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ORIGINAL ARTICLE

Outcome of Antenatally Diagnosed Cardiac Rhabdomyoma: Case Series from a Tertiary Fetal Medicine Center in India

Sushrut Dilip Ghaisas[1,2] · Suresh Seshadri[2] · Beena Suresh[3]

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Abstract The aim of this case series is to review our institution's experience with fetal cardiac rhabdomyoma, to document the clinical outcome and the incidence of associated tuberous sclerosis (TS) in these babies after birth. Eight cases with fetal cardiac rhabdomyoma were studied over a period of three years and the perinatal outcome was obtained. Out of these eight cases diagnosed antenatally, seven pregnancies continued till term and one woman opted for termination of pregnancy. There was one early neonatal death and of the six living, five developed TS with cutaneous and neurological manifestations. This association is similar with other larger multicentric studies and meta-analysis. Fetal cardiac rhabdomyoma is strongly associated with the development of TS in postnatal life, and the couples should be counseled regarding this association.

Keywords Cardiac rhabdomyoma · Tuberous sclerosis · Fetal echocardiography · Counseling

Introduction

The first prenatal diagnosis of a cardiac tumor was reported by De-Vore et al. [1] and the number of cases of cardiac tumors being detected is increasing with the widespread use of antenatal ultrasound with improvement in the imaging techniques and fetal echocardiography. Although primary cardiac tumors are rare with an estimated incidence of 0.27 % among pediatric autopsies [2], the most common type of cardiac tumor indentified in infancy and childhood is rhabdomyoma [3], which is a benign tumor of striated muscle. Rhabdomyoma is also the most common cardiac tumor diagnosed in utero [4], and is also a well-established prenatal marker for tuberous sclerosis (TS) which is a multisystemic autosomal dominant disorder characterized by the development of hamartomatous lesions in the viscera and skin, and with varying neurological outcomes. Knowledge about the incidence of TS in cardiac rhabdomyoma, prognostic factors, and clinical outcome of affected fetuses is vital for prenatal counseling. Although per se benign and rarely complicating cardiac function, a fetal diagnosis of cardiac rhabdomyoma may be of great clinical relevance. We have studied the outcome of eight fetuses with rhabdomyoma diagnosed at our center over a period of three years, and related the association with TS.

Materials and Methods

We identified 11 cases, diagnosed prenatally with cardiac rhabdomyoma, out of 97,867 second and third trimester obstetric ultrasound scans done at our center in MediScan Systems, Chennai, India, from January 2012 to March 2015. The data were retrieved by using the computer database (Sonocare) searching for words 'cardiac rhabdomyoma' and

✉ Sushrut Dilip Ghaisas
sdghaisas@gmail.com

1 Department of Fetal Medicine, Ashwini Hospital, 13/59 Nav Sahyadri Society, Karvenagar Opp. Sahyadri Park, Pune 411052, Maharashtra, India

2 Department of Fetal Medicine, Mediscan Systems, Chennai, Tamil Nadu, India

3 Department of Genetics, MediScan Systems, Chennai, Tamil Nadu, India

ICD 10 code D.15.1. Of the 11 cases, three have been lost to follow-up and the outcome of eight babies has been studied. For all these cases, the history of the mother and the family, gestational age at diagnosis, description of the rhabdomyoma with respect to tumor size, number, location, effect on hemodynamics, the antenatal and postnatal course, and follow-up of the infant for the development of TS were reviewed. Diagnosis of TS was done clinically and the postnatal workup including echocardiography, renal screening, and magnetic resonance imaging (MRI) was reviewed in whichever cases done. Postnatal follow-up was obtained through examination of infants visiting for evaluation at the center and also telephonically. The sensitivity of cardiac rhabdomyoma to predict the development of TS has been expressed as a percentage.

Results

The demographics of the eight cases of fetal cardiac rhabdomyoma are shown in Table 1. Of the eight cases of rhabdomyoma detected prenatally, five were nulliparous and three were multiparous. Two cases were detected before 24 weeks of gestation; the median gestational age at diagnosis was 26 weeks. One woman, who had rhabdomyoma diagnosed at 20 weeks (the earliest gestational age at diagnosis in the present series) opted for termination of pregnancy. Seven mothers continued till term. There were five cases with single and three with multiple tumors. The commonest location has been the left ventricle. None had prenatal evidence of cardiovascular compromise, arrhythmias or hydrops. Any other ultrasound presentations of TS like subependymal tubers or renal cysts in any fetus were not observed. One fetus had family history of TS, wherein the father was himself affected with the same, presenting with cutaneous angiofibromas, shagreen patch, and ocular affection (Fig. 1). However, no molecular diagnosis could be offered since the mutation in the index case (father) was not known and the couple presented in the third trimester for evaluation.

