Case Report

Fetal Rhabdomyoma Leads to Family Diagnosis of Tuberous Sclerosis Complex

Yan-Dong Yang[1], Dong-Zhi Li[2]*

[1]Department of Ultrasound, The Sixth Affiliated Hospital of Sun Yat-Sen University, Guangzhou, Guangdong, China, [2]Prenatal Diagnostic Center, Guangzhou Women and Children's Medical Center, Guangzhou, Guangdong, China

Abstract

Tuberous sclerosis complex (TSC) is a multisystem genetic disorder characterized by the growth of numerous noncancerous tumors in many parts of the body. It is highly variable in clinical presentations, including a wide range of cognitive, behavioral, and psychiatric manifestations. Of all the possible manifestations, cognitive and behavioral problems are the greatest concern to parents and physicians. In this study, two fetuses were identified to have rhabdomyomas by prenatal ultrasound. Carefully inquired familial medical history revealed other symptoms of TSC such as skin lesions or psychiatric problems in family members in the two families. Both fetuses and family members with positive clinical symptoms were confirmed to carry a familial *TSC2* variant. Our study indicates that fetal echocardiography is not just the evaluation of the fetal heart. When fetal cardiac rhabdomyomas are diagnosed, a full family medical history and clinical assessment for TSC in family members should be undertaken.

Keywords: Prenatal diagnosis, rhabdomyoma, tuberous sclerosis complex, ultrasound

Introduction

Tuberous sclerosis complex (TSC) is an uncommon autosomal dominant genetic disorder characterized by the development of hamartomas in many parts of the body, most commonly in the brain, eyes, kidneys, heart, lungs, and skin, although any part of the body can be involved.[1] The clinical guidelines for the diagnosis of TSC are based on the presence of two major features or one major feature and two minor features of the disease.[2] Major features include multiple angiofibromas, tubers in the brain, and cardiac rhabdomyomas or noncancerous heart tumors. Minor features are kidney cysts, "confetti" skin lesions, dental pitting, and retinal growths. However, a great phenotypic variability is observed in TSC.[3] Some patients have such mild signs and symptoms that they go undiagnosed, whereas others experience serious disabilities. This is also evident in the same family and even in monozygotic twins. We here report two families in which the findings of fetal cardiac rhabdomyomas by prenatal echocardiography helped to establish the diagnosis of previously unknown familial TSC.

Received: 14-04-2022 **Revised:** 30-04-2022 **Accepted:** 09-05-2022 **Available Online:** 24-08-2022

Access this article online

Quick Response Code:

Website: https://journals.lww.com/jmut

DOI: 10.4103/jmu.jmu_35_22

Case Reports

Case 1

A 26-year-old woman, primigravida nulliparous, was referred for echocardiography at 24 weeks of gestation due to the presence of fetal cardiac hyperechoic foci identified by a routine sonographic survey. Fetal echocardiography demonstrated two intracardiac masses on the right ventricular wall, measuring 13 × 6 mm and 8 × 8 mm, respectively [Figure 1a]. Both masses presented a hyperechogenic and homogeneous aspect and were diagnosed as cardiac rhabdomyomas. Both cardiac size and function were normal. No other intracardiac and extracardiac anomalies were identified. Fetal cranial magnetic resonance imaging (MRI) was normal. The possibility of fetal TSC was explained to the couple.

The couple was apparently healthy with no history of neuropsychiatric impairment. However, carefully inquired familial medical history revealed that the maternal mother had an

Address for correspondence: Dr. Dong-Zhi Li, Prenatal Diagnostic Center, Guangzhou Women and Children's Medical Center, Jinsui Road 9, Guangzhou, Guangdong 510623, China. E-mail: drlidongzhi2014@sina.com

How to cite this article: Yang YD, Li DZ. Fetal rhabdomyoma leads to family diagnosis of tuberous sclerosis complex. J Med Ultrasound 2023;31:245-7.

