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Case Report

Two cases of Vici syndrome presenting with corpus callosum agenesis, albinism, and severe developmental delay

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ABSTRACT

Background. Vici syndrome is a rare autosomal recessive disease with phenotypically heterogeneous presentation. Characteristic features of the disease are oculocutaneous albinism, corpus callosum agenesis, cataract, cardiomyopathy, and immunodeficiency.

Case. Here we report two Turkish patients with Vici syndrome. One of these patients had a novel mutation in *EPG5* and presented with idiopathic thrombocytopenic purpura (ITP) and maculopapular rashes similar to Stevens–Johnson syndrome, which has been previously reported in only a few cases in the literature.

Conclusion. Vici syndrome presents with a typical phenotype which may facilitate diagnosis for infants with multisystemic disorders. ITP and maculopapular rashes might be added to the spectrum of findings of patients with Vici syndrome.

Key words: Vici syndrome, autophagy, oculocutaneous albinism, EPG5 mutation.

Vici syndrome is a rare multisystemic autosomal recessive disease characterized by corpus callosum agenesis, oculocutaneous hypopigmentation, cataract, cardiomyopathy, severe developmental delay, combined immunodeficiency, and variable multisystemic features. It was first reported by Dionisi-Vici in two siblings in 1988.[1-3] It occurs as a result of biallelic loss-of-function mutations in the *EPG5* gene on chromosome 18q12.3, which encodes autophagy regulator ectopic P granular protein 5 (*EPG5*). It is a neurodevelopmental disorder of the autophagy pathway.[4,5] Impaired autophagy results in multisystemic defects affecting organs such as the heart, brain, and immune system.[6]

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Here we describe two patients who displayed the clinical features of Vici syndrome and carried homozygous mutations in the *EPG5* gene. One of these patients had a novel homozygous mutation in the *EPG5* gene and presented with idiopathic thrombocytopenic purpura (ITP) and maculopapular rashes similar to Stevens–Johnson syndrome, which has been previously reported in only a few cases in the literature.

Case Report

Case 1

Case 1 was a male infant born as the third child of healthy, consanguineous (first cousins) Turkish parents. The patient's brother had died an hour after birth due to respiratory insufficiency. He was born by normal vaginal delivery with meconium-stained amniotic fluid at gestational age of 36 weeks with a birth weight of 2.8 kg and normal head circumference.

The patient developed acute respiratory failure after birth and was monitored in the neonatal intensive care unit with mechanical ventilation for 20 days. He was hospitalized for 4 months due to recurrent respiratory tract infections. Corpus callosum agenesis was suspected in trans-fontanel ultrasound and confirmed by magnetic resonance imaging (MRI) of the brain. In echocardiography, biventricular hypertrophy, mild mitral insufficiency, and cardiomyopathy were detected. The patient also had feeding difficulties. Tracheal aspiration was noticed during deglutition studies. He had recurrent aspiration pneumonia, and a gastronomy tube was needed after 4 months.

Laboratory investigations performed upon suspicion of metabolic disease were normal, including serum lactate, pyruvate, carnitine, acylcarnitines, very-long-chain fatty acid levels, and urine organic acids. Plasma and urine amino acid levels were also normal, along with sweat chloride test, serological tests for cytomegalovirus, rubella, toxoplasma, and herpes simplex virus, and chromosome analysis (46, XY). At the age of 2 months, complete blood count revealed a low platelet count (15,000/ mm^3). ITP was suspected, and bone marrow biopsy findings were consistent with ITP. After two infusions of intravenous immunoglobulin (IVIG), his platelet count increased.

The patient was admitted to our hospital at the age of 5 months with bronchopneumonia requiring intubation and mechanical ventilation. His body weight, length, and head circumference were below the third percentile for sex and age. Hypopigmented skin and hair, micrognathia, high-arched palate, low-set ears, broad nasal bridge, almond-shaped eyes, and truncal hypotonia were observed on physical examination. He had no social smile or object tracking. In ophthalmologic examination, bilateral anterior subcapsular cataract was noted, while the retina was normal.

