J. Fetal Med. (December 2021) 8:267–272
https://doi.org/10.1007/s40556-021-00330-6

REVIEW ARTICLE

Unmasking Antenatal Tuberous Sclerosis and 13 Years Retrospective Review of Its Diverse Presentations, Clinical-Imaging Follow Up and Learning the Latest Advances in Management

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Received: 3 September 2021 / Accepted: 16 December 2021 / Published online: 1 February 2022

Abstract A 27 year old multigravida, presented with giant left ventricular cardiac rhabdomyoma at the 23rd gestational week. A previous bad obstetric history prompted amniocentesis. A heterozygous, pathogenic, missense variant in exon 40 of the Tuberous Sclerosis (TSC 2) gene with autosomal dominant inheritance was extracted from fetal DNA by targeted gene capture. Sanger's sequencing confirmed the same. This fetus highlighted the need for genetic assessment in every cardiac rhabdomyoma and a paradigm shift in fetal counseling protocol. We retrospectively reviewed our personal, multi-centric 13 years (2008–2020) database of cardiac rhabdomyomas in the fetal and pediatric cohort. Cardiac rhabdomyoma preceded extra-cardiac manifestations of Tuberous Sclerosis in 87.5% of our cohort. This article underscores this forgotten ominous association. We propose a paradigm shift in fetal counseling in such a scenario, remembering the heterogeneous timing and presentations of this widely variable genetic lesion.

Keywords Tuberous sclerosis · Rhabdomyoma · Shagreen patch · Adenoma sebaceum · Ventricular tachycardia

Introduction

The traditional concept regarding cardiac rhabdomyomas is that they are primarily benign masses and can be conservatively watched as the majority will spontaneously regress within the first three years of life. This probably leads to a misplaced sense of security while counseling the family. However, repeated encounters with fetal, neonatal, pediatric and adolescent TSC transformed our outlook. We proactively attempted to introspect on all our previous cases and assessed them longitudinally.

Case Report

A 27 year old multigravida (G4, A2, L1), married for 8 years, presented at 23 weeks of gestation with an anomaly scan at 22 weeks showing a cardiac mass. Both the spouses (maternal and paternal ages 27 and 33 years respectively) were phenotypically non-syndromic and married nonconsanguineously with an apparently healthy six years old daughter (pregnancy 1) delivered by a lower segment cesarian section (LSCS). Two subsequent pregnancies underwent a spontaneous miscarriage at the 10th and 12th weeks of gestation and were not investigated. The current (4th) pregnancy was conceived spontaneously. There was no history of teratogenic exposure, addictions,

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viral infections, pregnancy induced hypertension, gestational diabetes, uterine or placental complications thus far.

Fetal echocardiography was done with a Voluson E8 ultrasound machine (GE Medical Systems, Zipf, Austria) with a transabdominal 2–4 MHz curvilinear transducer with a customized cardiac preset. Four chamber, parasternal long and short axis views, subcostal and 3 vessel trachea view revealed multiple, giant (largest one measuring 8 mm × 6 mm) homogeneous, hyperechogenic avascular mass, attached to the mid and apical interventricular septum (total ventricular septal length = 9 mm), with margin indistinguishable from the adjacent septum (video 1a, 1b). Fetal heart rate was 144/min with a 1:1 atrioventricular conduction. There were no ectopics, sustained arrhythmias, inflow and/or outflow obstruction, valvular regurgitation, pericardial effusion, fetal heart failure or other cardiac anomalies. Both the foramen ovale and ductus arteriosus were shunting normally with normal biventricular function. The extracardiac fetal anomaly scan including neurosonogram was within normal limit.

After parental counseling and consent, amniocentesis was performed for targeted genomic sequencing particularly to exclude TSC complex. DNA analysis at 25 weeks of gestation revealed TSC2 gene coordinates at chromosome 16:2138118, location exon 40, variant NM_000548.5:c.5138G > A;p.Arg1713His with heterozygosity and pathogenic autosomal dominant inheritance. Trisomy 21 was negative.

Repeat fetal echocardiography at 26 and 34 weeks of gestation revealed a marginal reduction in size (6 × 6 mm) with a more spheroidal appearance localizing towards the left ventricular (LV) apex. Parents refused consent for fetal cranial MRI and genetic screening of the family.