Of the seven babies followed postnatally, one had a sudden death on Day 2 of life; this baby had presented antenatally with a solitary cardiac rhabdomyoma of 16 mm in size, close to the left ventricular outflow tract. Autopsy was not done for this neonate. Of the six babies living, five have developed manifestations of TS, putting the correlation statistic at 83 %. Four out of five children with TS had hypopigmented patches on the trunk and/or limbs, which have appeared or been noticed right from birth till six months of age (Fig. 2).

Three infants underwent postnatal echocardiography, and the size has been regressed (Fig. 3) in all. One infant has developed neurodevelopmental delay with partial

Table 1 Demographic and clinical analysis of cases with cardiac rhabdomyoma

Case	Parity	Gestational age	Number of tumors	Largest size (mm)	Location	Delivery	Family H/o	Age at presentation	Postnatal echo	Neurocutaneous markers	Neurological sequelae	MRI	Tuberous sclerosis
1	0	23	2	15	LV, RV	FT LSCS	NS	Birth	Size regressed	Hypopigmented patches	None	Not done	Yes
2	0	29	3	7	RV(2), LV(1)	FTND	Father with TS	6 months	Not done	Absent	Partial seizures, developmental delay	Not done	Yes
3	1	26	3	8	LV (2), RV (1)	FTND	NS	6 months	Not done	Hypopigmented patch on back	None	Not done	Yes
4	1	31	1	17	LV	FTND	NS	3 months	Regressed	Hypopigmented patches	Infantile spasms	Normal	Yes
5	0	27	1	8	LV	FTND	NS	–	Regressed	Absent	None	Normal	No
6	1	26	1	14	LV	FTLSCS	NS	6 months	Not done	Hypopigmented patches	None	Not done	Yes
7	0	28	1	16	LV, close to outlet	FTND	NS	Baby suddenly expired on day 2	–	–	–	–	?
8	0	20	1	14	IVS	TOP	NS	–	–	–	–	–	–

FTLSCS full term lower segment cesarean section, *FTND* full term normal delivery, *H/o* history of, *IVS* interventricular septum, *LV* left ventricle, *MRI* magnetic resonance imaging, *NS* not significant, *RV* right ventricle, *TOP* termination of pregnancy

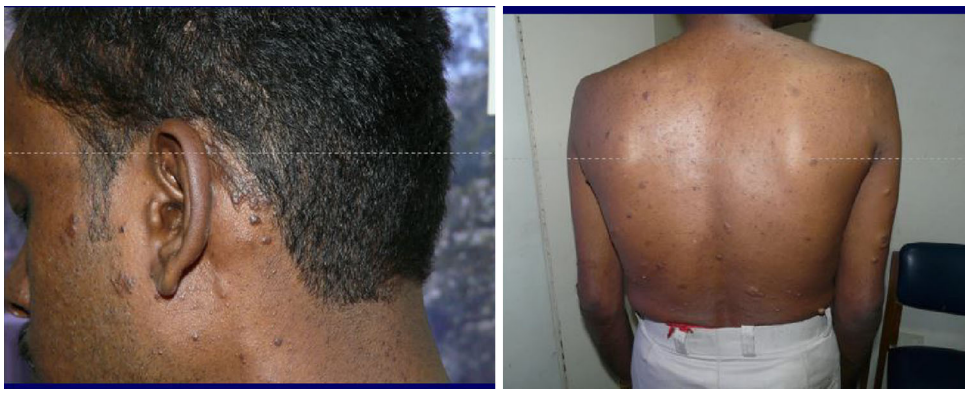

Fig. 1 Cutaneous manifestations of tuberous sclerosis in the parent—shagreen patch and cutaneous angiofibromas