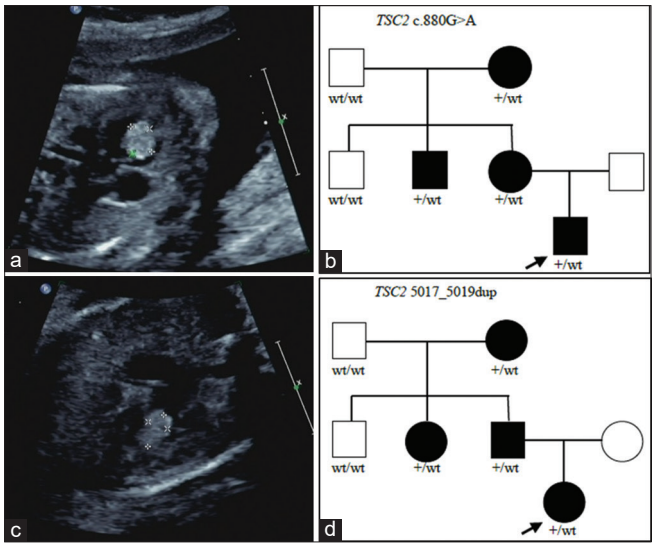

Figure 1: Sonography of rhabdomyomas and family pedigrees. (a) Cardiac rhabdomyoma in the right ventricle at 24 weeks; (b) *TSC2* c.880G>A variant in the family members of Case 1; (c) Cardiac rhabdomyoma in the left ventricle at 26 weeks; (d) the *TSC2* c. 5017_5019dup variant in the family members of Case 2

intellectual disability with no history of seizures. One of her two brothers had multiple cutaneous fibrous lesions with a history of epilepsy. His intelligence is the same as a normal individual. The other brother was completely normal. On detailed examination, the woman was noted to have two hypopigmented macules on her abdomen and right thigh, respectively. Her echocardiography, renal ultrasound, and brain MRI were normal. Tuberous sclerosis panel based on next-generation sequencing (NGS), including *TSC1* and *TSC2* genes, was arranged in the blood of the woman. A heterozygous likely pathogenic missense variant, c. 880G > A (p. G294R) of *TSC2,* was identified and confirmed by Sanger sequencing. This variant was also present in the maternal mother and the affected brother and not detected in the father and normal brother [Figure 1b]. The paternal family history is noncontributory.

The pregnancy was continued to term after genetic counseling, and a male newborn was delivered with a birth weight of 3110 g. Rhabdomyomas were confirmed. Hypomelanotic macules were observed on the infant's skin. Abdominal ultrasound reported normal kidneys. The c.880G>A variant was detected in the infant's lymphocytes. The baby was referred to the pediatric neurology department for the assessment and early prevention of epilepsy.

Case 2

A 25-year-old woman in her first pregnancy was referred for echocardiography at 26 weeks due to fetal cardiac anomaly. On fetal echocardiography, a round mass measuring 10 mm × 6 mm was found in the left ventricle with uniform echogenic internal structure [Figure 1c]. The mass did not obstruct the heart outflow tract. Both cardiac size and function were normal. No other major anomalies were found. Fetal brain MRI was normal. The couple was healthy and free of any clinical findings with the exception of the husband who had a large hypomelanotic macule on the back. His sister had a single hypomelanotic spot on the right arm with no neurological syndrome. His brother was normal. His mother had unexplained epilepsy, mild intellectual disability, and emotional problem with no dermatological lesions. He and his family members declined brain MRI examination. The maternal family history was insignificant.

Genetic counseling was offered to the couple, and the possibility of fetal TSC was explained. Tuberous sclerosis NGS panel was studied in the husband using his peripheral blood. A heterozygous pathogenic *TSC2* variant, c. 5017_5019dupGTC (p. V1673dup), was detected, which was validated by Sanger sequencing. This variant was also confirmed to be present in the husband's sister and mother and not in the normal brother and father [Figure 1d]. The pregnancy proceeded to term without complications when a female newborn was delivered. The birth weight was 3050 g, and the Apgar scores were 9 and 10 at 1 and 5 min, respectively. Rhabdomyomas were confirmed, and no dermatological lesion was found. The girl was under close neurological surveillance. The same *TSC2* variant was detected in the infant's lymphocytes.