Neonatal History: A term, male fetus was born through LSCS, with normal Apgar scores and no perinatal events. Immediate neonatal echocardiography confirmed the findings. Sinus rhythm with heart rate varying between 130 and 140/min was maintained. Postnatal neurosonogram was within normal limit and abdominal ultrasound showed a solitary kidney. A Pediatric neurologist's opinion was sought. Elective cranial MRI had been done at 2 months of age and found to be within normal limit. Cardiology follow up with echocardiography and ECG available up to 6 months of age revealed no deterioration.

This case motivated us to retrospectively analyze our personal cardiac rhabdomyoma database between 2008 and 2020. The results are depicted in Table 1 and chart 1.

Data Analysis

Our case series includes 8 fetuses and children with cardiac rhabdomyoma seen over a period of 12 years (2008–2021) with age at diagnosis ranging between 23 weeks of gestation to 12 years. Two had solitary, while 6 had multiple rhabdomyomas. Both atrial (n = 1) and ventricular locations (n = 7) were seen.

Four children (50%) had arrhythmias, refractory VT in 2 while atrial ectopics and trigeminy in one case each. Both children with ventricular tachycardia expired. A neonate (case 5) born with refractory VT and pericardial tamponade could not be saved inspite of emergency surgery. Preoperative morphological and histopathological findings confirmed the diagnosis of rhabdomyoma in this neonate. Fetal diagnosis of the cardiac tumor was established in the late third trimester in this pregnancy. This was beyond the then permissible legal age of termination of pregnancy in India. Another infant (case 8) had VT at 1 year of age and succumbed to that.

Cardiac findings were first to appear in all cases except case 4 presenting with adenoma sebaceum at 6 years of age.

Neurological lesions (epilepsy, mental retardation, tubers) were found in 57% excluding the index newborn who is barely six months old. Neurological presentation lagged cardiac tumors by 1–12 years of age. The only exception was case number 4 where epilepsy with neurocutaneous markers prompted retrospective cardiac evaluation. Instead of spontaneous involution, the rhabdomyoma underwent lipomatous degeneration and by virtue of its location in the interventricular septum and RV produced trigeminy and pre-syncope. The patient was started on prophylactic anti-arrhythmic and a detailed electro-physiological study is being planned.

Cutaneous features (ash-leaf macules, Shagreen and hypopigmented patches) presented late from six months of age.

Thus in 87.5% of this case series, cardiac rhabdomyoma was the earliest presentation of Tuberous Sclerosis. None of these subjects had a positive family history or clinical findings. Genetic assessment could be performed in only 50% of cases due to financial constraints.

Our institutional protocol of genetic assessment for tuberous sclerosis in every fetus/child with rhabdomyoma was started in 2016. This coupled with financial constraints explain the low diagnostic frequency of TSC mutation. Patient number 7 and 8 however fits into clinical diagnostic criteria of TSC. Latter increases the association of TSC with rhabdomyoma to 62.5% in our case series, a numeral which simply cannot be ignored.

Table 1 Clinical presentation with different systemic involvement in Tuberous sclerosis

Cases	Age at cardiac rhabdomyoma	Number and site of rhbdomyoma	Arrythmia	Age at neurological findings	Age at cutaneous findings	Age at renal involvement	Family history	Genetic diagnosis	Outcome and present age
1. (Index case)	23 weeks gestation (fetal)	Multiple LV (video 1a,b)	nil	NA	NA	Solitary kidney at 23 weeks	Nil	TSC2	On follow up, 6 months
2	32 weeks gestation (fetal)	Solitary RA (video 2)	Atrial ectopics	Nil	Nil	Nil	Nil	TSC negative	Regression at 3 years of age 10 years
3	14 days of life	Multiple LV and RV	Nil	2 year (Onset of epilepsy)	6 months (Ash-leaf macules)	Nil	Nil	TSC2 (denovo mutation)	On follow up 8 years
4	12 year old	Multiple septal and RV,Lipomatous degeneration (Fig. 1a)	Trigeminy (Picture -4)	10 years (epilepsy), Multiple Tubers in MRI brain (Fig. 1b)	6 years (Adenoma Sebaceum)	Nil	Nil	TSC2 (denovo mutation)	Poor scholastic performance. 12 years
5	At birth	Pericardial, giant (Movie 3)	Refractory VT;	At birth, Sub-ependymal nodules	Nil	Nil	Nil	NA	Expired
6	At birth	Multiple RV free wall, septum and LV wall(video 4a,b)	Nil	Nil	Nil	Nil	Nil	NA	On follow up, 1.5 years
7	2 weeks of life	Multiple RV and LV	Nil	At 1 year, Epilepsy	Hypopigmented patch (Fig. 2)	Nil	Nil	NA	Regression of tumors by 1 year of age, 6 years
8	6 month old	Multiple large tumors LV and RV	Intractable VT	Nil	Shagreen patch at 8 months	Nil	Nil	NA	Expired

