Vascular involvements are common in the branch arteries of the abdominal aorta rather than in the aorta in vascular Ehlers-Danlos syndrome

Koichi Akutsu, MD, PhD, Atsushi Watanabe, MD, PhD, Takeshi Yamada, MD, PhD, Tomoko Sahara, MA, Sayuri Hiraoka, MA, Wataru Shimizu, MD, PhD

PII: S2589-790X(22)00237-2

DOI: https://doi.org/10.1016/j.cjco.2022.11.001

Reference: CJCO 592

To appear in: *CJC Open*

Received Date: 30 July 2022

Revised Date: 29 October 2022

Accepted Date: 1 November 2022

Please cite this article as: RRH: Vascular Ehlers-Danlos syndrome complications

Vascular involvements are common in the branch arteries of the abdominal aorta rather than in the aorta in vascular Ehlers-Danlos syndrome

Short title: Vascular Ehlers-Danlos syndrome complications

Koichi Akutsu, MD, PhD[a], Atsushi Watanabe, MD, PhD[b,d,e], Takeshi Yamada, MD, PhD[c], Tomoko Sahara, MA[b], Sayuri Hiraoka, MA[b], Wataru Shimizu, MD, PhD[a]

[a] Department of Cardiovascular Medicine, Nippon Medical School, Tokyo, Japan

[b] Division of Clinical Genetics, Nippon Medical School Hospital, Tokyo, Japan

[c] Department of Gastrointestinal and Hepato-Biliary-Pancreatic Surgery, Nippon Medical School, Tokyo, Japan

[d] Division of Clinical Genetics, Kanazawa University Hospital, Ishikawa, Japan

[e] Support Center for Genetic Medicine, Kanazawa University Hospital, Ishikawa, Japan

Corresponding author: Koichi Akutsu, MD, PhD

Department of Cardiovascular Medicine, Nippon Medical School

1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan

Telephone: +81-3-3822-2131, Fax: +81-3-5814-1781

E-mail: koichi-a@nms.ac.jp

Brief summary:

Branch arteries of the abdominal aorta were most prevalent in Vascular EDS

Abstract

Background: Vascular Ehlers-Danlos syndrome (vEDS) is a rare disorder with poor prognosis because of associated vascular complications. However, the most prevalent arterial problems in patients with vEDS are not well known.

Methods: We retrospectively examined 20 consecutive patients diagnosed with vEDS and examined their clinical events, image findings, and therapies.

Results: The age at first complication requiring admission was 29±13 years old. The observational period was 67±30 months. Of the 20 patients, 17 took celiprolol at final assessment. At the final follow-up, the total number of complications requiring admission with respect to lesion was 16 for pulmonary lesions (8 patients), 16 for bowel lesions (8 patients), 5 for tendon/ligament lesions (2 patients), 18 for the branch arteries of the abdominal aorta (10 patients), 2 for the aorta (2 patients), and 7 for other arteries (6 patients). Of 54 arterial involvements (aneurysms, dissections, and ruptures), both with and without symptoms, 43 (80%) were in branches of the abdominal aorta (celiac artery and branches, 8; superior mesenteric artery, 4; renal arteries, 3; iliac arteries and branches, 28), 2 (4%) were in the aorta, and 9 were in other arteries. The diameter of the sinus of Valsalva was 29±5 mm, within the normal range. During follow-up, 3 patients died due to suspected ruptures in a branch of the celiac artery, the superior mesenteric artery, and the aorta.

Conclusion: Our findings indicate that lesions involving the branch arteries of the abdominal aorta rather than aorta were most prevalent in patients with vEDS.

