CASE REPORT

1. Maternal-Fetal Medicine Service, Instituto Nacional Materno Perinatal, Lima, Peru
2. Sedimedic Medical Diagnostics Training Center.
3. Neonatology Service, Instituto Nacional Materno Perinatal, Lima, Peru
a. OB/GYN physician
b. ORCID 0000-0001-6707-1063
c. Resident physician in Gynecology
d. ORCID 0009-0004-4990-3953
e. ORCID 0000-0002-9851-8419
f. ORCID 0009-0006-5548-2878
g. Medical Surgeon, ORCID 0000-0001-7393-5807
h. ORCID 0000-0002-1054-7398
i. Neonatology Resident, ORCID 0009-0001-8723-383X

Financing: Self-financed.

Ethical considerations: The authors declare that the procedures followed were in accordance with the ethical standards of the committee for responsible human experimentation and with the World Medical Association and the Declaration of Helsinki.

Conflicts of interest: The authors declare that they have no conflicts of interest of any kind.

Artificial intelligence: The authors declare that no artificial intelligence was used in the case study or in the preparation of the article.

Received: 4 January 2024

Accepted: 4 March 2024

Online publication: 30 March 2024

Corresponding author:
Dra. Rosa E. Vallenas Campos
Jr. Santa Rosa 941, Cercado de Lima, Instituto Nacional Materno Perinatal
996113439
medicinafetal.inmp@gmail.com

Cite as: Vallenas Campos RE, Eustaquio Briceño LA, Huertas Tacchino E, Ibáñez Rodriguez C, Sosa Paucar H , Castillo Urquiaga W, Torres Sotomayor KC. Prenatal diagnosis of tuberous sclerosis in association with rhabdomyomas: case report and discussion of the importance of molecular diagnosis. Re peru ginecol obstet. 2024;70(1). DOI: https://doi.org/10.31403/rpgo.v70i2610

Prenatal diagnosis of tuberous sclerosis in association with rhabdomyomas: case report and discussion of the importance of molecular diagnostics

Diagnóstico prenatal de esclerosis tuberosa en asociación con rabdomiomas: comunicación de caso y discusión de la importancia del diagnóstico molecular

Rosa E. Vallenas Campos[1,a,b], Luis A. Eustaquio Briceño[1,c,d], Erasmo Huertas Tacchino[1,a,e], Cecilia Ibáñez Rodriguez[1,a,f], Héctor Sosa Paucar[2,g], Walter Castillo Urquiaga[1,a,h], Katty C. Torres Sotomayor[3,i]

DOI: https://doi.org/10.31403/rpgo.v70i2610

ABSTRACT

Tuberous sclerosis complex (TSC) is characterized by the development of hamartomas in various tissues. We present the case of a 39-year-old female patient with a 24-week-old fetus with multiple rhabdomyomas in whom a prenatal molecular diagnosis of TSC was made. With the diagnosis confirmed, postnatal evaluation was extended, finding hypopigmented macules in the skin and multiple cortical and subependymal tubercles. In the family evaluation, the father presented cutaneous lesions and is under study to confirm TSC. At 6 months of age, the infant remains asymptomatic. The diagnosis of prenatal TSC has an impact on the prognosis of the patient and family. It improves the postnatal neurological prognosis, allows extending the search for the disease to parents and siblings, and provides tools for more accurate pregnancy counseling and family planning.

Key words: Rhabdomyoma, Tuberous sclerosis, Prenatal diagnosis, molecular

RESUMEN

El complejo esclerosis tuberosa (CET) se caracteriza por desarrollar hamartomas en diversos tejidos. Se presenta el caso de una paciente de 39 años con feto con múltiples rabdomiomas en quien se realizó diagnóstico prenatal molecular de CET. Con el diagnóstico confirmado se amplió la evaluación en el posnatal, encontrándose máculas hipopigmentadas en piel y múltiples túberes corticales y subependimarios. En la evaluación familiar, el padre presentó lesiones cutáneas y está en estudio para confirmar CET. A los 6 meses de vida, la lactante permanece asintomática. El diagnóstico de CET prenatal tiene un impacto en el pronóstico del paciente y su familia. Mejora el pronóstico neurológico posnatal, permite extender la búsqueda de la enfermedad a padres y hermanos, aporta herramientas para consejería más precisa del embarazo y planificación familiar.