TSC, Tuberous sclerosis; NA, not available; RA, right atrium; LV, left ventricle; RV, right ventricle; VT, ventricular tachycardia

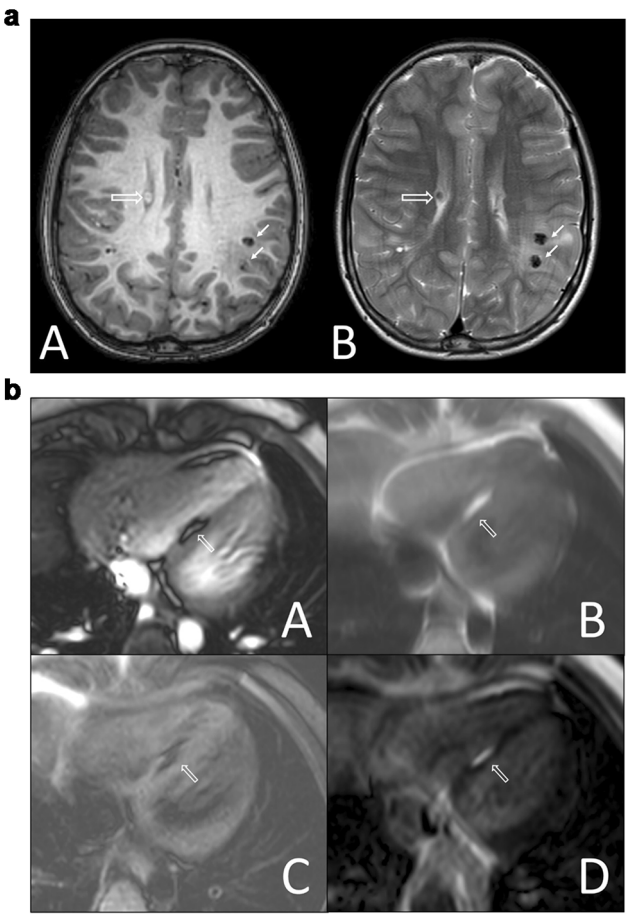

Fig. 1 **a** MRI of case 4 a. Cardiac MRI: Four chamber cine SSFP sequence (A) shows a hyperintense lesion in the inferior septum along the right ventricular side with peripheral blooming, the lesion is hyperintense on T1 (B) weighted images. Suppression of signal on STIR sequence (c). The lesion shows delayed contrast enhancement on PSIR sequence. **b** Brain MRI: Axial T1 weighted image (A) and T2 weighted image (B) of the brain at the level of corona radiata shows cortical/subcortical tubers (solid arrow) in the right parietal lobe which are hypointense on T1 WI (A) hyperintense on T2 WI (B) with central hypointensity. Subependymal nodule on right side (open arrow) which is hyperintense on T1 WI and hypointense on T2 WI (D)

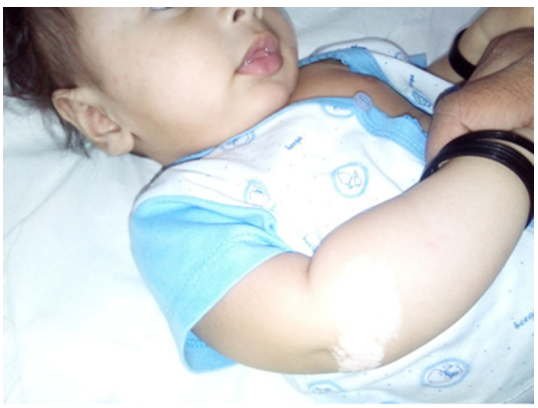

Fig. 2 Photograph of the child (case 7) showing hypopigmented skin lesion at elbow

Discussion

The focus of this study is to highlight the hitherto "*forgotten /missed"* coexistence of TSC and cardiac rhabdomyoma.