Keywords: Ehlers–Danlos syndrome type IV, arterial complication, connective tissue disorder

Vascular Ehlers-Danlos syndrome (vEDS) is a type of heritable connective tissue disorder, similar to other such disorders including Marfan syndrome (MFS) and Loeys-Dietz syndrome (LDS). vEDS is mainly caused by a *COL3A1* mutation that results in increased fragility in the connective tissues of the arteries, bowels, and uterus. In particular, arterial complications have been reported as determinants of prognosis in patients with vEDS.[1] However, the relative prevalence of arterial lesions and the management practices for patients with vEDS have not been fully clarified. This study aimed to clarify which arterial lesion is most prevalent in vEDS and the care practices for patients with vEDS in daily clinical practice.

Methods

In this single-center retrospective study, we analyzed the clinical records of 20 consecutive patients who had been referred to our institute and diagnosed with vEDS.

The vEDS diagnosis was confirmed by identifying *COL3A1* mutations (19 patients) and decreased type III collagen protein level (1 patient). We looked for *COL3A1* gene variants by screening the entire coding region. Briefly, we extracted genomic DNA from peripheral blood leukocytes and performed high-resolution melting curve analysis to screen for gene variants,[2] followed by polymerase chain reaction (PCR)-directed sequencing to ascertain the variant types. In some cases, reverse transcription (RT)-PCR was performed using total RNA extracted from skin fibroblasts. *TGFBR1* and *TGFBR2* genes were also investigated as potential mimics of *COL3A1*. As a result, we elucidated the following variant types in 19 patients with *COL3A1*

gene mutations: 6 missense mutations that changed a glycine residue to another amino acid, 9 splice site mutations (point mutations at splice junctions that disrupted a splice donor except in 1 case) with additional confirmation for abnormal mRNA synthesis in vitro caused by exon skipping, and 4 nonsense mutations caused by base substitutions in stop codons. Of the 19 patients with genetic variants, the levels of type III collagen protein were measured for 4 cases. The genetic variants were evaluated and classified in accordance with the American College of Medical Genetics (ACMG) evaluation system.[3] As a result, the pathogenicity of 19 variants was classified as follows: 11 genetic mutations were registered in ClinVar and evaluated by ACMG (pathogenic 7, likely pathogenic 4); 7 genetic mutations were registered in databases other than ClinVar and evaluated by ACMG (pathogenic 4, likely pathogenic 3); and details of the genetic mutations in the remaining 1 case were unknown, although the amino acid substitution of glycine was recorded and evaluated to be pathogenic. Of the 20 patients in the present study, 18 were probands (individuals who triggered the identification of a family with a hereditary disease) of 18 different families. The remaining 2 patients were related to 2 different probands (i.e., they were identified after family screening).

First, we examined the characteristics of the patients. These included their age at first complication requiring admission, age at referral to our institute, age at final visit to our institute, gender, family history, follow-up periods, celiprolol intake, number of patients with some complications requiring admission, and deaths. Second, we examined the number of complications requiring admission due to arterial rupture or dissection with respect to lesion, such as number of affected patients, number of patients at first complication requiring admission, total number of complications at each lesion that required admission, total number of

complications per patient at lesion, and therapeutic strategies for complications. Finally, we examined the pathologic lesions with arterial involvement including aneurysm, dissection, and rupture. These examinations included asymptomatic patients and incidental findings through imaging at final assessment.

For arterial branches of the abdominal aorta other than the iliac arteries, aneurysms were defined as those >10 mm. For iliac arteries, aneurysms were defined as those >15 mm. This is because in patients with vEDS, aneurysm rupture occurs at a smaller diameter than in healthy individuals. The diameter of the sinus of Valsalva was measured and was compared to the normal range determined by age and body surface area.[4] Body surface area was calculated using the Mosteller formula.[5] The diameters of the ascending and descending aorta were measured at the level of pulmonary artery bifurcation and the diameter of the abdominal aorta was measured at the level of celiac artery, as reported previously.[6, 7]

The Ethics Committee of our Institute Council approved this study. Data collection was announced on our institute website, and potential participants were given the opportunity to decline further access to their data (opt-out method).

