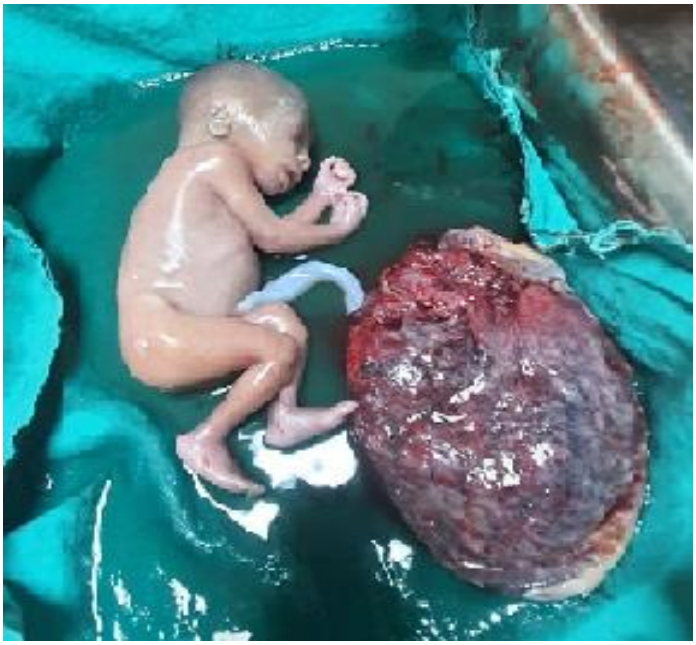

Figure 4: Fetus along with the placenta expelled after termination of pregnancy

Conclusion

IIAC is a rare disorder and has poor fetal outcome. Hence, careful and detailed history taking of risk factors and serial fetal echocardiography during antenatal period should be carried out. If IIAC is suspected, molecular testing of DNA for mutation will help in early diagnosis of the disease. Genetic counselling and preimplantation genetic diagnosis may be helpful in the future pregnancies.

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