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증 례

EPG5 유전자 변이가 확인된 Vici 증후군 1례

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Vici Syndrome with Novel Compound Heterozygous Mutations in *EPG5*

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Vici syndrome is a rare, autosomal recessive multisystem disorder characterized by agenesis of the corpus callosum, cataracts, cardiomyopathy, hypopigmentation, immunodeficiency, and delayed development. We report the case of a 3-year-old boy diagnosed with Vici syndrome. He initially presented with hypotonia and sucking problem. Whole-exome sequencing identified novel compound heterozygous mutations, namely c.2254C>T (p.Gln752Ter) and c.5511-5518+2 del TATGCAAAGT in the *EPG5* gene. The diagnostic challenges can be attributed to the diverse clinical manifestations. Thus, whole-exome sequencing is a useful diagnostic tool for the genetically and clinically heterogeneous Vici syndrome. This is the first Korean report of a patient with Vici syndrome.

Key words: Vici syndrome, *EPG5* gene, Hypotonia, Cataract, Cardiomyopathy, Autophagy, Development delay, Hypopigmentation

Introduction

Vici syndrome [MIM242840] is a rare, autosomal recessive, multi-system disorder. According to Cullep et al., mutations in the Ectopic P-Granules Autophagy Protein 5 Homolog (*EPG5*) gene in chromosome 18q12.3 play a causative role in Vici syndrome[1,3-7]. *EPG5* encodes a key autophagy regulator involved in the formation of autolysosomes. *EPG5* mutations cause Vici syndrome due to defects in autophagolysosome fusion. Doinisi Vici et al. first described two cases of Vici syndrome in 1988[1-3,5-7]. To date, approximately 80 cases have been reported worldwide and about 50 cases of genetic confirmation have been published [3,8]. The clinical presentation of Vici syndrome is quite diverse because it affects multiple organs. The typical phenotype includes severe developmental delay, agenesis of the corpus callosum, cardiomyopathy, cataract, hypotonia, generalized hypopigmentation and variable immunodeficiency[1-7].

We report the case of a 3-year-old boy with Vici syndrome. He had novel compound heterozygous mutations in *EPG5*. The findings were consistent with the aforementioned symptoms.

Case Report

The patient was the first child born to healthy non-consanguineous Korean parents. Prenatal ultrasound showed agenesis of the corpus callosum

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and ventriculomegaly. He was born via vaginal delivery at 38 weeks of gestation, following a normal pregnancy. His birth weight was 2.6 kg. After birth, he had been treated in the newborn intensive care unit for a few weeks due to neonatal apnea. He was referred to our hospital at the age of 2 months to evaluate metabolic disorders for generalized hypotonia, oculocutaneous hypopigmentation, poor sucking and failure to thrive. His weight, height, and head circumference were 4 kg (<3rd percentile), 57 cm (22–50th percentile), and 35 cm (<3rd percentile), respectively. He revealed unusual features with light hair color, oculocutaneous hypopigmentation and micrognathia on clinical examination. The levels of creatinine kinase and lactate dehydrogenase were high, at 850 U/L (35–232 U/L) and 1,006 IU/L (225–455 IU/L), despite normal metabolic screening except for a slight increase in serum alanine in initial laboratory test. Alanine transaminase (ALT) and aspartate aminotransferase (AST) were slightly elevated at 113 U/L (10–45 U/L) and 76U/L (10–45 U/L), respectively. The thyroid function and rental function tests were normal. The total lymphocyte and neutrophil count, leukocyte morphology, and serum immunoglobulin levels were normal for his age except for a slightly deceased CD4 count at 326/mcL (12.3%) (25.2–52.8%) with a low CD4/CD8 ratio.

Brain magnetic resonance imaging showed corpus callosum agenesis and ventriculomegaly (Fig. 1). He developed seizures at 9 months. Furthermore, electroencephalography showed bilateral epileptic activity on multifocal areas. Ophthalmological examination revealed bilateral nuclear and anterior polar cataracts, bilateral optic nerve atrophy, and mild fundus hypopigmentation. Following the diagnosis of severe bilateral cataracts, he underwent a cataract surgery. Cardiac assessment resulted in identification of hypertrophic cardiomyopathy.