Palabras clave. Rabdomioma, Esclerosis tuberosa, Diagnóstico prenatal, molecular

Introducción

Tuberous sclerosis complex (TSC) is an autosomal dominant multisystem syndrome of variable penetrance caused by mutations in the tumor suppressor genes TCS1 on chromosome 9q34 or TCS2 on chromosome 16p13.3 which encode hamartin and tuberin proteins, respectively. These mutations cause a disruption in the mammalian target of rapamycin (mTOR), favoring the development of hamartomas in organs such as the heart, brain, skin, kidneys, or eyes[1].

Primary cardiac tumors are extremely rare in children[2]. An incidence of 0.027% to 0.08% has been found in pediatric autopsies[2], while in fetal life some studies estimate an incidence of cardiac tumors between 0.05% to 0.14%[3]. About 90% of these tumors are benign[2]. Histologically, the most frequent benign tumors in the pediatric stage are rhabdomyomas (60%), composed of the characteristic 'spider' cells, followed by fibromas (12%), myxomas (10%), intracardiac teratomas (25%) and hemangiomas[4].

The present study reports a case of prenatal genetic diagnosis of tuberous sclerosis in the context of a fetus with multiple rhabdomyomas.

Clinical case

A 39-year-old female, gestation 3, para 2 with no medical or family history of importance, was initially evaluated at the primary care level. At 24 weeks 4 days she went to a private clinic for routine morphological ultrasound where they found 3 rhabdomyomas at the left intraventricular level, being the largest 9 x 4 mm (to rule out tuberous sclerosis) and referred the patient to the fetal medicine service of our institution.

The patient was evaluated at the Institute at 28 weeks, when the lesions were confirmed and there was evidence of an increase in number and size: 3 in the left ventricular cavity (the largest being 11 x 7 mm), 1 in the interventricular septum and 2 in the right atrial cavity (6 x 7 mm and 6 x 9 mm, respectively) (Figure 1). Fetal well-being was found to be preserved with biophysical profile 8/8 and normal fetal Doppler and myocardial performance index (MPI) 0.44, normal.

The probable syndromic association was explained to the patient and after counseling and consent, amniocentesis was performed at 29 weeks for molecular panel analysis of tuberous sclerosis complex and karyotype in amniotic fluid.

At 31 weeks the results of normal 46.XX karyotype were received, and control echocardiography was performed with an increase in the number of lesions and size, extending towards the right ventricle. Likewise, the myocardial performance index increased to 0.57, above the upper normal limit. There was no evidence of outflow or inflow tract obstruction, valvular regurgitation, or alteration of well-being tests.

In the control at 33 weeks, the rhabdomyomas increased in size generating decreased ventricular filling predominantly on the left side, with mild mitral regurgitation. In relation to the myocardial performance index, it was found at 0.6, progression to non-severe cardiac dysfunction.

At 35 weeks the result of the molecular panel in amniotic fluid reported a fetus with heterozygosity of the pathogenic variant NM_000548.4:C 1599+1G>A in the TSC2 gene, confirming tuberous sclerosis. The patient was hospitalized for uterine contractions and an emergency cesarean section was performed with the delivery of a female newborn weighing 2,595 g, Apgar 8 at 1 minute and 5 minutes, length 44.5 cm.

Physical examination of the neonate revealed hypopigmented macules on the skin (Figure 2) compatible with TSC, and echocardiography confirmed the prenatal findings. Evaluation by neurology and ophthalmology did not find hamartomas. She was discharged on the thirteenth day of life.