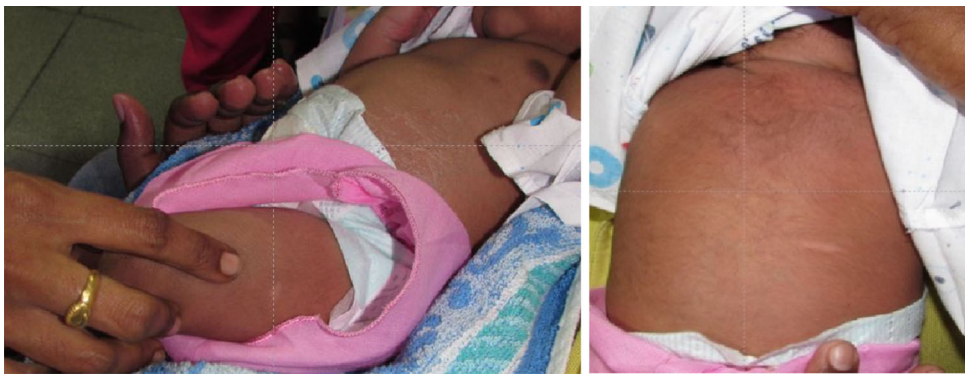

Fig. 2 Hypopigmented patches noted on the trunk and the thigh of an infant after birth, resembling ash leaf macules. This infant, noted as case 1 (Table 1), had two cardiac rhabdomyomas

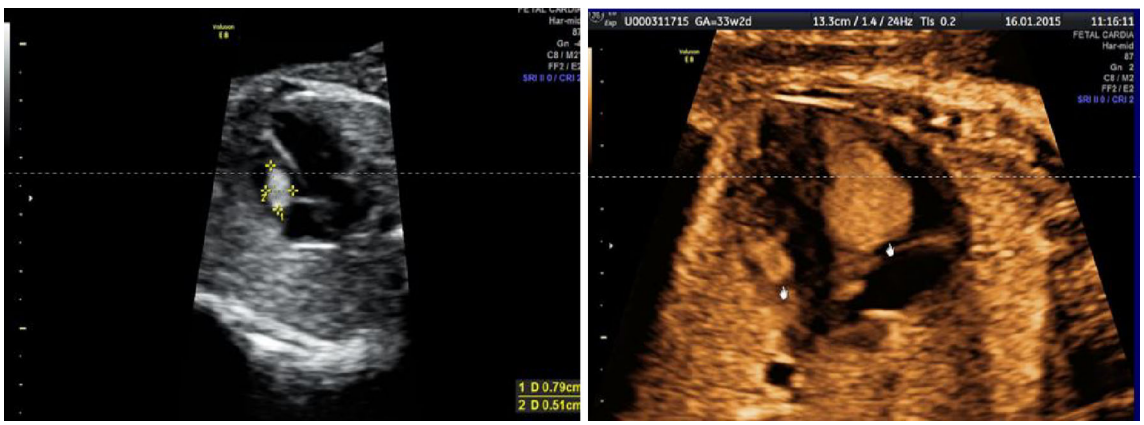

Fig. 3 *Left* ultrasound B-mode images of a cardiac rhabdomyoma measuring 8 × 5 mm in the *right ventricle* at 23 weeks. *Right* the same tumor increased to 15 × 14 mm in the *right ventricle*, with the appearance of an additional lesion in the *left ventricle* (Case 1 in Table 1)

seizures, and one has infantile spasms, the MRI in which case has been normal. This infant has his seizures controlled with vigabatrin (Fig 4).

Discussion

Fetal cardiac rhabdomyoma is a rare condition but is the most common cardiac tumor in fetal life, accounting for 60 %–86 % of primary cardiac fetal tumors [5]. They appear as round, homogenous, hyperechoic masses in the ventricles, and sometimes as multiple foci in the ventricles and the septal wall. Rhabdomyomas usually present in the late second trimester of pregnancy and thus the 18–20 weeks anomaly scan usually may not detect this mass. The earliest antenatal sonographic diagnosis has been made at 15 weeks of gestation [6]. The usual natural history is to increase in size under the influence of maternal hormones, and regress postnatally. Larger case series and meta-analyses [7] have concluded that when the tumor