Ultrasound abdomen showed mild increased hepatic echogenicity without associated liver dysfunction. In addition, renal involvement including hydronephrosis was not found. He did not pass a neonatal hearing test using a diagnostic auditory brainstem response test on one ear, but no further evaluation was performed. Furthermore, his feeding and respiratory condition deteriorated. He was hospitalized repeatedly for recurrent respiratory infections, aspiration pneumonia with swallowing difficulty. He was admitted to a pediatric intensive care unit for aspiration pneumonia followed by treatment requiring an invasive mechanical ventilator, and eventually underwent gastrostomy and tracheostomy at age of 6 months.

During follow–up, he presented with progressively severe delays in psychomotor development and severe growth impairment, including progressive microcephaly. Thus, we performed a muscle biopsy of the left thigh showed moderate to marked variation in myofiber size with scattered fibrosis. And we performed whole–exome sequ-

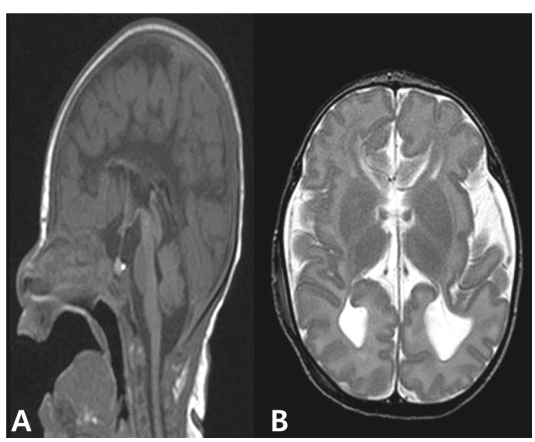

Fig. 1. Brain magnetic resonance imaging (MRI) of the patient with Vici syndrome at the age of 2 months. Sagittal T1 MRI showing agenesis of the corpus callosum (A). Axial T2 MRI showing ventriculomegaly and cerebral atrophy (B).

encing (WES) in trios (proband, mother, and father) to determine the cause of his clinical manifestation. Moreover, we mapped the sequenced reads to the human reference genome (UCSC hg 19). A targeted gene enrichment method was used to construct libraries for subsequent determination of sequences using an NGS method with HiSeq2000 (Illumina, San Deigo, CA, USA). The detected variants were classified as variant of uncertain significance according to the guidelines set by the American College of Medical Genetics and Genomics 2015[10]. The variants of the *EPG5* gene (NM_020964.2) c.2254C>T (p. Gln752Ter) and (NM_020964.2) c.5511–5518+2 del TATG CAAAGT were confirmed by sanger sequencing that each asymptomatic parent has one variant (Fig. 2). This was the first case of Vici syndrome in Korea with novel compound heterozygous mutations in *EPG5*.

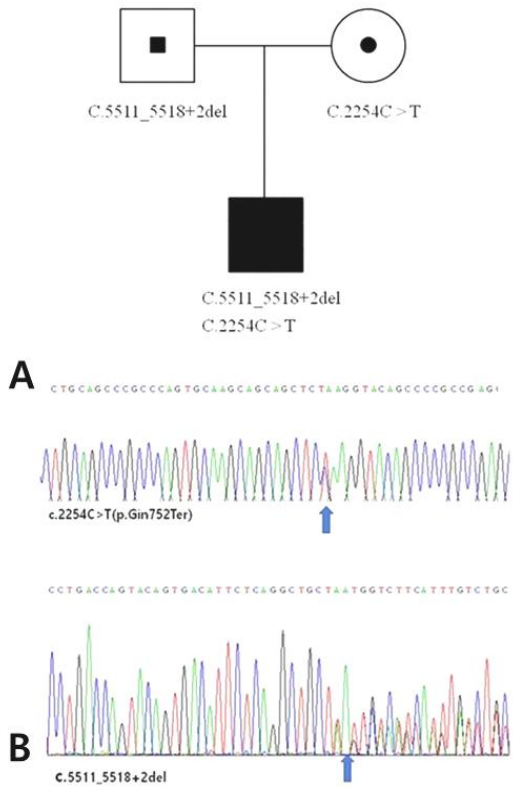

Fig. 2. Pedigree of the patient with results of familial mutation analysis. (A) Pedigree of the patient's family (B) The novel variants identified in *EPG5* (c.5511–5518+2 del TATGCAAAGT and c.2254 C>T) using whole exome sequencing was confirmed by sanger sequencing in both patient and asymptomatic parents.