The traditional concept regarding rhabdomyomas detected randomly in ante or postnatal echocardiograms is that they are primarily benign masses. Cardiologists focused on their number, location, size and mass effects and excluded arrhythmogenic, obstructive and hemodynamic compromise secondary to them. The traditional belief was they can be conservatively waited and watched as the majority shall spontaneously regress within the first three years of life [1]. This probably leads to a misplaced sense of security while counseling the family.

However, repeated encounters with fetal, neonatal, pediatric and adolescent TSC transformed our outlook. We proactively attempted to introspect on all our previous cases and assess them longitudinally.

TSC is a multisystem disorder clinically represented by cutaneous and neurological lesions and the development of hamartomas in the brain, heart, and kidneys. The genetic mechanism is mutations in either *TSC1* or *TSC2* gene which encode hamartin and tuberin respectively. This in turn creates a protein complex that is responsible for chaotic cellular hyperplasia and also modifications in a tumor suppressor gene. These mutations may be spontaneous (70%) or inherited autosomally dominant [2, 3]. In our index case, antenatal genetic testing was done and the benefits of this antenatal invasive testing were twofold: (1) it helped in accurate fetal counseling and making the family aware of the lifelong implications of this genetic syndrome- an informed decision was taken by the family to continue the pregnancy (2) it prepared the perinatal team including obstetrician, neonatologist, cardiologist and other caregivers to fully prepare for a *'high risk' pregnancy.*

Literature reports only 0.25% prevalence of pediatric primary cardiac tumors accounted in descending order by rhabdomyoma, teratoma, fibroma, hemangioma, eosinophilic myocardial hyperplasia and myxoma. Cardiac rhabdomyoma, the leader of these masses, were typically is considered to have a good prognostic outcome [4].

The alarming truth lies in the emerging data. The coexistence of cardiac rhabdomyoma and Tuberous Sclerosis (an autosomal dominant, neurocutaneous multi-organ disorder) is 80–90% [5–10]. Frudit et al. [1] have already reviewed the existing sparse database of 31 cases of coexistence of rhadbdomyoma and TSC till 2019 and published autopsy findings of the most dreaded version of cardiac rhabdomyoma, *similar to patient number 4 in our series*. However, the message goes unheard. A very

important point is to understand the heterogeneity or variability in clinical presentations of TSC complex. Non-cardiac manifestations may present even in mid-adult life. This should not lead to false complacency among caregivers. Rather an informed, customized protocol needs to be followed in every case.

Our combined retrospective analysis of two tertiary maternal and cardiology centers parallels the same viewpoint. In the previous decade, with limited availability of genetic assessment in India, we relied more on extracardiac clinical markers which typically lag behind the diagnosis of rhabdomyoma. In other words, rhabdomyoma is the first marker to appear.

Recent development in management:

1. Several reports have demonstrated the effectiveness of Everolimus, a serine–threonine kinase mammalian target of rapamycin inhibitor, in tuberous sclerosis presenting with refractory arrhythmias or severe outflow tract obstruction leading to hemodynamic compromise [11]. By inhibiting growth driven cell proliferation when given at a dose of 0.1 mg/kg/day it can potentially buy time or avoid surgery in cardiac rhabdomyomas with locations producing cardiac output compromise. This off label use has shown beneficial effects in reducing the size of tumor and echo Doppler gradients, and is another weapon in the physician's hand. The indexed case, fortunately, did not suffer from hemodynamic compromise and did not receive Everolimus.
2. Epilepsy develops in 70 to 90% of children with tuberous sclerosis complex (TSC) and is often resistant to medication. The recently published EPISTOP trial has demonstrated that preventive treatment with vigabatrin is safe and modifies the natural history of seizures in TSC, reducing the risk and severity of epilepsy [12].

Currently, our protocol has changed to include antenatal exclusion of Tuberous Sclerosis with fetal cardiac tumors. Multidisciplinary counseling of the family prepares them for understanding the cardiac mass as the "tip of the iceberg".

Limitations of our study: Due to the extremely low incidence of fetal and pediatric cardiac tumors (0.08–0.2%), number of patients is limited. A nation-wide registry simultaneously analyzing two separate groups namely (1) all cardiac rhabdomyomas and (2) all Tuberous Sclerosis patients may answer these questions better. However, even in this small cohort, the interrelation is alarming. The second limitation was that we could not perform a genetic assessment of all patients due to lack of resources. Thirdly, due to lack of parental consent, histopathological evaluation could not be obtained in any case.

