EDITORIAL

Utilizing Next-Generation Sequencing for the Diagnosis and Clinical Management of Vascular Ehlers-Danlos Syndrome

Daishi Fujita, MD

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Ehlers-Danlos syndrome (EDS) is a connective tissue disease famous for skin hyperextensibility and joint hypermobility. Vascular Ehlers-Danlos syndrome (vEDS), a subtype of EDS, is characterized by dissections and aneurysms mainly of the mid-sized artery. It is inherited in an autosomal dominant manner. The causative gene has been identified in COL3A1, a gene encoding pro-alpha 1 chain of collagen type III, which is distributed in the arterial wall, skin, and hollow organs. The COL3A1 mutation leads to a decreased production of normal collagen type III, thus bringing about fragility of the affected tissues.

Diagnosis of vEDS is made according to diagnostic criteria. It was established in 1997 and later revised in 2017. The revised criteria for vEDS comprise the following 5 major criteria: family history of vEDS (with COL3A1 mutation), arterial rupture, spontaneous sigmoid colon perforation, uterine rupture, and carotid-cavernous sinus fistula formation. Other features classified as minor criteria include easy bruising, thin translucent skin with increased venous visibility, characteristic facial appearance, spontaneous pneumothorax, acrogeria, talipes equinovarus, congenital hip dislocation, hypermobility of small joints, tendon and muscle rupture, keratoconus, gingival recession and gingival fragility, and early onset varicose veins. Additional examinations confirming the diagnosis are recommended when there is a positive family history, arterial rupture or dissection under the age of 40 years, unexplained sigmoid colon rupture, or spontaneous pneumothorax with other vEDS features. Confirmation of the diagnosis was traditionally done by measuring the collagen III protein levels in cultured fibroblast from skin biopsy, which was more or less invasive and also time consuming. The development and advances in genetic analysis has made it possible to identify genetic mutation in COL3A1 with less time and effort. The verification of the diagnosis is now mainly made through genetic analysis.

At present, there is no established curative treatment. Conservative therapy is occasionally preferred to invasive therapy unless in life-threatening situations in consideration of tissue fragility. Celiprolol, a β-blocking agent, has been reported to prevent arterial event in vEDS patients, but the investigations are still underway.

Pregnancy in a vEDS patient is considered to be high risk but the information is limited due to the rarity of this disease. Although there is no doubt that some special considerations are necessary regarding this issue, at present, the optimal management for vEDS pregnancy is unknown.

In this issue of the International Heart Journal, Koitabashi, et al. report the case of a vEDS lady with left common iliac arterial dissection at 34 weeks of pregnancy. The patient was conservatively treated after a delivery by cesarean section; however, she suffered rupture of the dissecting aneurysm in the right common iliac artery. Although previously undiagnosed, her clinical features indicated vEDS and the authors made a speedy confirmation of the diagnosis through next-generation sequencing before proceeding to invasive procedures. After the diagnosis, she was successfully treated with endovascular technique. This case report is a good example of genetic diagnosis in clinical practice, leading to correct diagnosis and optimal therapy.

The ultimate goal of vEDS patient care is to prevent a fatal event, mainly arterial dissections and ruptures, and early diagnosis is its first step. However, systemic features of vEDS are sometimes not as prominent as other hereditary aortic disease, i.e., Marfan syndrome (MFS) and Loeys-Dietz syndrome (LDS), and making a diagnosis may be challenging. In vEDS, skin hyperextensibility and joint hypermobility are not so remarkable as other types of EDS, thus making it difficult to detect an affected individual at a glance. Along with family history, genetic examination plays an important role in the diagnostic process. Compared with culturing skin fibroblast, genetic analysis enables speedy diagnosis that can be reflected to acute and subacute clinical management of the patient. A classical Sanger method required a primer for each target gene, and the analysis was performed for each suspected syndrome one by one. When clinical features were diffi-
cult to distinguish from other hereditary aortic diseases, such as MFS and LDS, each candidate gene needed to be examined until a reasonable result was obtained. Next-generation sequencing (NGS) now enables the simultaneous analysis of multiple target genes. Major candidate genes of hereditary aortic/arterial diseases can be examined at once using this method. In the case report, Koitabashi, et al. succeeded in making speedy diagnosis using the NGS panel and reflected the result for treatment decision.  

The advancements in genetic analysis and its widespread clinical appliance to making diagnosis has led to a detection of numerous variants. Determining which variant is pathogenic is the next step. In 2015, the American College of Medical Genetics and Genomics and the Association for Molecular Pathology released standards and guidelines for the interpretation of sequence variants.  