He was also admitted to the intensive care unit with aspiration pneumonia, disseminated intravascular coagulation at the age of 3 years. A few days later, the patient worsened even with appropriate antibiotics therapy and echocardiogram showed significant ventricle wall thickness up to 6.5 mm and depressed ventricular function with an ejection fraction under 45%. Despite administration of inotropics and furosemide, his cardiopulmonary function progressively declined. He died due to heart failure aggravation, following pneumonia.

This study was approved by the Institutional Review Board of Yonsei University Health System (IRB, 3–2020–0378).

Discussion

Vici syndrome manifests in the form of various clinical symptoms. Nonetheless, their degree differs across patients. This in turn makes symptom–based diagnosis difficult. Median survival time of Vici syndrome is approximately 24 months, and treatment consists of supportive therapeutic interventions. The main causes of death in these patients were recurrent infections due to immune dysfunction and cardiomyopathy[7].

Immunodeficiency reportedly varies, ranging from nearly normal immunity to combined immunodeficiency. Moreover, lymphopenia associated with combinations of specific T–cell subset defects is the most frequent immunological abnormality[2]. Mutations in *EPG5* gene, which regulates the transfer of intracellular nucleic acid into cells,

linking autophagy with innate and adaptive immunity is believed to the cause of the immunodeficiency in Vici syndrome[9]. Also. Cardiac involvement is shown in about 90% of patients with Vici syndrome. Both hypertrophic and dilated forms of cardiomyopathy have been reported, with left ventricular emphasis[3].

Our patient presented with symptoms consistent with Vici syndrome, such as agenesis of the corpus callosum, microcephaly, cataract, gross developmental delay, failure to thrive, oculocutaneous hypopigmentation, cardiomyopathy, and recurrent infection. Thus, we performed WES to confirm the clinical diagnosis. This resulted in the diagnosis of the aforementioned novel compound heterozygous *EPG5* mutations.

Vici syndrome is an inherited multi-system disorder caused by biallelic mutations in *EPG5*[1,3]. This gene is involved in autophagy and lysosomal degradation process, which has been linked to cardiomyopathy,neurodegeneration, immune dysfunction, and pigmentation defects[4].

In conclusion, we successfully identified novel compound heterozygous mutations in *EPG5* in a Korean patient with Vici syndrome. WES is a useful diagnostic tool for undiagnosed genetic disorders characterized by clinical manifestations involving other systems.

요 약

Vici 증후군은 18q12.3 염색체에 위치하는 *EPG5* 유전자의 돌연변이로 인해 발생하는 상 염색체 열성 증후군이다. EPG5 유전자는 리소좀 형성에 관여하는 자가 포식 경로의 중요한 조절자를 암호화하므로 이에 대한 돌연변이로 인해 다양한 임상증상을 나타나게 된다. 주요한 임상증상으로는 뇌량 무형성, 백색증, 백내장, 심근 병증, 중증 정신 운동 지체, 발작, 면역 결핍 등이 있으며 다양한 임상증상을 나타내는 만큼 다른 질환들과 임상적으로 구분하기가 어렵다. 저자들은 Vici 증후군으로 진단된 3세 남자 환아의 증례를 보고하고자 한다. 환아는 생후 2개월 경 근긴장 저하와 수유 곤란을 주소로 내원하였으며 이후 Vici 증후군에서 나타나는 특징적인 임상 증상들을 나타내었다. 임상증상들의 감별 진단을 위해 시행한 Whole-exome sequencing (WES) 결과, EPG5 유전자에서 c.2254 C>T (p.Gln752Ter)와 c.5511-5518+2 del TATGCAAAGT 새로운 변이가 이형접합체로 확인되었다.

Vici 증후군과 같이 임상적으로 구분이 어려우며 다양한 신체기관에 걸쳐 영향을 미치는 질환의 진단 시에는 Whole-exome sequencing (WES)가 유용하게 사용될 수 있다. 이 증례는 한국에서 확인된 첫 Vici 증후군 case로써 의의가 있다.

Conflicts of interest

The authors declare that they do not have any conflicts of interest.

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