At one month follow-up, brain MRI showed multiple cortical and subependymal tubers (Figure 3). At 6 months of life, the infant remains clinically asymptomatic and with decreasing size of rhabdomyomas at control echocardiography. In the family evaluation, the infant's father presents cutaneous lesions of similar characteristics and is currently undergoing studies to confirm TSC.

Figure 1. (A) Ultrasound at 24 weeks: radbomyomas in the left ventricle. (B) 28 weeks: rhabdomyomas in the left ventricle and right atrium. (C) 31 weeks: rhabdomyomas in both ventricles and right atrium. The number of lesions and their size increase with gestational age.

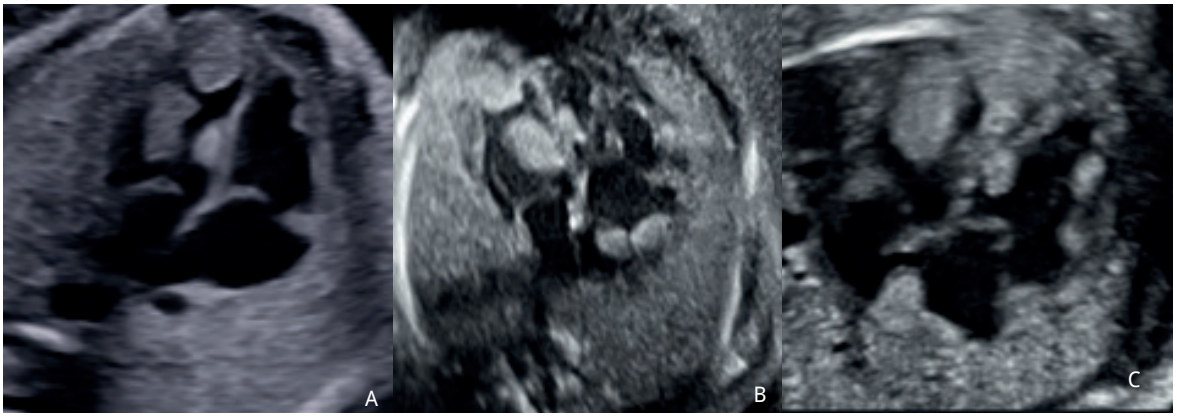
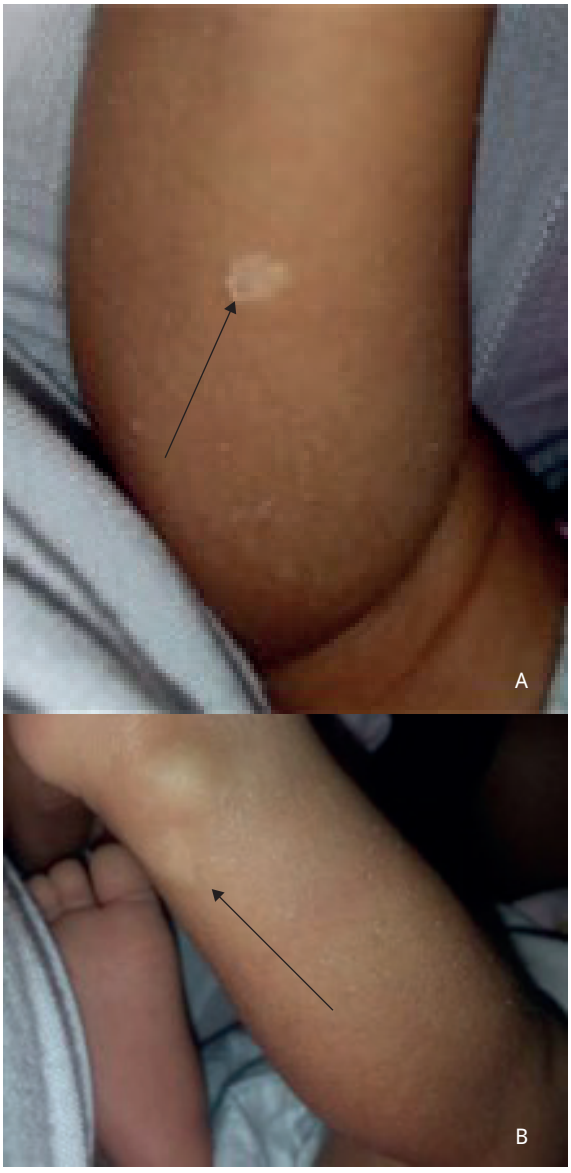


Figure 2. The arrows show hypopigmented macules on A. calf and B. posterior aspect of the ankle.



