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CASE REPORT

Case report: Vici syndrome

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ABSTRACT

Vici syndrome (OMIM242840) is a rare neurodevelopmental disorder with multisystem involvement such as agenesis of corpus callosum, oculocutaneous hypopigmentation, cataracts, failure to thrive, combined immune deficiency, cardiomyopathy, and progressive microcephaly. EPG5 (18q12.3) gene is responsible for the pathogenesis of Vici syndrome. In this report, we present a 3-month-old girl who was admitted to our outpatient clinic with dysmorphic appearance, neurodevelopmental delay, and respiratory tract infection symptoms. The child has an ex-sibling with documented homozygous EPG-5 mutation (-/-). The infant has been hospitalized for 15 times due to urinary, respiratory system infections, and sepsis. The patient died at 14 months of age due to multisystem failure secondary to bacterial septicemia.

Keywords: Cardiomyopathy, child, corpus callosum agenesis, Vici syndrome.

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INTRODUCTION

Vici syndrome (Dionisi-Vici-Sabetta-Gambarara syndrome) is a rare neurodevelopmental disorder characterized by corpus callosum agenesis, hypopigmentation, cataract, growth retardation, combined immune deficiency, cardiomyopathy, and progressive microcephaly.[1] The syndrome was first described by Vici et al.[2] in 1988 in two brothers born to parents who were consanguineous.

Nearly 100 cases have been reported in our country and various countries.[1,3–5] Vici syndrome (OMIM242840) is in the group of orphan diseases with an incidence of <1,000,000.[6] It is an C with multiple system involvement (heart, eye, nervous system, immune system, and skin). EPG-5 (18q12.3) mutation, which plays a role in regulating autophagy in cells, is responsible for the pathogenesis of the disease.[7,8]

Here, we present a female patient who was first admitted at 3 months due to dysmorphic appearance, growth retardation, and infection. She was hospitalized 14 times with the diagnosis of respiratory-urinary tract infections and sepsis.

CASE REPORT

A 3-month-old girl with a dysmorphic appearance was admitted to the pediatric outpatient clinic with the complaints of cough and wheezing. The patient, who had a history of antibiotic use for 5 days, was hospitalized for a lower respiratory tract infection (LRTI).

The patient was the second child of non-relative parents aged 29 and 30 years. She was born with C/S with a weight of 2300 g at the 36th gestational weeks. No vaccination was performed except for the first postnatal hepatitis vaccine. Turkish National Newborn Screening and Hearing tests were found to be expected.

The patient was healthy till the age of 2 months. However, she had a brother with a similar phenotype and genetically proven EPG-5 homozygous mutation. The brother was diagnosed with Vici syndrome and died when he was 27 months old. The family received genetic counseling, but our patient was born due to an unplanned pregnancy. There were no other children with a resembling appearance or loss of children in her family history. Colpocephaly, hypoplasia of the corpus callosum, ventricular, and septal hypertrophy of the heart were present in the fetus at prenatal screening; however, the family decided to continue the pregnancy.

On physical examination, we observed dysmorphic facial appearance, nystagmus, broad nose, long philtrum, high palate, light yellow brush-like hair, and pale skin color (Fig. 1, 2). Anterior fontanel was 2×2 cm in size and was no head deformation. Central hypotonia and neuromotor retardation were present, and the case was poor at head control and eye follow-up. Head circumference (38 cm) was in the 5th percentile. Other anthropometric measures were below the third percentile (weight: 4.4 kg, height: 55 cm, and Z scores: <-2,5 SD). There was no deformity of the chest, trunk, or extremities. Pyogenic granuloma was observed on the umbilicus. On all cardiac loci, ⅙ systolic murmur was heard. Excluding fine bilateral crackles in the respiratory system, the remaining system examinations revealed no abnormal findings.

