Case Report

Early Diagnosis and Management in an 11-Year-Old Girl with Vascular Ehlers–Danlos Syndrome

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Vascular Ehlers–Danlos syndrome (vEDS) is a severe connective tissue disorder caused by pathogenic variants in the collagen type III alpha I chain gene (*COL3A1*), characterized by increased fragility of arteries and hollow organs. Typically, vEDS is diagnosed after complications related to arterial or intestinal tissue fragility. We herein report a case of an 11-year-old girl who was asymptomatically diagnosed with vEDS owing to a family history of sudden death. She was referred to our hospital at 5 years of age, after her father died suddenly at 35 years of age due to a ruptured thoracoabdominal aortic aneurysm. Despite showing no significant clinical features or vascular abnormalities indicative of connective tissue disorders during follow-up, genetic testing at 11 years of age identified a missense mutation in *COL3A1*, confirming the diagnosis of vEDS. Brain magnetic resonance imaging (MRI) and contrast-enhanced MRI of the thoraco-abdominal viscera revealed no abnormalities. Oral celiprolol therapy was initiated to prevent cardiovascular complications. Although diagnosing vEDS in childhood can be challenging due to its rarity and subtle clinical presentation, it is vital to consider this syndrome in pediatric patients with a family history of early-onset arterial aneurysms, dissections, or gastrointestinal vascular rupture.

Keywords: vascular Ehlers–Danlos syndrome, *COL3A1* mutation, family screening

Introduction

Vascular Ehlers–Danlos syndrome (vEDS) is an autosomal dominant disorder caused by pathogenic variants in the collagen type III alpha I chain gene (*COL3A1*), characterized by arterial and/or visceral fragilities. The estimated prevalence is 1 in 50,000 to 200,000 individuals, representing approximately 5% of all cases of Ehlers–Danlos syndrome.[1)] The diagnosis is confirmed through molecular genetic testing in individuals who have at least one of major features including a family history, arterial rupture or dissection at age less than 40 years, unexplained sigmoid colon rupture, or spontaneous pneumothorax in the presence of relevant physical findings consistent with the disorder.[2)] Typically, vEDS is diagnosed after complications related to tissue fragility.[3)] We herein report a case of an asymptomatic child diagnosed as having vEDS based on a family history of sudden death.

Case Presentation

A 5-year-old girl was referred to our hospital after her father's sudden death at 35 years of age due to a ruptured thoracoabdominal aortic aneurysm. Her father was sus-

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pected to have a hereditary connective tissue disorder susceptible to aortic lesions, such as Marfan syndrome or Loeys–Dietz syndrome, but he did not exhibit any clinical findings suggestive of such a disorder. No other family members except for her father experienced sudden death or apparent complications relevant to hereditary connective tissue disorders. She had no siblings. She had no physical findings suggestive of these syndromes, such as tall and slender build (height, 102.3 cm [−1.8*SD*]; weight, 20.2 kg [+0.6*SD*]), dolichocephaly, malar hypoplasia, enophthalmos, cleft palate, or blepharoptosis. Echocardiography revealed a normal cardiac structure without ascending aortic dilation or significant mitral valve prolapse or regurgitation. After careful discussion with her mother, yearly follow-up examinations, including chest radiography, 12-lead electrocardiography, and echocardiography, were continued, which revealed no significant abnormalities. Through repetitive genetic counseling to her and her mother, they decided to undergo presymptomatic genetic testing in view of optimal activities after entering junior high school. A next-generation sequencing-based genetic testing for hereditary connective tissue disorders susceptible to aortic lesions (including *FBN1*, *TGFBR1*, *TGFBR2*, *ACTA2*, *COL3A1*, *EFEMP2*, *FBN2*, *FLNA*, *MYH11*, *MYLK*, *SLC2A10*, *SMAD3*, *TGFB2*, *TGFB3*, and *SMAD2*) was performed at 11 years of age, which revealed a previously reported pathogenic variant representing a glycine substitution in the triple helix domain (NM_000090.4:c.3437G>A,p.Gly1146Glu) in *COL3A1*,[4] confirming the diagnosis of vEDS. This variant was classified as likely pathogenic (PM1, PM2, PP2, and PP3) in accordance with the 2015 American College of Medical Genetics and Genomics/Association for Molecular Pathology guidelines.[5] Brain magnetic resonance imaging (MRI) and contrast-enhanced MRI of the thoraco-abdominal viscera showed no vascular aneurysms or dissections. Long-term administration of celiprolol to prevent arterial lesions was discussed with her mother based on published evidence[6–8] including the fact that no information was available in pediatric cases. Finally, celiprolol treatment was introduced, and the dose has been carefully titrated up to 300 mg/day at present, with a plan to increase it to 400 mg/day in the future, according to a previous report.[6] Regular genetic counseling for her and her mother was continued considering their psychosocial burden. Her father had a younger brother and a younger sister. Genetic counseling in view of presymptomatic genetic testing is currently being considered on her father's younger brother and sister who may share the same variant in *COL3A1*.