Discussion

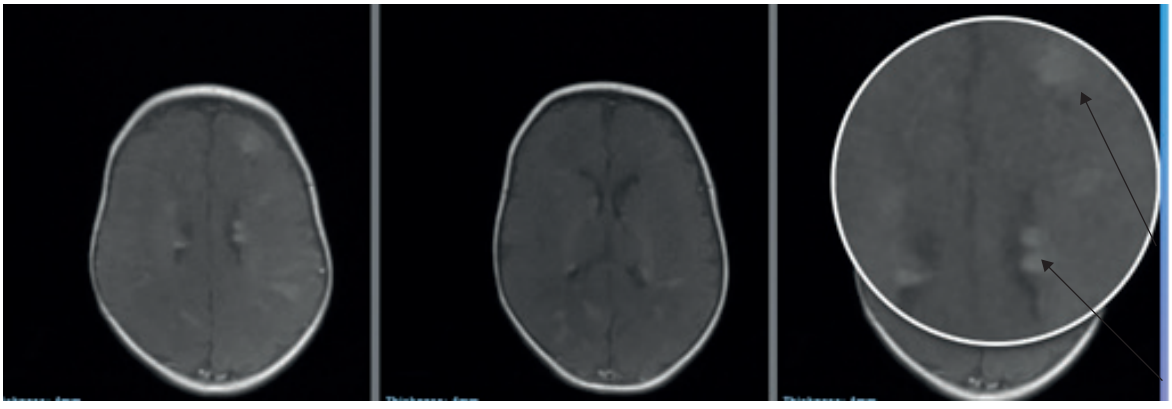
Evidence suggests that rhabdomyomas are actually myocardial hamartomas composed of cells resembling cardiac myocytes rather than true neoplasms[5]. They usually present as small, multiple tumors, mostly located in the ventricular myocardium, although cases of atrial involvement have also been described[6]. The site, number, and ventricular outflow tract obstruction of cardiac rhabdomyomas can be seen in the apical four-chamber view[7].

Fetal cardiac rhabdomyoma usually increases in size until birth, after which it gradually decreases and remits spontaneously in approximately half of the cases[6,8], coinciding with the evolution of the presented case. Although the clinical expression is wide, most of them are asymptomatic[9], so the clinical manifestations will depend on their size and intracardiac location and may cause adverse outcomes such as arrhythmias[6], hydrops fetalis, intrauterine death and sudden infant death[8,10].

Cardiac rhabdomyomas are present in 47% to 67% of people with tuberous sclerosis[11]. Therefore, it is essential that in fetal life, once a cardiac rhabdomyoma is identified, complementary studies are performed, especially molecular diagnosis in search of tuberous sclerosis.

The pediatric population with tuberous sclerosis has a probability of up to 90% of having neurological or neuropsychiatric manifestations, such as epilepsy, cognitive deficits and/or autism[12]. Fetal MRI in the third trimester of gestation may help in the prenatal diagnosis of tuberous sclerosis by allowing visualization of subependymal

Figure 3. MRI with multiple cortical and subcortical hyperintense foci in T1, poorly defined, scattered throughout the cerebral lobes and in the lateral ventricles.



nodules or cortical tubers that produce these postnatal manifestations[13,14]. However, the absence of brain lesions on fetal MRI does not rule out tuberous sclerosis[15].

