CASE REPORTS

FAMILIAL IDIOPATHIC INFANTILE ARTERIAL CALCIFICATION

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Abstract
Idiopathic infantile arterial calcification (IIAC) is a rare disease characterized by extensive arterial wall calcification. A 24 hours old girl child presented with respiratory distress. Echocardiography showed right ventricular dysfunction. She was detected to have hypercalcemia and imaging revealed diffuse calcification of the aorta and its branches. She subsequently developed hypertension in 2nd week of life. Antenatally there was presence of pericardial effusion leading to hydrops and polyhydramnios.

Keywords : Idiopathic arterial calcification, hypertension

Introduction

Idiopathic infantile arterial calcification (IIAC) is a rare autosomal recessive disorder associated with widespread calcification and degeneration of the elastic lamina of arteries. (1) A total of 200 cases have been reported to date and from India only 5 cases, with most cases diagnosed postnatally and less than 13 cases having been suspected antenatally. (2) We present a newborn with IIAC with refractory hypertension and persistent hypercalcemia. Both parents were subsequently found to be carrier of ectonucleotide pyrophosphatase/ phosphodiesterase 1 (ENPP1) mutation on one allele.

Case Report

A baby girl weighing 2.1kg born at 36 weeks gestation to a second gravida mother aged 34 years, was admitted at 24 hours of life to the Neonatal Intensive Care Unit (NICU) for respiratory distress. Baby was born after emergency caesarean section for polyhydramnios and fetal pericardial effusion. Baby cried immediately after birth. Mother had positive triple test at 16th week of pregnancy (high alpha feto protein, normal human chorionic gonadotropin & normal unconjugated estriol). Antenatal ultrasound (USG) revealed polyhydramnios with pericardial effusion. At admission, baby was euthermic and euglycemic. She had tachycardia (heart rate 180/min), tachypnea (respiratory rate 80/min) with normal blood pressure and required supplemental oxygen. Peripheral pulses were not palpable. Systemic examination was normal. On investigations, hemogram showed leucocytosis and normal platelet count. CRP was negative and blood culture was sterile. Her other serum metabolic parameters were sodium 150 meq/L, potassium 4.1 meq/l, chloride 112meq/L, creatinine 0.6mg/dl, calcium 11.0 mg/dl, magnesium 2.3mg/dl. Parathyroid hormone was 35pg/ml and 25 hydroxy Vitamin D was 46ng/ml. TORCH IgM was negative. Chest x-ray showed massive cardiomegaly and pulmonary edema. 2D Echocardiogram (2D echo) performed on the day of admission revealed minimal pericardial effusion with severe right ventricular dysfunction which gradually progressed to severe biventricular dysfunction on serial echocardiograms with evidence of calcified ascending aorta, arch of aorta & coronary arteries in second week of life. Electrocardiogram did not show ischemic changes. USG abdomen revealed diffuse calcification of abdominal aortic wall with right renal artery stenosis. CT abdomen revealed diffuse rim calcification of the entire aorta & its branches. Neurosonogram and CT brain were normal. Karyotype revealed 46XY. She was managed with diuretics, digoxin and inotropic support (dobutamine and milrinone) for 5 days. She had severe hypertension in the second week of life, with mean arterial pressures up to 90 mm Hg. Hypertension was initially managed with oral amlodipine and later on she was switched over to captopril 1.2 mg/kg/day over a period of 7 days. She was diagnosed to have IIAC. She was commenced on calcium chelation therapy with IV Pamidronate (0.1mg/kg) on the eleventh day of life. In next one week, heart rate stabilised. Repeat USGs showed resolution of renal arterial calcification. Repeat ECG done on 25th day of life showed normalization of the ventricular function. She was discharged on 32nd day of life and plan was to start oral etidronate on follow up. However the child did not follow up and died at 6 months of age. We could not do mutation analysis on the patient. Both the parents were screened and were positive got ENPP1 mutation on one allele.

Discussion

Idiopathic infantile arterial calcification (IIAC) was described by Bryant and White in 1901. (3) Most of the affected infants die before the age of 6 months, and very few have survived for more than 1 year. (4) IIAC is characterized by extensive calcification of medium and large arteries including the aorta, coronary arteries, and renal arteries. Loss-of-function mutation in ecto nucleotide pyrophosphatase/phosphodiesterase 1(ENPP1) gene is found in 80% of cases. (5)

The clinical manifestations of the disease are secondary to calcification of the large and medium sized arteries presenting antenatally as non-immune hydrops fetalis or polyhydramnios and postnatally as cardiac dysfunction with respiratory distress, refractory hypertension. Farquhar et al have reported a neonate with idiopathic infantile arterial calcification with persistent pulmonary hypertension. (6) Mortality rates of upto 85 % have been described in the first 6 months of life. (7) Mortality is usually secondary to cardiac dysfunction and occlusion of the coronary arteries. Various treatment modalities such as thyroid extract, estrogens, steroids and diphosphonates have been tried with different success rates.(8) Ramjan et al have described successful resolution of the arterial calcification with low dose third generation diphosphonates therapy in a neonate. (9) van der Sluis have reported successful use of etidronate therapy and long term follow up upto twenty five years of age. (10) The exact dose of bisphosphonates for treatment is not known, and data reported in the literature vary from 5 mg/kg per day of disodium etidronate over a period of a few weeks to 15–35 mg/kg per day over 18 months. (11) Glatz et al have discussed a potential role

for cardiac transplantation in view of lack of definitive pharmacological therapy. (7) Prolonged etidronate use in patients with IIAC has been associated with severe skeletal toxicity, including radiographic findings resembling hypophosphatasia or osteopetrosis. In our patient we could not comment on the same as the bisphosphonates were given for a very short time and subsequently was loss to follow-up.

Studies demonstrated that homozygous or compound heterozygous loss-of-function mutations in ENPP1 result in IIAC in about 80% of the cases. (12) Accordingly, in the family presented here, ENPP1mutational analysis was performed in the parents. Although the clinical diagnosis of IIAC is based on clinical features and typical radiographic signs, molecular analysis of ENPP1 is mandatory for genetic counselling in the affected family.

Conclusion

Idiopathic arterial calcification of infancy should be suspected when there is hypercalcemia with hypertension and hyper echogenicity of vessel walls and evidence of polyhydramnios. It is recommended that along with investigations like Computed CT, more advanced investigations such as fetal echocardiogram and molecular analysis of ENPP1 should be included in the work up of IIAC. It will help the clinician to treat as well as help in counselling of the affected parents for further pregnancies.

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