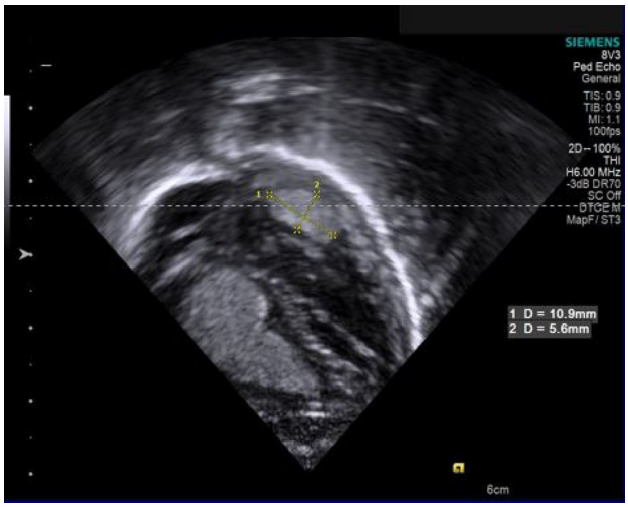

Fig. 4 Postnatal echocardiography of the neonate in Fig. 3 at 3 weeks of age—the rhabdomyoma in the *left ventricle* has completely regressed and that in the *right ventricle* has shrunk to 11 × 6 mm

mass is more than 20 mm in diameter, there is a higher risk of perinatal death from hemodynamic disturbances and dysrhythmias. Also, family history of TS and multiple fetal cardiac tumors are strongly associated with TS [7]. The earliest fetal MRI report of TS in the brain has been reported at 23 weeks [8], however, it is not routinely recommended after the diagnosis of a rhabdomyoma because the cerebral manifestations usually develop in late infancy and absence of cerebral involvement antenatally does not guarantee a good postnatal outcome. Therefore, evaluation of cardiac rhabdomyoma regression and neurological examinations that include MRI for at least one year after birth, are required to exclude the development of TS [7].

TS complex is an autosomal dominant multisystemic disorder with variable expressivity, the population frequency is 1:6000 to 1:10,000 [9], and about 80 % are caused by de novo mutations [10]. The International Tuberous Sclerosis Alliance has revised the criteria for diagnosis in 2014 (depicted in Table 2), with definitive diagnosis if 2 major/1 major + ≥2 minor features are

Table 2 Revised diagnostic criteria for tuberous sclerosis complex (TSC)

Genetic diagnostic criteria
The identification of either a TSC1 or TSC2 pathogenic mutation in DNA from normal tissue is sufficient to make a definite diagnosis of TSC. Apathogenic mutation is defined as a mutation that clearly inactivates the function of the TSC1 or TSC2 proteins (e.g., out of frame indel or nonsense mutation), prevents protein synthesis (e.g., large genomic deletion), or is a missense mutation whose effect on protein function has been established by functional assessment. Other TSC1 or TSC2 variants whose effect on function is less certain do not meet these criteria and are not sufficient to make a definite diagnosis of TSC. Note that 10 %–25 % of TSC patients have no mutation identified by conventional genetic testing, and a normal result does not exclude TSC, or have any effect on the use of clinical diagnostic criteria to diagnose TSC
Clinical diagnostic criteria
Major features
1. Hypomelanotic macules (≥3, at least 5 mm diameter)
2. Angiofibromas (≥3) or fibrous cephalic plaque
3. Ungual fibromas (≥2)
4. Shagreen patch
5. Multiple retinal hamartomas
6. Cortical dysplasias–includes tubers and cerebral white matter radial migration lines)
7. Subependymal nodules
8. Subependymal giant cell astrocytoma
9. Cardiac rhabdomyoma
10. Lymphangioleiomyomatosis (LAM)[a]
11. Angiomyolipomas (≥2)[a]
Minor features
1. "Confetti" skin lesions
2. Dental enamel pits (>3)
3. Intraoral fibromas (≥2)
4. Retinal achromic patch
5. Multiple renal cysts
6. Nonrenal hamartomas

[a] A combination of the two major clinical features lymphangioleiomyomatosis and angiomyolipomas without other features does not meet criteria for a definite diagnosis

present and possible diagnosis if 1 major or ≥2 minor features are noted [11].

The diagnosis of TS has practical implications for the family, so a molecular diagnosis can be requested for the fetus before the sighting of a rhabdomyoma, as there would be a 50 % chance of affection if a parent is affected. Genetic testing for TSC1 and TSC2 gene mutations can be done on chorionic villus sampling and amniocentesis samples. However, it roughly takes six weeks for the result to be procured despite being expensive. This also has implications for offering termination of pregnancy based upon the limit of gestational age stipulated by law. The detection of cardiac tumors, which can be achieved using prenatal echocardiography, should be used as a warning sign for TS during the counseling of at-risk patients [7]. Thus, cardiac rhabdomyoma may be the earliest sign of TS in utero preceding brain and kidney lesions, and fetal echocardiography is useful for detecting the same.

Conflict of interest None.

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