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Case Report

Neonatal Tuberous Sclerosis Complex with Large and Multiple Cardiac Rhabdomyomas

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ABSTRACT

The tuberous sclerosis complex (TSC) is most commonly diagnosed around the age of 5 years. Neonatal TSC is rare. The important neonatal manifestations include cardiac rhabdomyomas, central nervous system abnormalities, and skin manifestations. We describe a neonate suffering from the TSC with large and multiple cardiac rhabdomyomas. The largest rhabdomyoma measured 3.6 cm × 2 cm almost filling the right ventricle. The neonate did not have any symptoms. She continued to remain asymptomatic until 8 months' follow-up. ***(Iranian Heart Journal 2016; 17(3):51-54)***

Keywords: Cardiac rhabdomyoma ■ Neonate ■ Tuberous sclerosis

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The tuberous sclerosis complex (TSC) is an autosomal dominant neuroectodermal disorder affecting multiple organ systems.[1-5] The disorder is diagnosed in pediatric patients mostly at the age of 5 years or later. Neonatal TSC is rare, with an estimated incidence of 1 in 6000 to 12000 live births.[6] A 42-year retrospective review identified only 70 fetal/neonatal TSC patients.[2] Cardiac rhabdomyomas (CRs) and central nervous system (CNS) abnormalities are the distinct manifestations in fetal or neonatal cases. We describe a female neonate suffering from the TSC with predominant and distinct cardiac findings along with CNS and skin findings.

Case Report

A term (40 wk) appropriate for gestational age neonate born to a primigravida mother by cesarean section and uneventful perinatal history showed multiple hypopigmented ash leaf macules on the right hypochondrium (Fig. 1A), back, and right thigh (the largest measuring 1 cm × 2.5 cm). The antenatal scan at 22 weeks and fetal echocardiography at 28 weeks suggested a rhabdomyoma in the right ventricle (RV). She weighed 3240 g with a length of 50 cm and head circumferences of 35 cm. Her vital signs were normal. Cardiovascular system examination revealed a left-sided apex and a grade 3 systolic murmur

at the lower left sternal border. Other systemic examinations were normal.

Investigations revealed a normal complete blood count and serum creatinine of 0.6 mg/dL. Echocardiography showed multiple rhabdomyomas, with the largest measuring 3.6 cm × 2 cm almost filling the RV and causing right ventricular outflow tract (RVOT) obstruction. The pressure gradient across the RVOT was 27 mm Hg. Rhabdomyomas were also seen on the left ventricular (LV) wall, apex, and papillary muscle, and even extending to the pericardial cavity (Fig. 1B). LV systolic function was normal. There was a small patent ductus arteriosus with a left-to-right shunt. ECG was normal, and there was no conduction disturbance. Magnetic resonance imaging (MRI) of the brain showed well-defined, multiple (>10) T1 hyperintense subependymal nodules (Fig. 1C). Radial white matter bands in both frontal lobes were present in addition. There was no retinal hamartoma. Renal scans and hearing evaluation were normal. The baby was asymptomatic, feeding well, and was discharged on phenytoin. At 4 months' and 8 months' follow up, she was asymptomatic with normal growth and development and the same echocardiographic findings.

DISCUSSION

The TSC is characterized by pleomorphic features involving the brain, kidneys, heart, eyes, lungs, and skin.[1-4] A mutation in either the *TSC1* gene or the *TSC2* gene causes this autosomal dominant disorder. The expression of the disease varies substantially. A family history of the TSC is present in only 7–37% of newly diagnosed cases. About 60–70% of the cases occur sporadically.[6] In the present case, the mother had asymptomatic TSC.

Although the penetrance is complete in the TSC, the range of phenotypic changes such as age at onset, disease severity, and different signs and symptoms are highly variable. Hence, diagnostic clinical criteria including major and minor criteria have been proposed.[7] Two major or 1 major and 2 minor features confirm definite TSC. The fetal and neonatal manifestations include mainly cardiac, CNS, and skin manifestations. The present case had these characteristic manifestations and met the criteria for definite TSC. The major presenting findings in the fetus include CR(s) detected on routine antenatal sonography, arrhythmias, cerebral lesions, hydrops, and stillbirth, whereas the main signs initially in the neonate include respiratory distress, arrhythmias, murmurs, and cardiomegaly.[2]