Confirming the diagnosis of tuberous sclerosis with molecular genetics in the prenatal stage has an impact on the prognosis of the patient and his family. First, it provides tools for more accurate counseling in pregnancy, since the postnatal prognosis of an isolated rhabdomyoma is different from the prognosis of fetuses with rhabdomyomas in the context of TSC, because of their predisposition to have and develop more hamartomas postnatally and the neurological impact.

In addition, identifying the specific mutation responsible for tuberous sclerosis in the fetus facilitates information on predisposition to specific manifestations of TSC. For example, de novo mutation in TSC2 is a negative prognostic factor compared to mutation in TSC1[16]. Similarly, patients with large mutations affecting PKD1 polycystic kidney disease genes are more predisposed to develop subependymal giant cell astrocytomas (SEGAs) at an earlier age than other mutations in TSC2[1].

Likewise, as TSC is a condition of variable clinical expression, genetically confirming the diagnosis of tuberous sclerosis in a fetus with rhabdomyomas allows the search for the disease to be extended to parents and siblings, who may have TSC with nondiagnostic clinical manifestations. And it allows parents to make informed decisions about their reproductive future in case they also have the TCS1 or TCS2 mutation.

Additionally, prenatal diagnosis of TSC has been reported to improve neurological prognosis by decreasing the occurrence of epilepsy compared to those diagnosed postnatally, including significant improvement in cognitive, language and motor areas[12], especially in the population with tuberous sclerosis on the autism spectrum. Preventing epilepsy or improving seizure therapy in childhood would help mitigate the symptoms of autism in this population[17].

Inhibitors of mTOR are being studied for the prevention and treatment of epilepsy in children with TSC[18], which increases the importance of early diagnosis of tuberous sclerosis, especially in the asymptomatic population.

In view of the importance of prenatal diagnosis, in 2022 Xiao-Yan Yang et al. published a pilot study on the use of fetal DNA in maternal blood for TSC screening, with results similar to those obtained in invasive or confirmatory postnatal testing. However, further studies are still needed[19].

In conclusion, fetal or familial tuberous sclerosis should be suspected in the presence of fetal findings of cardiac rhabdomyomas, even if there are no obvious clinical manifestations in the family. The postnatal prognosis will depend on the location of the hamartomas and the degree of hemodynamic compromise and will be directly impacted by prenatal molecular diagnosis by allowing improved diagnosis, surveillance, and timely management of this genetic syndrome.

References

1. Dragoumi P, O'Callaghan F, Zafeiriou DI. Diagnosis of tuberous sclerosis complex in the fetus. Eur J Paediatr Neurol [Internet]. 2018;22(6):1027–34. doi:10.1016/j.ejpn.2018.08.005
2. Tzani A, Doulamis I, Mylonas K, Avgerinos D, Nasioudis D. Cardiac Tumors in Pediatric Patients: A Systematic Review. World J Pediatr Congenit Hear Surg. 2017;8(5):624–32. Doi: 10.1177/2150135117723904
3. Céspedes Almira Mariela, Suzarte Portal Judith, Mansito González Noel. Rabdomioma cardíaco. Rev Cubana Pediatr [Internet]. 2015;102-8. ISSN 1561-3119
4. Chía N, Fuentes G, Patiño E, Guillén A, Buendía A. Importancia del rabdomioma cardiaco en población pediátrica. Experiencia de 39 años. Serie de casos. Arch Cardiol Mex. 2020;91(1):84–92. Doi: 10.24875/ACM.19000381
5. Parato M, Nocco S, Alunni G, Becherini F, Conti S, Cucchini U, et al. Imaging of Cardiac Masses: An Updated Overview. J Cardiovasc Echogram. 2022;32(2):65–75. Doi: 10.4103/jcecho.jcecho_18_22
6. Ramírez M, Cuenca V, Zabala J, Conejo L. Remisión completa precoz de tumoraciones cardiacas múltiples sugestivas de rabdomiomas cardiacos. Rev Esp Cardiol. 2009;62(6):708–9. Doi: https://doi.org/10.1016/S0300-8932(09)71344-2
7. Yuan SM. Fetal Primary Cardiac Tumors During Perinatal Period. Pediatr Neonatol. 2017 Jun;58(3):205-10. doi: 10.1016/j.pedneo.2016.07.004
8. Yamamoto K, Maki Y, Sato Y, Tanaka H, Fukushima T, Ushijima J, Furukawa S, Sameshima H, Kataoka H. Multiple cardiac rhabdomyomas not associated with tuberous sclerosis in a dizygotic twins: a case report. J Med Case Rep. 2021 Jul 5;15(1):334. doi: 10.1186/s13256-021-02943-x
9. Lince R, Gomez C, Arteaga A, Montoya J, Vasquez L. Rabdomioma cardiaco como manifestación de esclerosis tuberosa. Presentación de dos casos y revisión de la literatura. Rev Colomb Cardiol. 2009;16(5):224–8. ISSN 0120-5633