Prospective active trials in the future should involve fetal medicine practitioners, perinatologists, cardiologists, pediatricians, neurologists, dermatologists, nephrologists and ophthalmologists to perform data analysis on this combination. It may also serve as a point of research for deciphering echocardiographic markers of cardiac rhabdomyoma which can predict an underlying Tuberous Sclerosis (like nuchal thickness correlation with Trisomy 21 assessment). Unlike Western researches where autopsy and histopathological examinations are the norm, our country needs a more clinical-imaging protocol to diagnose and treat these children.

Conflict of interest

The authors declare that they have no conflict of interest.

Author contributions Writing manuscript, Drafting article,concept design: Dr Munesh tomar and Dr Maitri Chaudhuri, Analysis of data: Dr Maitri Chaudhuri, Dr Munesh Tomar, Dr Seema Gaonkar. Data collection(radiology images):Dr BalaSubramanyam Shankar. Critical revision of article: Dr Munesh Tomar, Dr Arvind Shenoi, Dr Maitri Chaudhuri.

Funding None.

References

1. Frudit P, Kusznir BV, Navarro FC, Rondelli I, Pozzan G. Multiple cardiac rhabdomyomas in tuberous sclerosis complex: case report and review of the literature. Autops Case Rep. 2019;9(4):e2019125.
2. Rosset C, Vairo F, Bandeira IC, Correia RL, de Goes FV, da Silva RTB, et al. Molecular analysis of TSC1 and TSC2 genes and phenotypic correlations in Brazilian families with tuberous sclerosis. PLoS ONE. 2017;12(10):e0185713. https://doi.org/10.1371/journal.pone.0185713.
3. Roach ES. Applying the lessons of tuberous sclerosis: the 2015 Hower Award lecture. Pediatr Neurol. 2016;63:6–22. https://doi.org/10.1016/j.pediatrneurol.2016.07.003.
4. Beghetti M, Gow RM, Haney I, Mawson J, Williams WG, Freedom RM. Pediatric primary benign cardiac tumors: a 15-year review. Am Heart J. 1997;134(6):1107–14.
5. Northrup H, Krueger DA. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 international Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol. 2013;49(4):243–54. https://doi.org/10.1016/j.pediatrneurol.2013.08.001.
6. Krueger DA, Northrup H. International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex surveillance and management: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol. 2013;49(4):255–65. https://doi.org/10.1016/j.pediatrneurol.2013.08.002.

7. Hinton RB, Prakash A, Romp RL, Krueger DA, Knilans TK. Cardiovascular manifestations of tuberous sclerosis complex and summary of the revised diagnostic criteria and surveillance and management recommendations from the International Tuberous Sclerosis Consensus Group. *J Am Heart Assoc*. 2014;3(6)
8. Thatte NM, Guleserian KJ, Veeram Reddy SR. New-onset cardiac rhabdomyoma beyond infancy in a patient with tuberous sclerosis complex. Cardiol Young. 2016;26(2):396–9.
9. Wang F, Xiong S, Wu L, Chopra M, Hu X, Wu B. A novel TSC2 missense variant associated with a variable phenotype of tuberous sclerosis complex: case report of a Chinese family. BMC Med Genet. 2018;19(1):90.
10. Caylor RC, Grote L, Thiffault I, Farrow EG, Willig L, Soden S, et al. Correction to: Incidental diagnosis of tuberous sclerosis complex by exome sequencing in three families with subclinical findings. Neurogenetics. 2018;19(4):261–2. https://doi.org/10.1007/s10048-018-0554-8.
11. Shibata Y, Maruyama H, Hayashi T, et al. Effect and complications of everolimus use for giant cardiac rhabdomyomas with neonatal tuberous sclerosis. AJP Rep. 2019;9(3):e213–7. https://doi.org/10.1055/s-0039-1692198.
12. Kotulska K, Kwiatkowski DJ, Curatolo P, Weschke B, Riney K, Jansen F, et al. EPISTOP investigators. Prevention of epilepsy in infants with tuberous sclerosis complex in the EPISTOP trial. Ann Neurol. 2021;89(2):304–314. https://doi.org/10.1002/ana.25956