Factors to be considered are types and locations of the mutation, its accordance with previous reports, exclusion of SNPs, cosegregation with the disease in affected family members, and the results of computational predictive programs. Extra caution is necessary to interpret variants in intron regions. In the present case report, the location of the detected variant was in accordance with the previous report, and the impact of the variant was also validated in both RNAs and proteins. Definite and cautious diagnosis is important as it influences not only clinical management and treatment decision but also the patient’s daily activity and life plan.

Genotype-phenotype correlation is another subject that may need attention when interpreting variants. Shalhub, et al. showed the difference in clinical features according to the anticipated collagen production level of the mutation. Type III collagen is a homotrimer of 3 procollagen peptides. In missense and exon skipping mutations, normal and abnormal procollagen peptides are produced at a 1:1 ratio; therefore, only 1/8 of type III collagen is normal as a homotrimer. On the other hand, in nonsense and frameshift mutations leading to premature termination codons, abnormal RNA is removed through nonsense-mediated decay. This results in the production of only normal type III collagen half in its amount. The former group of mutation with smaller anticipated collagen amount was more prominent for vEDS features (involvement of mid-sized arteries, thin translucent skin, and small joint hypermobility) at a younger age, whereas the latter group showed more involvement in the aorta. Pepin, et al. also reported longer survival in patient with mutations causing premature termination codons. Although the small number of studied patients makes it difficult to reach a firm conclusion at present, genotype-phenotype correlations may be taken into consideration.

Additional considerations are necessary in the management of pregnancy in hereditary aortic/arterial syndromes. The patient needs to be accurately informed of the possibility of inheritance to the offspring, ideally through genetic counseling. Sufficient attention and care during pregnancy is necessary because the possibility of aortic/arterial event is considered to increase through increased circulating plasma volume and heart rate, fluctuation in blood pressure before and after delivery, and changes in hormone levels. In MFS and LDS pregnancy, blood pressure management and periodic monitoring of aorta are recommended. Beta blockers are mainly chosen for blood pressure management, and fetal growth must be closely monitored. However, there is no strong evidence to prefer cesarean section to vaginal delivery. Even less is known in literature regarding pregnancy in vEDS patients. Mid-sized arterial dissection and rupture are difficult to predict, and the benefit of periodic imaging examination of the whole aortic tree is unclear. Uterine rupture and laceration are unique complications in vEDS, which may give priority to cesarean section. Although the mortality of pregnancy in vEDS has been reported to be as high as 5.3%, no difference was observed between mortality in pregnant and non-pregnant vEDS patients. The actual mechanism in which pregnancy affects conditions in vEDS is still unclear, and thus the optimal management for vEDS pregnancy is unknown. At present, pregnant vEDS patients need to be attended by a team of obstetrician, vascular surgeon, and genetic counselors in well-experienced medical centers.

In 2010, Ong, et al. reported the preventive effect of celiprolol in vEDS. In their multicenter randomized open trial with blinded endpoint assessment, 53 vEDS patients were enrolled with a mean follow-up period of 47 ± 5 months. A primary endpoint consisting of any arterial rupture or dissection occurred in 20% (5/25) of celiprolol group and 50% (14/28) of the control group, reaching statistical significance. Whether protective effect is common among all β-blockers or unique to celiprolol is unclear. Rarity of the disease has not enabled further research at a larger scale. However, in light of the relatively safe property of celiprolol in terms of side effects, celiprolol may be a choice when vEDS is strongly suspected, needless to say when definitely diagnosed.

A basic policy in decision making for vEDS treatment is to be conservative except in life-threatening situations when surgery is the only chance for survival. Fragility of the organ tissue markedly increases the difficulty of invasive procedures. Endovascular treatment for aortic/arterial conditions has evolved and widely spread and its appliance to hereditary aortic/arterial syndrome is a topic gathering attention. While the risk of damaging the fragile aorta is considered to exceed the benefits of low invasive property of endovascular therapy compared with open surgery in MFS and LDS, in vEDS, the high mortality of open vascular surgery and its complication makes endovascular therapy an option for consideration. Bergqvist, et al. reported the 30-day mortality in vEDS patients to be 30% (13/44) for open surgery and 24% (8/33) for endovascular therapy. The main reason of death was bleeding for open surgery and embolization or rupture for endovascular therapy. Shalhub, et al. emphasized the importance of pre-surgery diagnosis and elective procedure, reporting post-operative complications to be the highest when the diagnosis was unknown and when the procedures were undertaken in an emergency setting. The advancements in materials, technology, and techniques in endovascular therapy may further improve the treatment results in the future.

Although there are no established optimal and cura-
tive therapy for vEDS patients and little is known regarding pregnancy care in such patients, at present, the most important and practically effective measure lies in early recognition and diagnosis of the syndrome along with comprehensive care offered by experienced medical team.

Disclosures

Conflicts of interest: None.

References