Discussion

TSC results from variants within either the *TSC1* or *TSC2* gene. Approximately 85% of TSC patients can be detected to carry a disease-causing variant of *TSC1*/*TSC2* genes, with *TSC1* variants accounting for 31% and *TSC2* variants accounting for 69%.[4] Before the introduction of molecular testing, TSC diagnosis is based on the presence of two major features or one major feature plus two minor features. The identification of a pathogenic variant in *TSC1* or *TSC2* was added as a major diagnostic criterion in 2012.[5] There are studies which found that *TSC2* pathogenic variants are associated with a more severe clinical phenotype than *TSC1* variants.[6,7] Although the majority of cases result from *de novo* germline variants, about one-third of cases exhibit an autosomal dominant pattern of inheritance in the families. In our two families, the clarification of *TSC2* variants in the affected family members helped to establish the confirmatory diagnosis of TSC. However, the prospective parent's very subtle manifestations in these two families were only identified and considered after the findings of fetal rhabdomyomas. Cardiac rhabdomyoma is a rare condition, but it is the most common cardiac tumor *in utero*, accounting for 60%–86% of primary fetal cardiac masses.[8] Rhabdomyomas present on ultrasound as round, homogeneous, hyperechogenic nodules in the ventricles or appear as multiple foci in the ventricles and septal wall. As a histologically benign tumor, rhabdomyomas are usually not hemodynamically relevant and do not increase in size. However, larger tumors (≥20mm) can be encountered in rare cases and may cause hemodynamic disturbance and dysrhythmia which are associated with poorer outcomes at fetal and neonatal stages.[9] There is a strong correlation between cardiac rhabdomyomas and tuberous sclerosis,

where the incidence rate of tuberous sclerosis is 51%–86% in patients with cardiac rhabdomyoma.[10] Furthermore, cardiac rhabdomyomas are the most frequently reported sign in fetuses or neonates affected with TSC. Therefore, the presence of cardiac rhabdomyomas is highly suggestive of TSC.

TSC is characterized by lesions in multiple organ systems, including the brain, skin, heart, eyes, kidneys, and lungs. The phenotype is highly variable, although penetrance is reportedly complete. Our report demonstrates the wide intrafamilial phenotypic variability of TSC in members with the same TSC-causing variants. The two expectant parents had only subclinical features which did not meet clinical criteria for a possible or definite diagnosis of TSC. Lyczkowski *et al*. assessed clinical manifestations in five families with TSC, including one pair of monozygotic twins.[11] They found that the severity of epilepsy and cognitive profiles varied both between and within families, particularly between the monozygotic twins. Although the monozygotic twins displayed similar physical manifestations of TSC (renal and cardiac hamartomas), they differed markedly in neurocognitive profiles. Other studies also reported TSC individuals exhibiting extreme intrafamilial variability, including the incidental diagnosis of asymptomatic family members.[12,13] Given the importance of a timely TSC diagnosis for clinical management, such cases will benefit from an unbiased molecular approach to genetic testing.

Fetal echocardiography is the best choice for detecting fetal cardiac space-occupying lesions because it is noninvasive, free of radiation exposure, easy to repeat, and it has a high diagnostic rate. Our report highlights that fetal echocardiography should not be regarded as just an evaluation of the fetal heart. When fetal cardiac rhabdomyomas were found, a detailed family history, especially with searching for the signs of TSC in familial members, should be undertaken. This disciplinary approach may be useful in clarifying the proper diagnosis in those families associated with a mild phenotype, with most carriers not meeting the clinical criteria for definite TSC. Prenatal ultrasound is not sensitive for the evaluation of the brain. Fetal MRI is the imaging modality of choice for the evaluation of cerebral manifestations of TSC. Hulshof *et al.* reported that (sub) cortical lesions detected by third-trimester MRI were recorded in 97.6% of children with definite TSC, and fetal cerebral lesion scores correlated with neurodevelopment and autism spectrum disorder at 2 years in these patients.[14] Although the absence of cerebral involvement by MRI could not guarantee a better postnatal outcome, fetal MRI provides an additional imaging modality for the detection of subependymal nodules and cortical tubers. The quality of life of affected patients is impaired, particularly due to epilepsy and psychomotor retardation. Therefore, for parents with a fetus of cardiac rhabdomyomas, the prognostic counseling should include TSC and its consequences.