CRs are the most common finding in the fetal/neonatal TSC (up to 79%). CRs can be detected by early prenatal scan or fetal echocardiography as in the present case. CRs can be multiple, more frequent on the left side and in the ventricles, and usually measure 5–15 mm in diameter. Multiple CRs can be the sole manifestations of perinatal TSC as well.[4] The neonatal echocardiography in the present case showed multiple CRs and the 1 in the RV was unusually large, even causing RVOT obstruction. CRs are usually asymptomatic and regress spontaneously, mostly within 6 years of life. Occasionally CRs may cause cardiac failure (2–4%) and arrhythmias (9%) depending on their size or location.[1,2] LVOT obstruction may lead to death.[1] In a review of 33 CR cases, Sciacca et al.[8] reported significant obstruction in 12%, arrhythmia in 24.2%, and death in 1 neonate. The neonate who died due to heart failure following birth had enormous septal CRs. Despite having unusually large and multiple CRs, the present case was asymptomatic until 8 months' follow-up. As CRs demonstrate benign pathological characteristics and tend to regress over time, a conservative approach is preferable and useful in most cases. The chance of spontaneous regression does not depend on the initial size, number, or location of rhabdomyomas. A spontaneous involution of CRs was observed in 30 out of 31 TSC cases in a study by Sciacca et al.[8] As

mutations in TSC genes result in increased mammalian target of rapamycin (mTOR) pathway activation leading to hamartomatous lesions of the TSC, therapy with mTOR inhibitors such as everolimus has been suggested. The beneficial effects of everolimus in a symptomatic neonate with inoperable multiple CRs were reported by Dogan V et al.[9] Everolimus at a dose of 0.25 mg twice per day, 2 days per week for 3 months—maintaining the therapeutic levels between 5 and 15 ng/mL—resulted in dramatic improvement in hemodynamic instability and significant reduction in the size of most of the CRs in that neonate. Surgical approach may only be considered when there is critical obstruction or dysrhythmias.

The 2nd characteristic finding in the fetal/neonatal TSC is subependymal nodules on brain MRI.[1,2,5,6] The present case had multiple subependymal nodules and frontal radial bands on brain MRI. The median subependymal nodules may vary (4–13/patient). A median of 13 nodules was reported by Baron and Barkovich[6] in neonates and young infants with the TSC. The usual percentage of patients with >10 subependymal nodules is 12%, but it could be as high as 57%.[6] The increased number of nodules may be associated with greater morbidity and mortality. White matter anomalies and subependymal giant cell astrocytomas (SGCA) are the other characteristic MRI findings. For the detection of these abnormalities on MRI, T1-weighted sequences in 2 orthogonal planes, section thickness ≤4 mm, and the gap as small as possible (0.5–1 mm) have been suggested.

Nearly all patients with the TSC have 1 or more of the skin lesions characteristic of the disorder. The present case had multiple ash leaf macules. Renal manifestations are rare in neonates.[2]

The TSC is a progressive disorder. Hence, a systematic follow-up of all cases is suggested; it may include ophthalmology evaluations, renal scans, electroencephalography, echocardiography, and brain MRI.[10] Some of the recent research works being done on the treatment of tuberous sclerosis using mTOR inhibitors such as sirolimus and everolimus are promising.[9,11] Early mTOR inhibition in patients with the TSC may prevent the development of the TSC lesions and alter the natural history of the disease. A significant decrease in brain tumor volume and prevention of facial angiofibromas and renal angiomyolipomas by using everolimus over a 24-month period without significant side effects have been reported.[11]

In conclusion, CRs of the TSC are mostly silent, despite being large and multiple in numbers. However, because of their rare but serious consequences, they warrant follow-up and may need an early treatment.

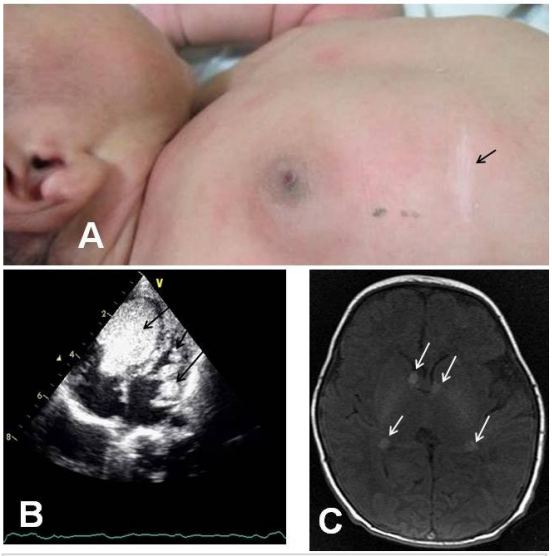

Figure 1.
A Hypopigmented ash leaf macule on the right hypochondrium.
B Echocardiography shows multiple rhabdomyomas.
C Multiple subependymal nodules in brain magnetic resonance imaging.

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