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Research Letter

Prenatal diagnosis of tuberous sclerosis complex using fetal ultrasonography and magnetic resonance imaging and genetic testing

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Dear Editor,

Tuberous sclerosis complex (TSC) was first described by von Recklinghausen in 1862 [1]. Tuberous sclerosis is also called TSC because of its diverse clinical manifestations. TSC is extremely variable and unpredictable in terms of disease phenotypes and clinical presentations. Its clinical features are a principal means of diagnosis [1]. TSC is an autosomal dominant disorder that can be associated with multiple major and minor disorders [2]. The estimated incidence of TSC is about 1 in 10,000 person/year with a prevalence between 1 in 6800–17,300 person/year [3]. Cardiac rhabdomyomas are associated with certain genetic disorders, particularly tuberous sclerosis, which account for two-thirds of cases of TSC. Fetal cardiac rhabdomyoma is the earliest clinical sign of tuberous sclerosis, which can be detected in the uterus. Mammalian target of rapamycin (mTOR) inhibitor therapy for TSC may be a treatment option. We describe a case of TSC and focus on the prenatal diagnosis and management of TSC.

A 24-year-old woman (gravida 2, para 0) presented to our outpatient obstetric department at 32 weeks of gestation. She was healthy without a remarkable family medical history. The fetus was diagnosed as having multiple cardiac rhabdomyomas, which were found on an ultrasonography at a local obstetric clinic (Fig. 1). Fetal MRI was subsequently performed, and we observed several subependymal nodules in both ventricles (Fig. 2). A diagnosis of TSC was confirmed by fetal genetic testing. Results of the blood genetic tests showed normal maternal *TSC1* and *TSC2* genes. The paternal genetic testing showed a heterozygote of *TSC1* at codon 654, which belonged to the normal variation. Cytogenetic analysis of the amniotic fluid from the fetus focused on the *TSC1* and *TSC2* genes, and both genes had a heterozygote (*TSC1*: c.1960C > G, p. Gln654Glu; *TSC2*: c.2713C > T, p. Arg905Trp). The heterozygote of *TSC1* at codon 654 was inherited paternally, and the heterozygote of *TSC2* at codon 905 belonged to the de novo mutation. After consulting with the medical ethics committee in our hospital, termination of the pregnancy is indicated due to a high risk of neonatal seizure and mental retardation.

Disease progression and the development of TSC persist over the life span of affected individuals. An accurate diagnosis is necessary to determine appropriate medical surveillance and treatment [1]. Autosomal dominant inheritances of TSC account for one-third of cases, and de novo mutations account for the remaining two-thirds of cases [4]. About 85% of patients with definite TSC can be attributed to mutations of the *TSC1* and *TSC2* genes, with incidence rates of 31% and 69% for *TSC1* and *TSC2* mutations, respectively [5]. Mutations occur in either the *TSC1* gene on chromosome 9q34, which encodes hamartin, or the *TSC2* gene on chromosome 16p13.3, which encodes tuberin [6]. Hamartin and tuberin are specific proteins that interact as a tumor suppressor complex. The tumor suppressor complex TSC1/TSC2 transfers the inhibitory signal to Ras homolog enriched in brain, and it subsequently inhibits activation of the mTOR complex 1 (mTORC1). Once *TSC1* or *TSC2* is affected, uncontrolled cell growth occurs, which facilitates duplication and protein synthesis. We found disagreements in the literature regarding the specific relationships between the genotype and phenotype in TSC genes. It is generally considered that mutations in the *TSC2* gene are more severe in the clinical manifestations of TSC [7].

The clinical diagnosis of TSC is based on the presence of major and minor features, as defined by the Tuberous Sclerosis Consensus Conference [1]. A definite diagnosis of TSC requires the presence of two major features or one major feature with two or more minor features. A possible diagnosis means either observing one major feature or two or more minor features. Major features include hypomelanotic macules, angiofibromas or fibrous cephalic plaques, ungual fibromas, shagreen patches, multiple retinal hamartomas, cortical tubers, subependymal nodules, subependymal giant cell astrocytomas, cardiac rhabdomyomas, lymphangioleiomyomatosis, and angiomyolipomas. Minor features include confetti-like skin lesions, dental enamel pits, intraoral fibromas, retinal achromic patches, multiple renal cysts, and nonrenal hamartomas. Major