Continuous variables were expressed as the mean ± standard deviation. All statistical analyses were performed using SPSS for Windows, version 27.0 (SPSS Inc., Chicago, IL, USA).

Results

The characteristics of 20 patients with vEDS are listed in Table 1. The ages at first complication

requiring admission and at final visit to our institute were 29±13 and 42±11 years old, respectively. The observational period for outpatients of our institute was 67±30 months. In total, 17 of 20 patients took celiprolol. Of these, 71% took 400 mg of celiprolol daily at a maximum dose at final assessment.

The number of complications requiring admission for each lesion is shown in Table 2. The most common lesions that required admission were in the branch arteries of the abdominal aorta (18 lesions in 10 patients), accounting for 67% of 27 total arterial complications requiring admission. Among 27 arterial complications, 7 were treated with emergency endovascular therapies (stent-grafting, 1; stent implantation, 2; embolization, 4), and 1 with craniotomy. There were 16 pulmonary lesions (8 patients) and 16 bowel lesions (8 patients). The number of complications per patient was highest among those with tendon and ligament lesions (2.5). We did not find any uterine complications in our study population. Among 10 female patients, 7 experienced 12 deliveries including 3 caesarean sections. Only one patient delivered via prophylactic caesarean section after a vEDS diagnosis.

A total of 54 arterial involvements (aneurysm, dissection, and rupture of arteries—including asymptomatic patients and incidental findings through imaging at final assessment) are listed in Table 3. Arterial involvements were observed in 43 (80%) branch arteries of the abdominal aorta (celiac artery, 2; common hepatic artery, 2; splenic artery, 4; superior mesenteric artery (SMA), 4; renal arteries, 3; iliac arteries and their branches, 28) in 12 patients, 2 (4%) in the aorta (2 patients), and 9 (17%) in other arteries (6 patients). The diameter of the sinus of Valsalva was 29±5 mm at final assessment, and there was no dilatation beyond the normal range. Moreover, the thoracic aorta and abdominal aorta were not dilated. Overall, branch arteries of the

abdominal aorta accounted for 80% of the 54 cases with arterial involvement and were the most common arteries for lesion development.

Three patients died during follow-up period due to suspected arterial lesion ruptures. The first patient was 41 years old and suffered cardiopulmonary arrest shortly after complaining about abdominal pain. Autopsy imaging with CT scans revealed massive hematoma around the collapsed SMA, suggesting rupture of SMA. It was impossible to determine the diameter of SMA from autopsy imaging as SMA collapsed on autopsy imaging (SMA was 16 mm 13 months before rupture). The second patient was 35 years old and complained of sudden abdominal pain with shock during hospitalization due to perforation of the descending sigmoid colon and stoma creation. CT scans revealed hematoma near the celiac artery, suggesting rupture of the celiac artery. The diameter of the celiac artery was 14 mm 5 days before rupture. The third patient was 34 years old and suffered cardiopulmonary arrest shortly after complaining about back pain. Autopsy imaging with CT scans showed massive pleural effusion in the right thoracic cavity linked to hematoma around collapsed descending thoracic aorta with dissection, suggesting aortic rupture with dissection. The diameter of the descending aorta was 23 mm at 12 days before death. The autopsies of these three patients with sudden death were not available.

Discussion

The main finding of the present study is that in patients with vEDS, arterial involvement is most common in the branch arteries of the abdominal aorta, more prevalent than in the aorta.

Moreover, we did not observe dilatation of the aortic root at the level of the sinus of Valsalva, which is one of the characteristic features of MFS.

vEDS, formerly known as EDS type IV, is one of the 13 subtypes of EDS[8] and is caused primarily by *COL3A1* mutations. It is characterized by rupture of the arteries, bowels, and the uterus during pregnancy. The clinical presentation for vEDS is thin, translucent skin of the anterior chest, easy bruising, and small joint hypermobility.[9] Arterial complications are known determinants of prognosis in patients with vEDS.[1] From this perspective, vEDS is considered similar to other inherited aortic diseases such as MFS and LDS.