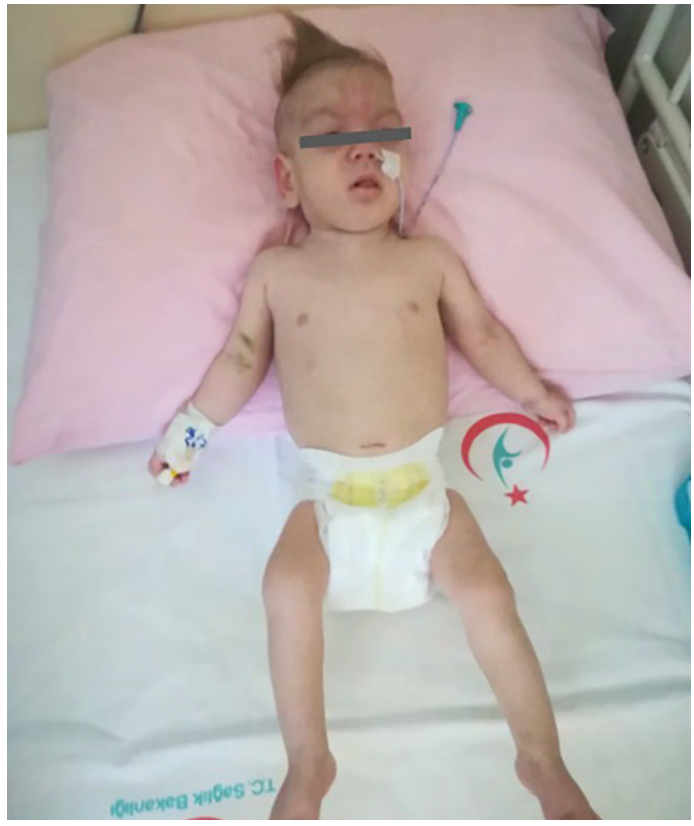

Figure 1: Pale skin color, light yellow brush-like hair, and central hypotonia.

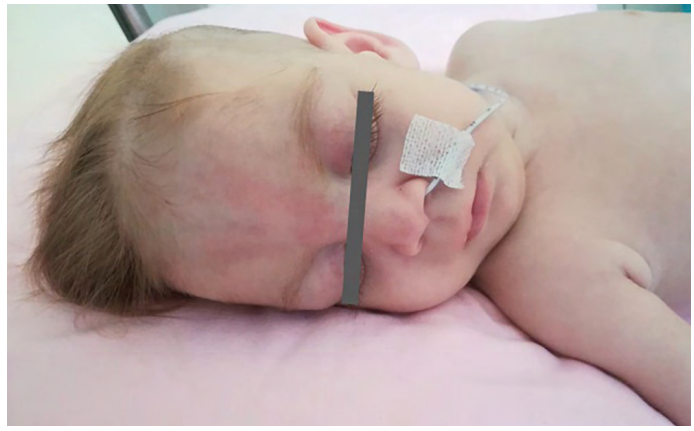

Figure 2: Dysmorphic facial appearance broad nose, long philtrum.

The patient's complete blood count at admission was as follows: WBC: 9.400/mm^3, absolute neutrophil count (ANC): 6.240/mm^3, and absolute lymphocyte count: 2.470/mm^3. There were no anemia and thrombocytopenia. Acute-phase reactants were positive. Serum biochemistry and thyroid function tests were within the normal range.

Paracardiac infiltration and the presence of thymic shadow were observed on PA chest X-ray. The cardiothoracic index was 0.6. The family refused imaging and genetic examination because of patient discomfort and no additional benefit since the case showed similar characteristics to her deceased brother. After appropriate anti-biotherapy for LRTI, she was discharged without further investigation.

The patient presented for the 2nd time at the age of 4.5 months with fever and foul-smelling urine complaints. *Klebsiella pneumoniae* (80,000 CFU/ml) was isolated in the urine culture. Abdominal and urinary USG were reported as normal. The corpus callosum was found hypoplastic by transfontanelle USG. Ventricular dimensions were within the normal range without midline shift. Cerebral hemispheres and posterior fossa were free of mass.