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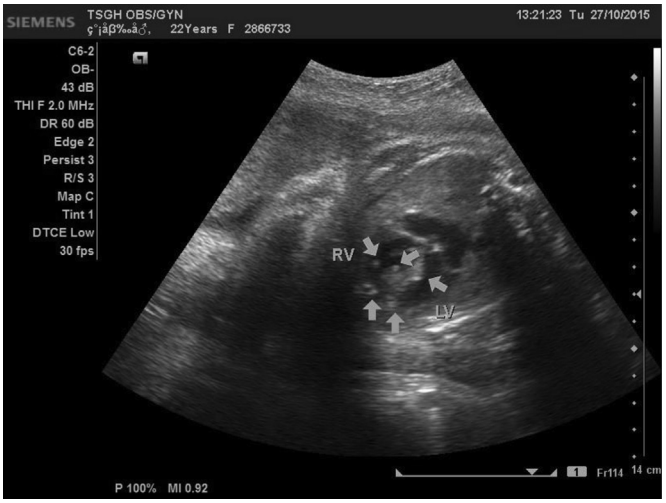

Fig. 1. Fetal ultrasonography showing multiple nodules in the myocardium (White arrows), compatible with cardiac rhabdomyomas.

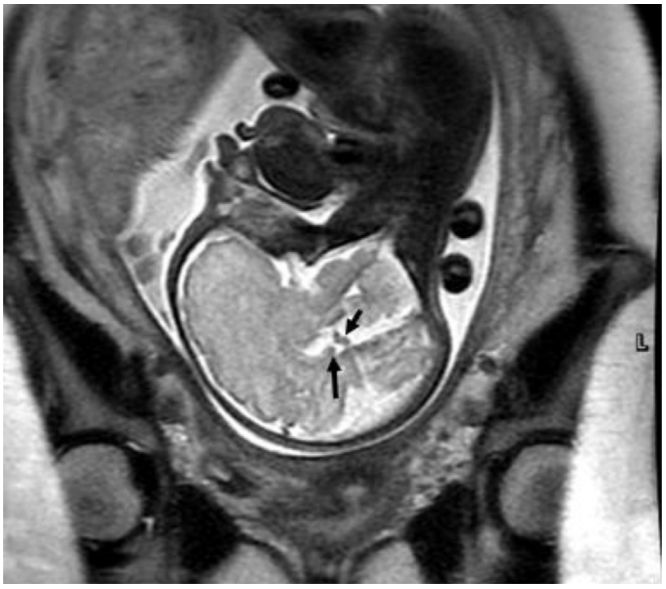

Fig. 2. T2-weighted magnetic resonance image of the fetal head in the sagittal view showing several subependymal nodules in both ventricles (Black arrows).

features that can be detected on prenatal imaging include cardiac rhabdomyomas, cortical tubers, subependymal nodules, and renal angiomyolipomas.

Cardiac rhabdomyomas always present as multiple nodules, and they less commonly present as a unique, well-defined, round, higher echogenic than normal myocardium and a homogeneous mass with various sizes in multiple myocardial spaces on a regular ultrasonographic survey in the late trimester. An ultrasonographic examination is the best choice for detecting fetal cardiac space-occupying lesions because it is non-invasive, free of radiation exposure, easy to repeat, and it has a high diagnostic rate. When using ultrasonography for diagnosing fetal cardiac tumors, it may be difficult to identify differences between strong hyperechoic spots in the ventricular myocardium and some normal cardiac structures such as the papillary muscle [8]. A detailed series of sonograms should be obtained and archived, because physicians can compare them to prior examinations, which may ultimately lead to a rapid diagnosis.

Central nervous system lesions may result in intractable epilepsy, learning disabilities, mental retardation, and developmental and behavioral disorders such as autism. Epilepsy is the most common neurological disorder, which occurs in up to 90% of patients, and it usually presents in the first year postnatally [9]. The early onset of epilepsy may present as infantile spasms, and in patients with TSC, it is always highly associated with motor and cognitive disorders in the future. A current review of the literature suggests that the early treatment of epilepsy can significantly improve developmental and cognitive outcomes [10].