10. Morales J, Espínola N, Caballero R, Brunner G, Uribe S. Rabdomioma cardiaco múltiple asociado a muerte intrauterina. Arch Cardiol Mex. 2011;81(3):217–20. ISSN 1405-9940

11. Northrup H, Koenig M, Pearson D, Sing K. Tuberous Sclerosis Complex [Internet]. Washington; 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1220/pdf/Bookshelf_NBK1220/

12. Wang X, Ding Y, Zhou Y, Yu L, Zhou S, Wang Y, et al. Prenatal diagnosis and intervention improve developmental outcomes and epilepsy prognosis in children with tuberous sclerosis complex. Dev Med Child Neurol. 2022;64(10):1230–6. Doi: 10.1111/dmcn.15265

13. Bekiesinska-Figatowska M, Sobieraj P, Pasieczna M, Szymkiewicz-Dangel J. Early Diagnosis of Tuberous Sclerosis Complex: Prenatal Diagnosis. AJNR Am J Neuroradiol. 2023 Sep;44(9):1070-6. doi: 10.3174/ajnr.A7952

14. Jin N, Wu Y, Meng Q, Luo Q. Prenatal diagnosis of tuberous sclerosis complex: Echocardiography, cranial magnetic resonance, and genetic testing of 40 cases with fetal cardiac tumors. Heliyon. 2023 Jun 2;9(6):e16980. doi: 10.1016/j.heliyon.2023.e16980

15. Santana EFM, Esteves AMF, Delorenzo DG, Hygino C, Werner H, Araujo Júnior E. Tuberous Sclerosis Complex: Prenatal Diagnosis Using Ultrasound and Magnetic Resonance Imaging-A Report of Two Cases. Indian J Radiol Imaging. 2022 Nov 24;33(1):113-6. doi: 10.1055/s-0042-1758196

16. Touraine R, Hauet Q, Harzallah I, Baruteau AE. Tuberous Sclerosis Complex: Genetic counselling and perinatal follow-up. Arch Pediatr. 2022 Dec;29(5S):5S3-5S7. doi: 10.1016/S0929-693X(22)00283-4

17. Curatolo P, Scheper M, Emberti Gialloreti L, Specchio N, Aronica E. Is tuberous sclerosis complex-associated autism a preventable and treatable disorder? World J Pediatr. 2024 Jan;20(1):40-53. doi: 10.1007/s12519-023-00762-2

18. Śmiałek D, Kotulska K, Duda A, Jóźwiak S. Effect of mTOR Inhibitors in Epilepsy Treatment in Children with Tuberous Sclerosis Complex Under 2 Years of Age. Neurol Ther. 2023;12(3):931–46. DOI: 10.1007/s40120-023-00476-7

19. Yang XY, Meng Y, Wang YY, Lu YP, Wang QH, You YQ, Xie XX, Bai L, Fang N, Zou LP. Noninvasive prenatal diagnosis based on cell-free DNA for tuberous sclerosis: A pilot study. Mol Genet Genomic Med. 2022 Jul;10(7):e1952. doi: 10.1002/mgg3.1952