Pediatric neurology consultation was performed. The patient's TANDEM MS was normal. Creatine kinase (CK): 318 IU/L (29–168 U/L), CK-MB: 47.3 ng/ml (0–3.4 ng/ml), ferritin: 300 ng/ml (8.7–71.6 ng/ml), triglyceride: 199 mg/dl, and total cholesterol: 111 mg/dl. No pathology was found in viral serology for *Toxoplasma*, *Rubella*, CMV, HSV-1, HSV-2, Parvo-B19, and EBV. On eye examination, the disk, macula, and peripheral retina were in normal appearance. There were bilateral cataracts. Biventricular hypertrophy, deep Q waves, and mild ST changes were present in her ECG. Echocardiographic (ECHO) evaluation revealed marked left hypertrophic cardiomyopathy, mild tricuspid regurgitation, and trace mitral insufficiency. Contraction and ejection fraction measurements (EF: 58% and CF: 28%) were similar to previous ECHO controls.

Pediatric genetic counseling recommended EPG-5 gene mutation analysis for Vici syndrome for an exact diagnosis. Unfortunately, the patient was discharged after completing urinary tract infection treatment.

Ten days after discharge, the patient was admitted with fever and difficulty breathing. *Parainfluenza virus* 3 antigen was detected in the nasopharyngeal secretions. Nutritional support was given by the nasogastric tube due to swallowing difficulty. The family refused treatment and left the hospital.

A few days later, the patient was admitted to the emergency department with vomiting and diarrhea. No infectious etiology was found in the stool examinations. She was discharged after rehydration.

One week later, the patient was admitted with fever and respiratory distress. Since clinical and laboratory findings did not improve, we performed pediatric infectious disease consultation. Piperacillin-tazobactam and fluconazole therapy was administered after isolation of *Acinetobacter lwoffii* and *Candida albicans* in the patient's blood culture.

The patient's difficulty in swallowing and the inability to gain weight due to insufficient calorie intake facilitated infections by repeated aspiration. Percutaneous gastrostomy was recommended, but the family did not consent.

After 45 days of hospitalization, blood, cerebrospinal fluid, and urine cultures were sterile.

Overall the patient, who generally presented with fever and respiratory system complaints, was hospitalized 14 times until her postnatal age of 13 months. In addition, she had a hospitalization approximately every month in the autumn and winter seasons. The patient's nasopharyngeal secretion analysis using real-time multiplex PCR intermittently detected *Parainfluenza virus* type 3 and *Rhinovirus* twice.

Staphylococcus hominis, *Acinetobacter lwoffii*, and *Candida albicans* were isolated in blood cultures drawn at different hospitalizations. In addition, *Klebsiella pneumoniae* and *Enterococcus faecalis* were isolated in urine cultures.

Since her first admission, serum levels of AST ranged between 51 and 238 IU/ml and ALT between 51 and 185 IU/ml. Coagulation parameters, fibrinogen, and albumin were within normal limits. The patient received an erythrocyte transfusion due to iatrogenic anemia. During these hospitalizations, she was followed up by pediatric cardiology for cardiomyopathy. Findings similar to previous follow-ups were obtained.

We consulted the patient with recurrent hospitalization history to pediatric immunology. Serum immunoglobulin levels were within the normal range for age (IgA: 111 mg/dl, IgG: 715 mg/dl, IgM: 52 mg/dl, and total IgE: 29.1 IU/ml). Inflow cytometry of peripheral blood mononuclear cell analysis CD3+(total lymphocyte): 49.9, CD19+(B cell): 44.8, CD16/56+(natural killer cell): 4.8, CD3+CD4+(T helper): 23.6, CD3+CD8+(T cytotoxic): 26.1, and CD4 +/CD8+: 0.9 was evaluated within the normal range for age. IVIG was given to the patient who was thought to have functional immunodeficiency.

Our case died at 14 months due to multiorgan failure following bacterial septicemia.

DISCUSSION

Vici syndrome is diagnosed by clinical findings and demonstration of an autosomal recessive (AR) mutation in the EPG-5 (18q12.3) gene. Corpus callosum agenesis, cataract, cardiomyopathy, oculocutaneous hypopigmentation, and combined immunodeficiency are the five main findings for the diagnosis of Vici syndrome.[7] In addition to the primary findings, other symptoms affecting different organs and systems have also been reported.[1] When developmental retardation, progressive microcephaly, and growth retardation are added to these five main findings of the syndrome, 97% specificity and 89% sensitivity are achieved for the presence of EPG-5 gene mutation.[1,9]

Since there was the presence of proven Vici syndrome in her family history and those mentioned earlier eight diagnostic criteria suggested by Byrne et al.,[1,9] we accepted our case as Vici syndrome due to the family's lack of consent. Nevertheless, homozygous EPG5 mutation was shown in the older brother of our patient who died at the age of 27 months. The parents were not investigated genetically for mutations in EPG-5 gene. Consanguinity of parents was emphasized in most of the reported cases with Vici syndrome due to AR inheritance pattern. We reported this case since the disease is very rare among siblings of unconsanguineous parents.