Muscles enzymes were elevated (CPK: 604 U/L, AST: 195 U/L, and LDH: 2504 U/L). He also had elevated levels of ALT (126 U/L) and GGT (112 U/L). Electroencephalogram revealed no epileptic activity, and there were no abnormal findings on abdominal ultrasonography or electromyography. The parents did not consent to a muscle biopsy. Immunological investigations revealed low IgA and CD19 levels. ITP recurred at 6 months of age, and again platelet count increased after administration of IVIG. He also developed diffuse maculopapular rash similar to Stevens–Johnson syndrome at 6 months of age without accompanying fever or other signs of viral infection. Diagnostic tests to determine the etiology of the rash did not yield positive results. Skin biopsy was performed because the rashes persisted for more than two weeks and revealed nondiagnostic inflammatory cells.

The patient's respiratory functions progressively declined and he died at 3 years of age due to pulmonary infection. Autopsy could not be performed.

Because the patient showed the typical features of Vici syndrome, a molecular study of the *EPG5* gene was performed and homozygous c.2653delA (p.Thr885fs) mutation was detected in exon 14 (Fig.1). The variant was not found on publicly available databases of human genetic variations.

Case 2

Case 2 was another male infant born as the second child of healthy, consanguineous (first cousins) Turkish parents. He was born by normal vaginal delivery at 37 weeks' gestation

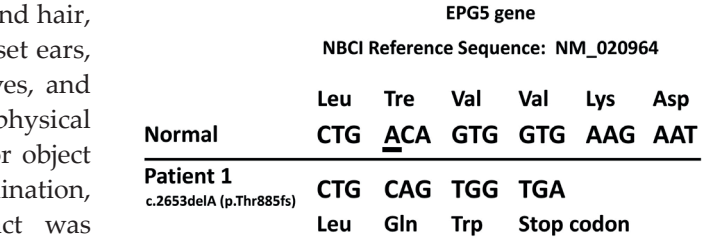

Fig. 1. Schematic presentation of *EPG5* mutation in Patient 1. c.2653delA (p.Thr885fs) mutation results in the occurrence of a premature stop codon (TGA) leading to cessation of synthesis of the protein encoded by the *EPG5* gene.

with a birth weight of 3.0 kg and normal head circumference. He presented at 2 weeks of age with poor feeding and failure to thrive. He was hospitalized with pneumonia at 2 months of age.

He was admitted to our hospital at the age of 5 months with poor weight gain and frequent upper respiratory tract infections. His family history included a sister who had died at the age of 4 months due to similar complaints. Physical examination revealed hypopigmented skin and hair, micrognathia, low-set ears, and truncal hypotonia. He was unable to hold his head up, could not track objects, and lacked social smile. Complete blood count, liver and kidney function tests, and metabolic analyses were normal.

On ophthalmological examination, macular reflexes were absent and peripapillary atrophy was detected. Echocardiography demonstrated hypertrophic cardiomyopathy and left ventricular hypertrophy. Cranial MRI revealed corpus callosum agenesis and delayed myelination. Lymphocyte subgroups and immunoglobulin levels were normal in immunological investigations.

The patient had difficulty feeding. Aspiration was observed during deglutition studies and a nasogastric feeding tube was placed. There were no abnormal findings in abdominal ultrasound and he had no history of seizure.

Because his clinical presentation was consistent with Vici syndrome, a molecular study of the *EPG5* gene was performed and revealed a homozygous c.7447C>T (p.Arg2483*) mutation. The patient was discharged from the hospital after his pneumonia resolved. He is now 24 months of age and still under follow-up.

Informed consent was received from the families for publication of cases.

Discussion

The incidence of Vici syndrome is unknown. To date, approximately 80 cases have been reported in the literature.[7] In addition to its principal features, other nonspecific characteristics have also been reported, including severe developmental delay, acquired microcephaly, and progressive growth failure, which can support the diagnosis.[8,9]

Vici syndrome occurs as a result of biallelic mutations of the *EPG5* gene.[10,11] In our patients, genetic testing showed c.2653delA (p.Thr885fs) and c.7447C>T (p.Arg2483*) mutations in *EPG5*, confirming the diagnosis of Vici syndrome. This is the first report of homozygous c.2653delA (p.Thr885fs) mutation in exon 14 in the literature.

