

A Newborn with Multiple Cardiac Rhabdomyomas, Tuberous Sclerosis and Mosaic Turner Syndrome

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Abstract

Cardiac rhabdomyoma (CR) is a benign tumor and the most common type of cardiac tumors in children. They appear with multiple lesions and usually regress spontaneously. The great majority of cases are associated with Tuberous Sclerosis Complex (TSC).

Turner syndrome (TS) is an important cause of short stature in girls. More than one-half of all patients with TS have a mosaic chromosomal complement (45,X/46,XX).

We present a case of a newborn with prenatal ultrasound at 32 weeks' gestation showing fetal cardiac tumor. Postnatal echocardiography confirmed CR with multiple heart myomas. The baby later on, developed skin hypopigmentation and moderate motor delay. Mutational analysis of TSC1 and TSC2 genes using next-generation sequencing revealed that the proband has a likely pathogenic variant c.1283_1285delCCT, P.(Ser428del) in TSC2. Microarray detected mosaic Turner syndrome. This correlation with these two diseases as in our case, remains unclear and is not described in the literature.

Keywords: *Cardiac Rhabdomyoma; Tuberous Sclerosis Complex; Turner Syndrome*

Background

Cardiac rhabdomyoma (CR) is a benign tumor and the most common type of cardiac tumors in children. They appear with multiple lesions and usually regress spontaneously. The great majority of cases are associated with Tuberous Sclerosis Complex (TSC). Despite being pathologically benign and generally asymptomatic, the tumors size, number and location can produce a mass effect and lead to blood flow abnormalities or organ dysfunction (heart failure and arrhythmia).

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder with multisystem syndrome clinically characterized by dermatologic lesions (hypomelanotic macules, confetti skin lesions, facial angiofibromas, shagreen patches, fibrous cephalic plaques and unguis fibroma), neurologic disorders - mostly seizures and development delay, benign tumors including rhabdomyomas in the heart and subependymal giant cell astrocytomas in the brain. There are also increased risks for kidney tumors. The diagnosis of TSC is genetically determined by mutations in either the TSC1 or TSC2 gene [1-5].

Turner syndrome (TS) is an important cause of short stature in girls. More than one-half of all patients with TS have a mosaic chromosomal complement (45,X/46,XX).

The TS phenotype can be seen with a variety of structural abnormalities, such as isochromosomes, rings or terminal deletions [6].

Case Report

A newborn female with 40 weeks of gestational age was delivered by cesarean section. Birth weight: 3530g. Apgar 10/10/10. She was admitted in neonatal intensive care unit after birth for study, because her mother, a 37-year-old woman, gravida 3 para 2, with an uncomplicated pregnancy until prenatal ultrasound at 32 weeks' gestation showed fetal cardiac tumor. Postnatal echocardiography confirmed CR with multiple heart myomas in apex (17 mm x 30 mm), interventricular septum, bilateral ventricular wall, papillary muscle region (bigger one 5 mm x 10 mm) RVOT. Trivial mitral and tricuspid regurgitation. LVFS - 44% (Figure 1). The baby was clinically stable and asymptomatic with normal phenotype, no heart murmur or any dermatology signs. Mutational analysis of TSC1 and TSC2 genes using next-generation sequencing and variant confirmed by Sanger sequencing was performed and revealed that the proband has a likely pathogenic variant c.1283_1285delCCT, P.(Ser428del) in TSC2 (Figure 2).

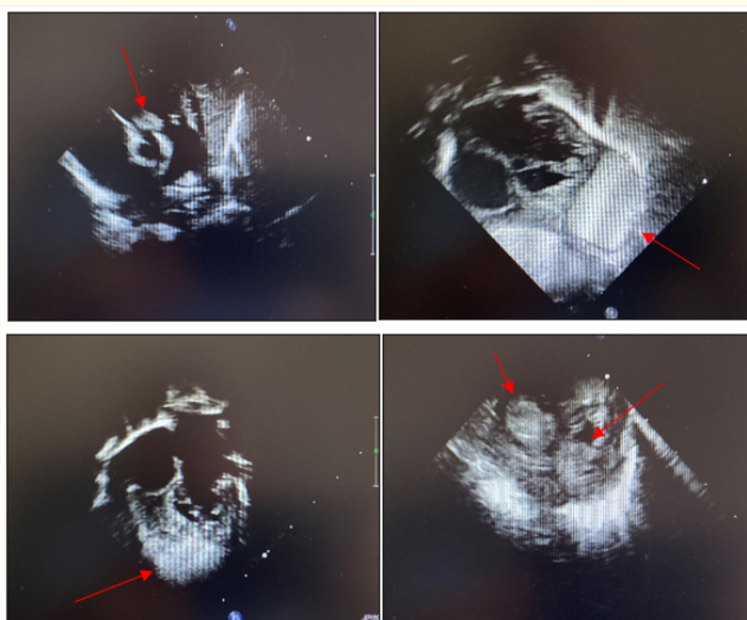


Figure 1: Multiple cardiac rhabdomyomas

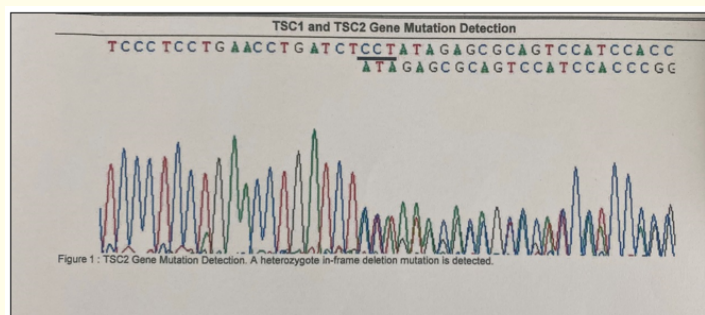


Figure 2: Pathogenic variant c.1283_1285delCCT, P.(Ser428del) in TSC2.

