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

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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 tüberes 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

INTRODUCCION

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:C1599+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.
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...
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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**