mTOR is a kinase that regulates protein synthesis, cell growth, and metabolism. There are two different multiprotein complexes of mTOR: mTORC1 and mTOR complex 2. mTORC1 controls cell growth and protein synthesis, which is activated by growth factors, hormones, and nutrients [11]. As tumor suppressors, hamartin and tuberin transmit a negative signal to inhibit the mTOR pathway. Mutations of the *TSC1* or *TSC2* gene lose the ability to transmit a negative signal to the mTOR signaling pathway, and this leads to rapid and unlimited cell growth. Agents that act as mTOR inhibitors may be effective for controlling cell growth. Everolimus is the first and most commonly used mTOR inhibitor, which is derived from sirolimus (rapamycin) [12]. A long-term study that assessed the use of everolimus to treat subependymal giant cell astrocytomas and control seizures showed a significant efficacy in terms of reducing the tumor size and frequency of seizure attacks. This study also indicated that the most common adverse event is an upper respiratory tract infection (67.9%), followed by sinusitis (42.9%), cellulitis (32.1%), otitis media (32.1%), stomatitis (28.6%), and gastroenteritis (25.0%) [13]. Adverse events were mostly mild or moderate but occasionally life-threatening. Trelinska et al. published the first report of two young patients with TSC with bacterial sepsis, including one patient who died of a deep immunodeficiency during everolimus treatment [14].

We think that TSC affects the multi-organ system in a patient with this disease. Current medical therapy with everolimus may be effective for tumor reduction and seizure control. However, further systematic research is required to determine the long-lasting effects of treatment with everolimus.

Conflict of interest

The authors declare no conflict of interest.

References

[1] Northrup H, Krueger DA. International tuberous sclerosis complex Consensus group. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 international tuberous sclerosis complex Consensus conference. Pediatr Neurol 2013;49:243–54.
[2] Lee KA, Won HS, Shim JY, Lee PR, Kim A. Molecular genetic, cardiac and neurodevelopmental findings in cases of prenatally diagnosed rhabdomyoma associated with tuberous sclerosis complex. Ultrasound Obstet Gynecol 2013;41:306–11.
[3] Yates JR. Tuberous sclerosis. Eur J Hum Genet 2006;14:1065–73.
[4] Sancak O, Nellist M, Goedbloed M, Elfferich P, Wouters C, Maat-Kievit A, et al. Mutational analysis of the TSC1 and TSC2 genes in a diagnostic setting: genotype–phenotype correlations and comparison of diagnostic DNA techniques in Tuberous Sclerosis Complex. Eur J Hum Genet 2005;13:731–41.
[5] Chen CP, Chang TY, Guo WY, Su YN, Chen YY, Chern SR, et al. Detection of maternal transmission of a splicing mutation in the TSC2 gene following prenatal diagnosis of fetal cardiac rhabdomyomas mimicking congenital cystic adenomatoid malformation of the lung and cerebral tubers and awareness of a family history of maternal epilepsy. Taiwan J Obstet Gynecol 2013;52:415–9.
[6] Crino PB, Nathanson KL, Henske EP. The tuberous sclerosis complex. N Engl J Med 2006;355:1345–56.
[7] Hung CC, Su YN, Chien SC, Liou HH, Chen CC, Chen PC, et al. Molecular and clinical analyses of 84 patients with tuberous sclerosis complex. BMC Med Genet 2006;7:72.
[8] Yu Q, Zeng W, Zhou A, Zhu W, Liu J. Clinical value of prenatal echocardiographic examination in the diagnosis of fetal cardiac tumors. Oncol Lett 2016;11:1555–9.

[9] Mlczoch E, Hanslik A, Luckner D, Kitzmüller E, Prayer D, Michel-Behnke I. Prenatal diagnosis of giant cardiac rhabdomyoma in tuberous sclerosis complex: a new therapeutic option with everolimus. Ultrasound Obstet Gynecol 2015;45:618–21.
[10] Jozwiak S, Kotulska K, Domańska-Pakieła D, Lojszczyk B, Syczewska M, Chmielewski D, et al. Antiepileptic treatment before the onset of seizures reduces epilepsy severity and risk of mental retardation in infants with tuberous sclerosis complex. Eur J Paediatr Neurol 2011;15:424–31.
[11] Tran LH, Zupanc ML. Long-term everolimus treatment in individuals with tuberous sclerosis complex: a review of the current literature. Pediatr Neurol 2015;53:23–30.
[12] Lebwohl D, Thomas G, Lane HA, O'Reilly T, Escudier B, Yao JC, et al. Research and innovation in the development of everolimus for oncology. Expert Opin Drug Discov 2011;6:323–38.
[13] Franz DN, Agricola K, Mays M, Tudor C, Care MM, Holland-Bouley K, et al. Everolimus for subependymal giant cell astrocytoma: 5-year final analysis. Ann Neurol 2015;78:929–38.
[14] Trelinska J, Dachowska I, Kotulska K, Fendler W, Jozwiak S, Mlynarski W. Complications of mammalian target of rapamycin inhibitor anticancer treatment among patients with tuberous sclerosis complex are common and occasionally life-threatening. Anti Canc Drugs 2015;26:437–42.