MFS is a representative heritable aortic disease with fragile connective tissues. Common causes of death included aorta-related death, such as that caused by dissection and rupture of aneurysms in the aorta.[10] The branch arteries of the aorta are also dilated in MFS; however, only 4.8% of these patients were treated during follow-up, and there were no spontaneous ruptures.[11] In contrast, in patients with vEDS, complications in the aorta were not as common as in those with MFS. One study of patients with vEDS reported that aortic events occurred in 13% of patients, and events in the branch arteries of the abdominal aorta occurred in 12%.[12] Another study reported that involvement of the aorta and visceral arteries was observed in 24% and 42% of patients with vEDS, respectively.[13] Further, a study reported that involvement of the aorta and branch arteries of the abdominal aorta accounted for 17.4% and 29.5% of cases with arterial involvement, respectively.[9] In the present study, pathologic lesions with complications requiring admission in the aorta and the branch arteries of the abdominal aorta were observed in 10% and 55% of cases, respectively. In addition, involvement of the aorta and branch arteries of the abdominal aorta accounted for 4% and 80% of 54 arterial involvements, respectively.

Therefore, clinicians should focus on the diameter of the arterial branch of the abdominal aorta rather than the aorta in daily medical practice. The low prevalence of aortic complications may be associated with celiprolol intake. In the present study, 85% of patients took celiprolol, which is considered a possible medical therapy for vEDS.[14-16] It is unclear why arterial involvement is more prevalent in the branch arteries of the abdominal aorta. In terms of the fragility of connective tissues, the arteries of patients with vEDS are thought to be more fragile than those of patients with MFS. If arteries are extremely fragile, branch arteries may be more affected by blood pressure than aorta with its richer elastic fiber. Similar to vEDS, the involvement of the arterial branch of the aorta is also often seen in patients with LDS.[17]

The dilatation of the sinus of Valsalva is known to be common in patients with MFS and LDS;[18] therefore, it should be carefully observed in patients with MFS and LDS, as dilatation in this region often causes type A aortic dissection and cardiac tamponade, leading to sudden death. However, in the present study, we did not observe any dilatation of the sinus of Valsalva beyond normal ranges as determined by age and body surface area. It is possible that in patients with vEDS, the sinus of Valsalva may not be as dilated as in patients with MFS, although we were unable to make this comparison in our study.

Therapies for arterial involvement are challenging in patients with vEDS due to the extreme fragility of their connective tissue. Clinicians often avoid invasive therapeutic procedures for potentially fatal arterial complications as much as possible, as these can lead to iatrogenic complications. Therefore, previous guidelines have not recommended an arterial diameter for prophylactic interventional therapy. We experienced rupture of a celiac artery with a diameter of 14 mm 5 days before rupture and a rupture of a SMA with a diameter of 16 mm 13 months

before rupture. Due to our small sample size, we were unable to determine the diameters of branch arteries from the abdominal aorta for interventional therapy. Therefore, we can only comment that invasive therapy should be considered for aneurysms of branch arteries from the abdominal aorta in vEDS with smaller diameters than those of normal individuals. Endovascular therapy is preferred because it is less invasive. In the present study, we found that of 27 arterial complications that required admission, 7 were treated with emergent endovascular therapies and one with emergent craniotomy. However, none were treated with emergent open thoracic or abdominal surgeries.

