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TSC1 mutation in neonatal tuberous sclerosis: A case report

Jiwon Moon[1]; Hong Yeon Lee[1]; Jisook Yim[2]; Myungshin Kim[2]; In Yang Park[3]; Ji Hye Jo[1]*

[1]Department of Obstetrics and Gynecology, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea.

[2]Department of Laboratory Medicine, College of Medicine, The Catholic University of Korea, Republic of Korea.

[2]Catholic Genetic Laboratory Center, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea.

[3]Department of Obsterics and Gynecology, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea.

***Corresponding Author: Ji Hye Jo, MD**

Department of Obstetrics and Gynecology, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea Republic of Korea.

Tel: +82-3-779-1613, Fax: +82-3-779-1614;

Email: jjjihhh.jo@gmail.com

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Abstract

A 32-year old woman, gravida 1 para 0, was referred to Seoul St. Mary's Hospital for fetal cardiac mass by ultrasound at 38 weeks of gestation from a local obstetric office. Detailed fetal echocardiogram was performed and the presence of multiple cardiac tumors was observed, suggesting rhabdomyoma. After birth, fetal echocardiography and genetic screening were performed. A targeted Sanger sequencing analysis was performed for TSC1 and TSC2 genes. Molecular analyses revealed a heterozygous gene variant with a novel frame shift mutation in TSC1, confirming the diagnosis of Tuberous Sclerosis (TSC). A segregation study of the causal mutation was performed by Sanger sequencing for both parents, revealing no mutation in either parent. Thus, the novel frameshift mutation occurred de novo. For fetuses with suspected cardiac rhabdomyoma identified by ultrasound, perinatal genetic testing for TSC should be performed for both the fetus and family members for early detection, early diagnosis, and better prognosis. Early diagnosis of TSC can provide greater opportunities for infants to obtain timely neonatal treatment and better outcome.

Keywords: Tuberous sclerosis; Rhabdomyoma; Fetal ultrasonography; TSC1 protein.

Introduction

Tuberous Sclerosis Complex (TSC) is an autosomal dominant multisystemic neurocutaneous disorder characterized by non-cancerous tumors in various organ systems of the body [1]. The brain, skin, heart, kidney, lungs, and eyes are frequently affected. Although classic manifestations of TSC include mental retardation, epilepsy, and sebaceous adenoma, signs, symptoms, and severity of this disorder vary from one patient to another due to specific organs involved. The incidence of TSC has been estimated to be 1 in 6,000 to 10,000 live births [2].

TSC is caused by mutations of tumor suppressor gene *TSC1* or *TSC2. TSC1* gene is located on chromosome 9q34. It encodes a growth inhibitory protein named hamartin. *TSC2* is located on chromosome 16p13.3. It provides instructions for producing tuberin [3,4]. Hamartin and tuberin are known to suppress cell growth by inhibiting the activation of mTOR (mammalian target of rapamycin), a serine/threonine protein kinase that reconfigures cellular metabolism and regulates translation, cytokine responses, antigen presentation, macrophage polarization and cell migration [5,6]. In TSC patients, mTOR is dysregulated due to changes of hamartin or tuberin, leading to abnormal differ-

entiation and development of cells. In this report, we present a newborn with multiple cardiac rhabdomyoma who showed a de novo mutation in *TSC1* gene.

Case presentation

A 32-year old woman, gravida 1 para 0, was referred to Seoul St. Mary's Hospital for a fetal cardiac mass by ultrasound at 38 weeks of gestation from a local obstetric office.The mother had no history of drug ingestion, alcohol use, or smoking during pregnancy. There was no familial history of genetic or neurodevelopmental disorders. There was no other antenatal problem.

Detailed fetal echocardiogram was performed and multiple cardiac tumors (one in right atrium, two in right ventricle, and two in left ventricle, Figure 1) were observed, suggesting rhabdomyoma. Ventricular function seemed to be normal. Our multidisciplinary team planned to perform cardiac ultrasound after birth.

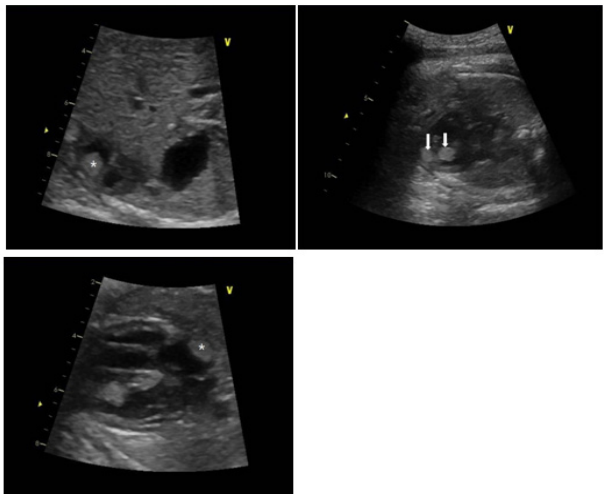

Figure 1: Fetal echocardiogram showing multiple cardiac tumors. (A) A 0.7 cm mass at the apex of right ventricle (asterisk), (B) Two masses with sizes of 0.8 cm and 0.4 cm in the left ventricle (arrows). These masses are attached to the septum and connected to each other. (C) A 0.8 cm mass in the right atrium (asterisk).