The peripheral blood mononuclear cell counts and lymphocyte subgroups, serum immunoglobulin, and anti-hemagglutinin levels were normal. Lymphocyte response studies could not be performed for immunological evaluation. In the literature, some cases of Vici syndrome show no quantitative impairment in the immune system as our patient.[4,10–13]

Most patients with Vici syndrome have recurrent respiratory, gastrointestinal, and urinary system infections during infancy. In addition, septicemia, mucocutaneous candidiasis, and conjunctivitis can be observed.[1] Therefore, we evaluated our case as functional immunodeficiency due to frequent respiratory and urinary tract infections, plus sepsis. We planned to show quantitative immunologic changes during follow-up.

Parainfluenza virus type 3 and *Rhinovirus* were viral agents in respiratory tract infections. In addition, we applied long-term antibiotic treatment to the patient because of *Staphylococcus hominis*, *Acinetobacter lwoffii*, *Candida albicans* isolated in the blood, and *Klebsiella pneumoniae* and *Enterococcus faecalis* isolated in the urine acquired at different times.

Additional clinical findings have been reported in the literature. Myopathies, seizures, absence of reflexes, sensorineural hearing loss, optic atrophy, cleft palate, rough facial appearance, thymic aplasia, renal tubular acidosis, and hepatomegaly during the neonatal period have been reported in some cases.[1] These additional findings were not present in our patient. A cataract is the most common ocular anomaly in the syndrome. Optic nerve hypoplasia, nystagmus, and photophobia can also be seen.[1] Nystagmus and bilateral cataracts were diagnosed and followed by an ophthalmologist in our patient.

As one of the main diagnostic criteria, cardiomyopathy is found in 90% of patients and develops in the early period of life. The left ventricular involvement is predominantly reported in patients with hypertrophic or dilated cardiomyopathy.[1] Therefore, heart failure due to impaired cardiac functions is expected. Our patient had signs of systolic hypertrophic dysfunction and hypertrophic cardiomyopathy.

Vici syndrome is a progressive disorder involving different organs and systems (immune, thyroid, liver, and kidney), which should be considered during follow-up. In addition, Marinesco-Sjögren syndrome, Chédiak-Higashi syndrome, Griscelli syndrome, DiGeorge syndrome, and ataxia-telangiectasia should be considered in the differential diagnosis. All of which were ruled out during our case follow-up.

The life expectancy of affected children is short: the median survival time was 42 months (1–102 months) in large case series. In addition, patients with homozygous mutations (median 9 months) die earlier than those with heterozygous mutations (median 48 months).

Our patient's brother, with homozygous mutation, died when he was 27 months old. The cause of death in cases is often cardiac complications and infections. Our case died at 14 months due to multiorgan failure following bacterial septicemia.

CONCLUSION

Anamnesis and physical examination are essential in diagnosing Vici syndrome, as in all other genetic syndromes. Vici syndrome should be considered in cases with concomitant hypotonicity, hypopigmentation, growth retardation, corpus callosum agenesis, and cardiomyopathy. Genetic counseling should be given to families having children with Vici syndrome, and in case of a planned pregnancy, a healthy embryo transfer with a pre-implantation diagnosis would be appropriate.

Statement

Informed Consent: Written, informed consent was obtained from the patient's family for the publication of this case report and the accompanying images.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – KG, NUK, ÖE, ES, RGSY, AB; Design – KG, NUK, ÖE, ES, RGSY, AB; Supervision – KG, NUK, ÖE, ES, RGSY, AB; Literature Search – KG, NUK; Writing – KG, NUK; Critical Reviews – ÖE, ES, RGSY, AB.

Conflict of Interest: The authors have no conflict of interest to declare.

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