The present study has some limitations. First, the most important limitation is that the study population was small, which may have caused incidental biases and complications. We should take into consideration that our data may be affected by sampling bias. However, the prevalence of vEDS is assumed to be 1/50,000–250,000,[19] so it is difficult to collect large-scale patient data. Therefore, accumulation of results obtained from even this small population is considered to be meaningful. Furthermore, our data may be helpful for future meta-analyses. Second, the prevalence of arterial aneurysm depends on its definition. In the present study, aneurysms in the iliac arteries were defined as lesions >15 mm. This is a stricter definition than that used in other studies (>25 mm),[11] which adopts the definition of 1.5 times the normal diameter of the iliac artery in healthy individuals. However, smaller diameter arterial aneurysms tend to rupture more frequently in patients with vEDS. Therefore, we believe that arterial aneurysms should be defined using a smaller diameter in such patients in order to prevent arterial dissection and rupture. Third, patients were requested to provide their daily blood pressure records so we could try and maintain their blood pressure levels within the normal

range. However, these data were not available. Finally, this study does not provide detailed information on genetic abnormalities in the 19 cases for which genetic testing was performed. However, our aim is to upload our data to the public gene database after obtaining requisite patient consent and ethics committee approval.

Conclusion

Our data demonstrate that lesions involving the branch arteries of the abdominal aorta were most prevalent in patients with vEDS. In daily clinical practice, clinicians caring for patients with vEDS should pay special attention to the branch arteries of the abdominal aorta rather than to the aorta.

Acknowledgement

We deeply thank Rie Aoyama and Tetsuro Sekine for collecting additional clinical data, and Yasunobu Maruoka for re-confirming genetic data.

Funding source

The authors have no funding sources to disclose.

Disclosure

The authors have no conflicts of interest to disclose.

References

1. Pepin M, Schwarze U, Superti-Furga A, Byers PH. Clinical and genetic features of Ehlers–Danlos syndrome type IV, the vascular type. N Engl J Med 2000;342:673–80.
2. Naing BT, Watanabe A, Shimada T. A novel mutation screening system for Ehlers-Danlos Syndrome, vascular type by high-resolution melting curve analysis in combination with small amplicon genotyping using genomic DNA. Biochem Biophys Res Commun. 2011;405:368-72.
3. Richards S, Aziz N, Bale S, et al; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17:405-24.
4. Roman MJ, Devereux RB, Kramer-Fox R, O'Loughlin J. Two-dimensional echocardiographic aortic root dimensions in normal children and adults. Am J Cardiol 1989;64:507–12.
5. Mosteller RD. Simplified calculation of body-surface area. N Engl J Med 1987;317:1098.
6. Itani Y, Watanabe S, Masuda Y, et al. Measurement of aortic diameters and detection of asymptomatic aortic aneurysms in a mass screening program using a mobile helical computed tomography unit. Heart Vessels. 2002;16:42-5.
7. Guthaner DF, Wexler L, Harell G. CT demonstration of cardiac structures. AJR Am J Roentgenol. 1979;133:75-81.
8. Malfait F, Francomano C, Byers P, et al. The 2017 international classification of the Ehlers-Danlos syndromes. Am J Med Genet C Semin Med Genet 2017;175:8–26.

9. Oderich GS, Panneton JM, Bower TC, et al. The spectrum, management and clinical outcome of Ehlers-Danlos syndrome type IV: a 30-year experience. J Vasc Surg 2005;42:98–106.
10. Murdoch JL, Walker BA, Halpern BL, Kuzma JW, McKusick VA. Life expectancy and causes of death in the Marfan syndrome. N Engl J Med 1972;286:804-8.
11. Lopez-Sainz A, Mila L, Rodriguez-Palomares J, et al. Aortic branch aneurysms and vascular risk in patients with Marfan syndrome. J Am Coll Cardiol 2021;77:3005–12.
12. Pepin MG, Schwarze U, Rice KM, Liu M, Leistritz D, Byers PH. Survival is affected by mutation type and molecular mechanism in vascular Ehlers–Danlos syndrome (EDS type IV). Genet Med 2014;16:881–8.
13. Shalhub S, Black JH 3rd, Cecchi AC, et al. Molecular diagnosis in vascular Ehlers–Danlos syndrome predicts pattern of arterial involvement and outcomes. J Vasc Surg 2014;60:160–9.
14. Ong KT, Perdu J, De Backer J, et al. Effect of celiprolol on prevention of cardiovascular complications in vascular Ehlers-Danlos syndrome: a prospective randomised, open, blinded-endpoints trial. Lancet 2010;376:1476–84.
15. Baderkhan H, Wanhainen A, Stenborg A, Stattin EL, Björck M. Celiprolol treatment in patients with vascular Ehlers-Danlos syndrome. Eur J Vasc Endovasc Surg 2021;61:326–31.
16. Frank M, Adham S, Seigle S, et al. Vascular Ehlers-Danlos syndrome: long-term observational study. J Am Coll Cardiol 2019;73:1948–57.
17. Loeys BL, Schwarze U, Holm T, et al. Aneurysm syndromes caused by mutations in the