Discussion

To the best of our knowledge, this is the youngest reported patient who had presymptomatic diagnosis and prevention through celiprolol therapy. vEDS is one of the most severe forms of Ehlers–Danlos syndrome, primarily due to life-threatening complications such as arterial rupture, dissection, and rupture of hollow organs, particularly the bowel and uterus.[9] This serious nature of the disease arises from a dramatic reduction in mature type III collagen production. It has been reported that 25% of vEDS patients experience these complications by 20 years of age, with >80% experiencing them by 40 years of age.[10] Jorgensen et al. reported an individual who developed aortic dissection and suffered sudden death at the young age of 15 years.[11] Menni et al. reported a 5-year-old individual who developed bowel perforation.[12] These reports suggest serious vascular and/or organ complications could occur in childhood, though they might be quite rare. Furthermore, glycine substitution variants, like the current case, were evaluated to show a 5.66-fold higher risk of mortality, with the median survival as 34 years, compared to null variants.[4] Because of its low prevalence and minimal clinical symptoms in childhood,[2] vEDS can be challenging to diagnose. Thus, it is crucial to consider a potential of vEDS in patients with a family history of early-onset arterial rupture. Celiprolol, a vasodilating β1-blocker, effectively prevents arterial morbimortality in patients with this syndrome. This medication is believed to reduce arterial fragility by alleviating mechanical stress on the collagen fibers in the arterial wall.[6] We initiated celiprolol at a dose of 100 mg/day, which was gradually increased to 300 mg/day, while monitoring for side effects such as bradycardia and hypotension. In this case, we established an emergency care protocol to promptly differentiate complications such as pneumothorax or thoracic arterial lesions in the event of chest pain, abdominal arterial lesions or sigmoid colon rupture in the event of abdominal pain, and carotid-cavernous fistula in the event of headaches or pulsatile tinnitus. Future management includes regular surveillance of cardiovascular lesions using echocardiography, computed

tomography, and MRI.

Female patients with this syndrome are at high risk for obstetric complications, with an estimated maternal mortality rate of 11.5% due to uterine or major vessel rupture during delivery.[13] It is important to counsel these patients on perinatal complications and monitor the aortic diameter and presence of aneurysms during pregnancy. For these patients, cesarean delivery is recommended between 32 to 36 weeks of gestation prior to the onset of labor to prevent uterine rupture during vaginal delivery.[13] The prognosis of pregnancy and delivery in vEDS patients may improve through deepening their understanding of the disease via genetic counseling, the introduction of celiprolol, and the collaboration of multiple medical departments, including obstetrics and emergency medicine. In asymptomatic children with suspected vEDS, genetic testing provides several advantages, including early identification and management of potential complications, guidance on restricting high-risk activities, and the exclusion of vEDS in the absence of pathogenic variants.[1] While vEDS is often regarded as an adult-onset condition, it is noteworthy that one in four patients experience a major complication by the age of 20. As missense or exon deletion variants in *COL3A1* represent close to 100% penetrance,[1] parents of at-risk children usually request genetic testing before complications arise or before the child reaches adulthood, aiming to clarify the diagnosis and proactively address medical risks.[1] Conversely, some experts recommend delaying genetic testing until after 20 years of age, when individuals can fully comprehend the implications of the diagnosis for conditions manifesting in adulthood.[14] Because individuals with a positive diagnosis from genetic testing may face the possibility of social discrimination and its psychological impacts, greater caution should be exercised when considering the application of genetic testing for minors.[14]

In this case, over the course of six years, annual cardiovascular examinations were conducted, and thorough discussions were repeated with her and her mother, including genetic counseling for genetic testing. This led to presymptomatic genetic testing followed by preventive celiprolol therapy. Based on these experiences, we advocate for early genetic testing in suspected cases of vEDS, even in childhood, given the life-threatening events associated with this syndrome in young patients and the availability of effective treatments for these complications.

In conclusion, although vEDS is a rare disorder with potentially fatal consequences, an early and accurate diagnosis is critical for preventing and detecting cardiovascular complications and managing pregnancy-related risks. Clinicians should bear vEDS in mind in children with a family history of early onset arterial aneurysms, dissections, or gastrointestinal vascular ruptures, and should consider genetic testing even in asymptomatic cases.

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None.

Conflicts of Interest

Tomomi Yamaguchi and Tomoki Kosho are members of an endowed chair named "Division of Clinical Sequencing, Shinshu University School of Medicine" sponsored by BML, Inc. and Life Technologies Japan Ltd. of Thermo Fisher Scientific Inc. The authors declare no conflicts of interest in association with the present study.

Ethic Approval and Consent to Participate

Informed consent was obtained from the parent and the patient for publication of this case report, while preserving the patient's anonymity.

Author Contribution

Daisuke Masui and Takamichi Ishikawa drafted this manuscript. Hiroki Uchiyama, Masafumi Utsumi and Tomoki Kosho critically reviewed the manuscript. Tomomi Yamaguchi helped with interpretation and description of the variant. All the authors have read and approved the final manuscript.

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