In conclusion, we reported two fetuses of rhabdomyomas identified by fetal echocardiography which led to an incidental detection of previously unknown familial inheritance. Both fetuses and family members with positive clinical symptoms were confirmed to carry a familial *TSC2* variant. A prenatal identification of cardiac rhabdomyomas with a family history of manifestations associated with TSC should include a differential diagnosis of TSC in family members.

Declaration of patient consent

The authors certify that they have obtained appropriate patients' consent form. In the form, the patients have given their consent for the prenatal images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Randle SC. Tuberous sclerosis complex: A review. Pediatr Ann 2017;46:e166-71.
2. Northrup H, Krueger DA, International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex diagnostic criteria update: Recommendations of the 2012 Iinternational Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol 2013;49:243-54.
3. Sparagana SP, Roach ES. Tuberous sclerosis complex. Curr Opin Neurol 2000;13:115-9.
4. Curatolo P, Moavero R, Roberto D, Graziola F. Genotype/phenotype correlations in tuberous sclerosis complex. Semin Pediatr Neurol 2015;22:259-73.
5. 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;49:255-65.
6. Rosset C, Netto CB, Ashton-Prolla P. TSC1 and TSC2 gene mutations and their implications for treatment in Tuberous Sclerosis Complex: A review. Genet Mol Biol 2017;40:69-79.
7. Ogórek B, Hamieh L, Hulshof HM, Lasseter K, Klonowska K, Kuijf H, *et al.* TSC2 pathogenic variants are predictive of severe clinical manifestations in TSC infants: Results of the EPISTOP study. Genet Med 2020;22:1489-97.
8. Isaacs H Jr. Fetal and neonatal cardiac tumors. Pediatr Cardiol 2004;25:252-73.
9. Chao AS, Chao A, Wang TH, Chang YC, Chang YL, Hsieh CC, *et al.* Outcome of antenatally diagnosed cardiac rhabdomyoma: Case series and a meta-analysis. Ultrasound Obstet Gynecol 2008;31:289-95.
10. Harding CO, Pagon RA. Incidence of tuberous sclerosis in patients with cardiac rhabdomyoma. Am J Med Genet 1990;37:443-6.
11. Lyczkowski DA, Conant KD, Pulsifer MB, Jarrett DY, Grant PE, Kwiatkowski DJ, *et al.* Intrafamilial phenotypic variability in tuberous sclerosis complex. J Child Neurol 2007;22:1348-55.
12. Chen CP, Chang TY, Guo WY, Su YN, Chen YY, Chern SR, *et al.* Detection of maternal transmission of a splicing mutation in the TSC2 gene following prenatal diagnosis of fetal cardiac rhabdomyomas mimicking congenital cystic adenomatoid malformation of the lung and cerebral tubers and awareness of a family history of maternal epilepsy. Taiwan J Obstet Gynecol 2013;52:415-9.
13. Caylor RC, Grote L, Thiffault I, Farrow EG, Willig L, Soden S, *et al.* Incidental diagnosis of tuberous sclerosis complex by exome sequencing in three families with subclinical findings. Neurogenetics 2018;19:205-13.
14. Hulshof HM, Slot EM, Lequin M, Breuillard D, Boddaert N, Jozwiak S, *et al.* Fetal brain magnetic resonance imaging findings predict neurodevelopment in children with tuberous sclerosis complex. J Pediatr 2021;233:156-62.e2.