These findings support an association between a TSC2 and prenatally detected CR. The father and her sister are carriers and already has tuber in the brain.

We also performed microarray and found a copy loss of X chromosome in approximately 30% of cells. A mosaic monosomy X is associated with mosaic Turner syndrome.

Discussion

The association of CR and TSC is common and well described. Our case, the patient has also TS. To our knowledge, these 3 diseases together are not mentioned before in the literature. In a review of 33 cases of CR associated with TSC by Sciacca P, *et al.* in 2014, they detected 205 masses, mostly localized in interventricular septum, right ventricle and left ventricle. Only in 4 babies (12%) the presence of a mass caused a significant obstruction. A baby, with an enormous septal rhabdomyoma associated to multiple rhabdomyomas in both right and left ventricular walls died just after birth due to severe heart failure. During follow-up we observed a reduction of rhabdomyomas in terms of both number and size in all 32 surviving patients except in one child. Eight patients (24,2%) had an arrhythmia and in 2 of these cases rhabdomyomas led to Wolf-Parkinson-White Syndrome. For all patients the arrhythmia spontaneously totally disappeared or was reduced gradually. Regarding the association with tuberous sclerosis, they diagnosed tuberous sclerosis clinically in 31 babies (93,9%) [7].

In our case, the last heart ultrasound showed rhabdomyomas in the apex (10m x 3m) and left ventricle cavity (1 mm x 6 mm) with LVSE - 41%. Until now, ECG is normal with no clinical signs of heart failure and arrhythmia.

Concerning the TSC symptoms, our case around 19 months of age, developed hypopigmentation on the left chest near the nipple (7m x 3m) (Figure 3). No episodes of seizures. She showed moderate development delay with motor oral impaired and poor self-regulation and impulsive. The brain Magnetic Resonance was normal at 3 months of age but at 24 months, revealed a small triangular focus of intermediate signal intensity on T1W1 and heterogeneous hyper intensity on long TR sequences is found in the cortex of left posterior para-sagittal frontal lobe with slight enhancement after intravenous contrast, without significant change. A few striped enhancing images are found in the subcortical region inferiorly adjacent to the above cortical lesion and in the white matter of left parietal lobe (Figure 4).



Figure 3: Hypopigmentation on the left chest near the nipple (7m x 3m).

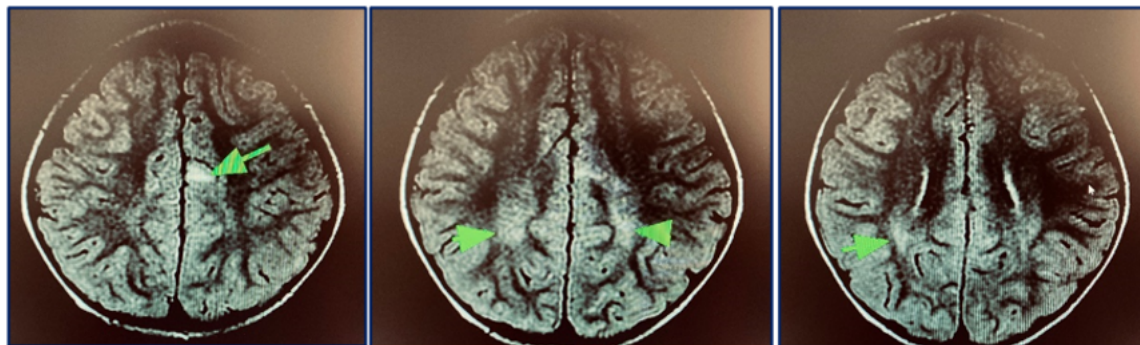


Figure 4: Cortical and subcortical tubers in the left frontoparietal lobes.

The patient has at 3 years of age: weight- 13.4 kg (P50) and height - 89 cm (P10). The mid parental height (MPH) is Percentile 25. The only change that we observed is short stature, if we compare with the MPH, but no others features of TS.

Hearing test and abdominal ultrasound revealed normal results.

We didn't start growth hormone therapy in this case for two reasons. First because the karyotype is mosaic and affected only 30% of cells and the final stature will not be so much affected. The other reason is the high risk of brain tumor cause by TSC.

Genetic counseling is recommended since the father and her sister are both carriers.

Conclusion

CR tumors has favorable prognosis because they frequently do not cause symptoms and they often regress in numbers and size. Due to frequent association with tuberous sclerosis complex and the resulting neurological impairment, the prognosis can result unfavorable. Turner syndrome and its correlation with these two diseases as in our case, remains unclear and is not found in the literature. This association is a pure coincidence or in all patients with CR with or without TSC, we need to exclude TS?

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