TGF-beta receptor. N Engl J Med 2006;355:788–98.

18. Attias D, Stheneur C, Roy C, et al. Comparison of clinical presentations and outcomes between patients with TGFBR2 and FBN1 mutations in Marfan syndrome and related disorders. Circulation 2009;120:2541–9.

19. Chohan K, Mittal N, McGillis L, et al. A review of respiratory manifestations and their management in Ehlers-Danlos syndromes and hypermobility spectrum disorders. Chron Respir Dis. 2021 Jan-Dec;18:14799731211025313.

Table 1. Characteristics of the patients

Total number of patients	20
Age at first event requiring admission (years)	29±13
at referral to our hospital (years)	36±12
at final visit to the hospital (years)	42±11
Male (n, %)	10 (50%)
Family history (n, %)	11 (55%)
Follow-up period (months)	67±30
Reason for diagnosis	19 COL3A1 mutations 1 decreased Type III collagen
Celiprolol intake at final assessment (n, %)	17 (85%)
Daily dose at final assessment (mg/day)	324±125
Patients taking 400 mg daily (n, %)	12 (71%)
Patients with complications requiring admission (n, %)	18 (90%)
Deaths (n, %)	3 (15%)

Table 2. Complications requiring admission with respect to lesion

Pathologic lesion	Affected patients	First complication	Total number of complications	Complications /patients	Therapy
Arterial branch of the abdominal aorta (n)	10	4	18	1.8	Embolization (4) Stent (1)
Aorta (n)	2	1	2	1.0	Stent-graft (1)
Other arteries (n)	6	3	7	1.2	Stent (1) Craniotomy (1)
Pulmonary (n)	8	7	16	2.0	VATS (2) Pneumonectomy (1)
Colon/intestine (n)	8	3	16	2.0	Surgical repair (16)
Tendon/ligament (n)	2	0	5	2.5	Surgical repair (5)
Uterus	0	-	-	-	-

VATS, Video-assisted thoracic surgery

Table 3. Pathologic arterial involvement lesion both with and without symptoms

Pathologic lesions	Affected patients	Details
Age at final assessment (years)		41±11
All arterial involvement (n)	14 (70%)	54
Branch of the abdominal aorta (n, %)	12 (60%)	43 (80%) Celiac (2); common hepatic (2); splenic (4); superior mesenteric (4); renal (3); common iliac (16); external iliac (9); internal iliac (2); jejunal (1)
Aorta (n, %)	2 (10%)	2 (4%) Abdominal (1); descending (1)
Height		159±12 cm
Annulo-aortic ectasia (n, %)	0	Sinus of Valsalva; 28.8±4.7 mm
Thoracic aortic aneurysm	0	Ascending aorta; 29.0±3.6 mm Descending aorta; 20.5±3.0 mm
Abdominal aortic aneurysm	0	Abdominal aorta; 17.3±2.6 mm
Other arteries (n, %)	6 (30%)	9 (17%) Intercostal (2); carotid (3); vertebral (1); cerebral (2); coronary (1)

Arterial involvement (aneurysm, dissection, and rupture) includes asymptomatic patients and incidental findings through imaging at final assessment