The two patients described in this report both had postnatal growth retardation, oculocutaneous hypopigmentation, agenesis of corpus callosum, cardiomyopathy, significant hypotonia, and recurrent respiratory tract infections, all of which support a diagnosis of Vici syndrome.

Developmental delay is common in patients with Vici syndrome.[6] Our patients also had severe developmental delay. Affected children can acquire social smile and some degree of head control, but these were absent in both of our patients.[6] In contrast, although two-thirds of patients have refractory seizures, this was not observed in our cases.

Although head circumference is generally normal at birth, microcephaly develops progressively within the first year of life in Vici syndrome.[6] Both of our patients had acquired microcephaly despite normal head circumference at birth. In addition to corpus callosum agenesis, cranial imaging may demonstrate pontine hypoplasia, delayed myelination, and reduced white matter.[9,12] However, no additional findings aside from agenesis of corpus callosum were detected in cranial imaging studies of our patients.

Oculocutaneous hypopigmentation is among the principal features of Vici syndrome.[13] Maculopapular rashes similar to Stevens–Johnson syndrome were also reported

in 6 children, though the cause has not been identified.[9] One of our patients had maculopapular rashes and we were unable to determine the cause based on laboratory investigations and skin biopsy. Considering the multisystem involvement of Vici syndrome, there are numerous mechanisms that may be responsible for these rashes. The underlying pathophysiology of this phenomenon may be elucidated in the future as more cases are reported and evaluated in light of emerging evidence.

In this article we present a case of Vici syndrome with attacks of ITP in addition to the classic features of the disease. To our knowledge, ITP has been previously reported in only one pair of siblings with Vici syndrome.[14] One of these siblings had a single ITP attack, while the other had recurrent attacks. Although immune dysfunction is often described in patients with Vici syndrome, autoimmune syndromes such as ITP are not yet recognized as a feature of the disease. Defective autophagy affects many organs and may also trigger an autoimmune mechanism by unknown pathways. In children, ITP is frequently triggered by an infectious illness. This finding may explain by the recurrent infections as well. Further case reports and investigational studies are needed to understand the association between ITP and autophagy disorders.

Bilateral cataract is known as a main finding of Vici syndrome. However, in a study including 50 patients, the prevalence of cataract was approximately 75%.[12] Similarly, only one of our patients had cataract. The ophthalmological features of Vici syndrome were described by Filloux et al.[13] as optic nerve hypoplasia, visual defect, nystagmus, and fundus hypopigmentation. The second patient in this study exhibited peripapillary atrophy. Ophthalmologic evaluation has essential for these children, not only to detect cataract but also to identify other ophthalmologic pathologies.

Combined immunodeficiency is common in Vici syndrome, with highly variable severity.[15] Although one of the patients in this report had normal immunologic evaluation, the other had some degree of hypogammaglobulinemia and low CD19 level. However, both of our patients had frequent respiratory tract infections. There are many contributing factors in recurrent respiratory tract infections in Vici syndrome. Although patients seem to have a normal immune status, they can present with recurrent infections starting early in life. Investigation of these other factors is important. It should be kept in mind that these patients may have swallowing disorders, as in our cases, particularly due to the underlying hypotonia.

Vici syndrome is a progressive disease with poor prognosis. Median survival time is approximately 24 months, and treatment consists of supportive therapeutic interventions. The main causes of death in these patients are recurrent infections due to immune dysfunction and cardiomyopathy.[7] A better understanding of the underlying pathophysiology might facilitate the development of targeted treatments in the future.

In conclusion, Vici syndrome presents with a typical phenotype characterized by corpus callosum agenesis, cataract, hypopigmentation, cardiomyopathy, immunodeficiency, developmental delay, and acquired microcephaly. Keeping this in mind may facilitate diagnosis for infants with multisystemic disorders. We report a case of Vici syndrome with ITP and maculopapular rashes resembling Stevens–Johnson syndrome, which has been reported in only a few cases to date. ITP and maculopapular rashes might be added to the spectrum of findings of patients with Vici syndrome.

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