She delivered a female infant at 39 weeks and 3 days of gestation through an emergency cesarean section owing to non-reassuring fetal status. The infant weighted 3590 g. Her 1-minute and 5-minute Apgar scores were 6 and 9, respectively. After birth, the infant was admitted to the neonatal intensive care unit for thorough examination. One day after birth, fetal echocardiography and genetic screening were performed.

Cardiac ultrasound

Cardiac ultrasound revealed the presence of at least five cardiac tumors in the fetus. One elliptical mass was localized in the right atrium. The mass did not interfere with Superior Vena Cava (SVC) or Inferior Vena Cava (IVC) flow. Two masses with sizes of 0.7 cm and 0.6 cm were found in the apex of right ventricle. Two masses of 0.8 cm and 0.4 cm were detected in the left ventricle. These masses were attached to the septum and connected to each other. These observations strongly suggested multiple cardiac rhabdomyomas. There was no obstruction of Left Ventricular Outflow Tract (LVOT) or Right Ventricular Outflow Tract (RVOT). The ventricular function was observed to be normal.

Genetic screening

Definite features of TSC strongly suggested the presence of a genetic modification in one of the two genes, TSC1 and TSC2, commonly associated with the disease. A targeted Sanger sequencing analysis was performed for TSC1 and TSC2 genes. Informed consent was obtained from the patient's parents before genetic analyses were conducted. Resutls of molecular analyses revealed a heterozygous c.2643dup variant (NM_000368.4) that led to a p.(Ala882Serfs*22) novel frameshift mutation in TSC1, thus confirming the diagnosis of TSC (Figure 2). A segregation study of the causal mutation was performed by Sanger sequencing for both parents, revealing no mutation in either parent (Figure 2). Thus, the mutation had a de novo origin.

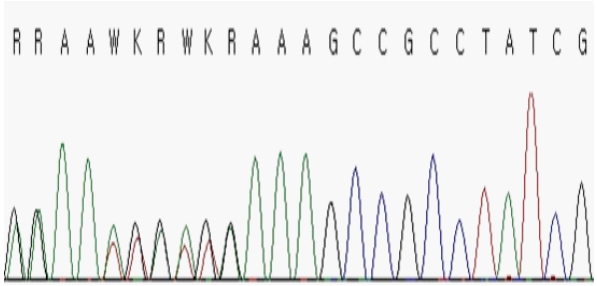

Figure 2: A segregation study was performed by Sanger sequencing and results suggested TSC.

After detecting TSC1 mutation, detailed examination was performed to find other manifestations associated with TSC. Her brain MRI showed a few small, T1W high SI nodular lesions in both subependymal zones, suggesting tuberous sclerosis involvement and subependymal hamartomas (Figure 3). Whole body spine and extremities X-ray revealed no significant bony abnormality. Other examinations including Visual Evoked Potentials (VEP)/Auditory Evoked Potentials (AEP) and kidney sonography were also normal. The infant is followed up right now on an outpatient basis.

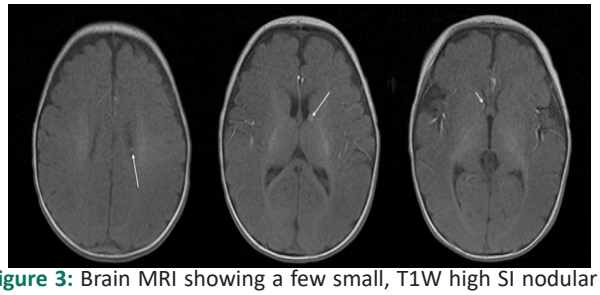

Figure 3: Brain MRI showing a few small, T1W high SI nodular lesions (arrows) suggesting subependymal hamartomas.

Discussion

TSC is a multisystem disorder with a highly variable phenotype characterized by hamartomas in multiple organ systems including the brain, heart, skin, lungs, and kidneys. TSC is known to be caused by autosomal dominant mutation of TSC1 located on chromosome 9q34 or TSC2 gene located on chromosome 16p13.3. TSC1 and TSC2 gene mutations account for 31% and 67% of TSC mutations, respectively. These variants often occur de novo, attributing 70-80% of all TSC.

The 2012 International Tuberous Sclerosis Complex Consensus Recommendations have added genetic diagnosis to the di-

agnostic criteria for TSC and pointed out that genetic diagnosis can be used as an independent diagnostic criteria [7]. Primary cardiac tumor is rare with a prevalence of 0.25% in infants and young children. Cardiac rhabdomyoma is the most common cardiac tumor, accounting for 60% of such cases. Fetal cardiac rhabdomyoma is usually detected after 20 weeks of gestation. It frequently occurs in the ventricular cavity. It is well known that cardiac rhabdomyoma and TSC are strongly related regardless of the number of tumors. With the development of prenatal ultrasound technology, an increasing number of fetal cardiac tumors have been reported in recent years [8,9].

In our case, the fetus showed rhabdomyoma prenatal features that continuously existed after birth. We immediately performed a targeted Sanger sequencing analysis to rule out TSC. Early detection of de novo mutation can lead to monitoring of TSC for the infant. The patient is followed up currently without other developmental disabilities.

Conclusion

In conclusion, we present this case to alert the importance of antenatal diagnosis of TSC by fetal cardiac rhabdomyomas. For fetuses with suspected cardiac rhabdomyoma identified by ultrasound, perinatal genetic testing for TSC is recommended for both fetus and family members for early detection, early diagnosis, and better prognosis. Early diagnosis of TSC can provide greater opportunities for infants to obtain early neonatal treatment and better outcome.

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