Molecular diagnosis in vascular Ehlers-Danlos syndrome predicts pattern of arterial involvement and outcomes

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Objective: **The management of arterial pathology in individuals with vascular Ehlers-Danlos syndrome (vEDS) remains a challenge. Here we describe the correlation between *COL3A1* gene mutation type and the clinical phenotype in individuals with vEDS.**

Methods: **Individuals with confirmed molecular diagnoses of vEDS were enrolled in a multi-institutional natural history study. Data collected included demographics, clinical and family histories, arterial pathology (aneurysm, dissection, and rupture), operative details, and autopsy reports. Individuals were classified into two cohorts by the type of *COL3A1* mutations and their effect on the amount of normal collagen produced: those with mutations that lead to minimal (MIN) production (10%-15%) of normal type III collagen and those with haploinsufficiency (HI) mutations that lead to production of 50% of the normal type III collagen.**

Results: **A cohort of 68 individuals (72%) from 56 families had arterial pathology (44% male) with 13% HI. The HI group was older at the time of their first vascular event (mean, 42 [range, 26-58] years vs 33 [range, 8-62] years; $P = .016$) and had a higher incidence of aortic pathology than the MIN group (56% vs 21%; $P = .025$). Visceral arterial pathology was seen in 43 arteries in 23 individuals in the MIN group vs only one artery in five individuals in the HI group. Emergency surgical procedures were more likely to be undertaken when vEDS diagnosis was not known (81% vs 41%; $P = .005$), and 81% of these procedures were open surgical repair compared with 19% endovascular repairs ($P = .019$). Open and endovascular repairs were equally used in the elective setting. Postoperative complications were highest when the diagnosis of vEDS was not known (62% vs 14%; $P < .001$) and when procedures were undertaken in an emergency setting (5% vs 55% $P < .001$). Mortality due to arterial complications was 0% in the HI cohort and 21% in the MIN cohort ($P = .132$).**

Conclusions: **Arterial pathology in vEDS individuals is related to the underlying *COL3A1* mutation type. The arterial pathology in individuals with HI mutations occurs at later ages with a higher incidence of aortic disease compared with other *COL3A1* mutation types. Molecular diagnosis is recommended because diagnosis confirmation, appropriate surveillance, and prophylactic interventions in an elective setting improve surgical outcomes. (J Vasc Surg 2014;60:160-9.)**

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Vascular Ehlers-Danlos syndrome (vEDS) is a syndrome inherited in an autosomal-dominant manner that leads to spontaneous arterial dissection or rupture. Management of these arterial complications remains a challenge. The disorder is due to heterozygous mutations in *COL3A1*, which encodes the procollagen peptide for type III collagen.[1] Type III collagen is especially abundant in the skin, blood vessels, and hollow organs such as the bowel and uterus. The complications of vEDS reflect the expression pattern of the gene and include rupture and dissection of primarily medium-sized arteries, spontaneous rupture of the intestine or the gravid uterus, and thin, fragile skin that bruises easily and heals poorly.

Although the estimated minimum prevalence is one in 200,000,[2] vEDS diagnosis is increasing due to improvements in molecular diagnosis and recognition of mutations that lead to a milder phenotype. More than 700 *COL31A* mutations have been identified, with 50% of affected individuals inheriting the mutation from an affected parent, and 50% due to de novo mutations.[2,3]

Two-thirds of the *COL3A1* mutations are caused by "mis-sense mutations," which are glycine substitutions in

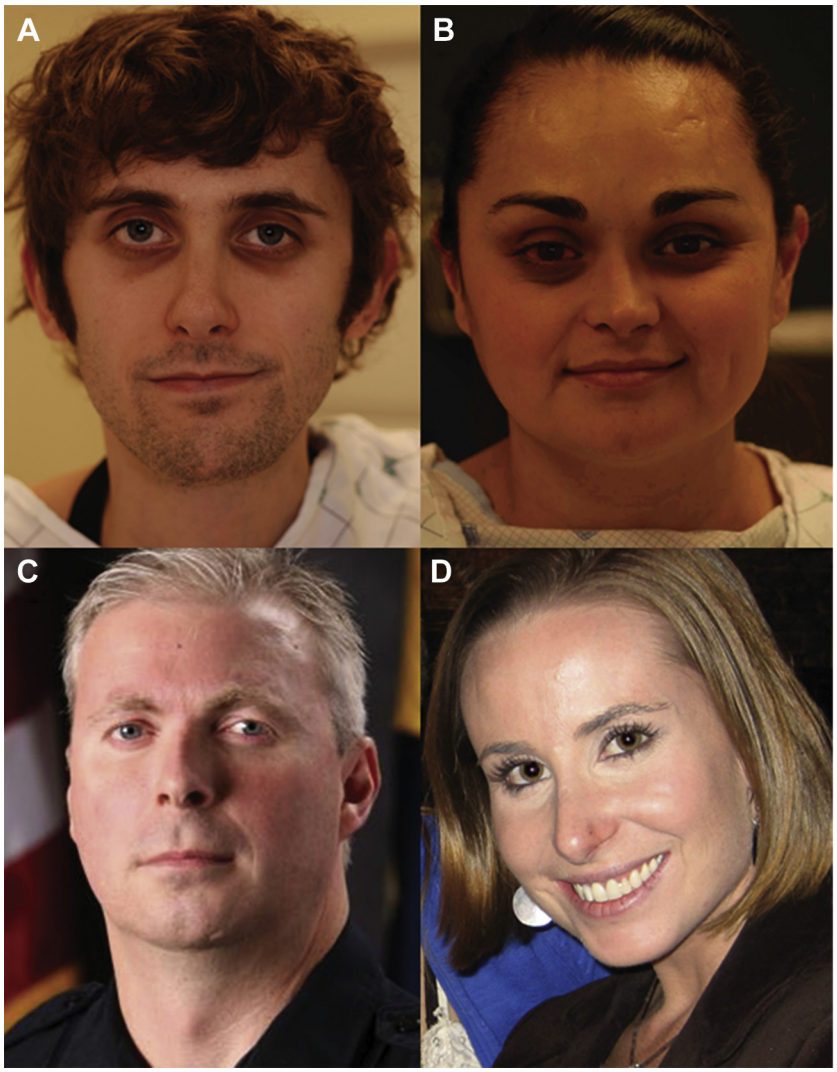

Fig 1. Spectrum of facial features in individuals with vascular Ehlers-Danlos syndrome (vEDS) shows variability among patients and does not necessarily correlate with the severity of the underlying arterial pathology. These four individuals died of vascular complications. **A,** Caucasian man (MIN mutation, c.2553+1delG) presenting with characteristic vEDS facies, including proptotic eyes, long and thin nose, minimal subcutaneous facial fat, and a triangular-shaped face. **B,** Hispanic woman (MIN mutation, c.3545G>A p.G1182E) with mildly proptotic eyes, a long thin nose, and a hypotrophic forehead scar, but otherwise normal facial features. **C,** Caucasian man (MIN mutation, c.2870G>T, p.G957D) with downslanting palpebral fissures, long thin nose, thin lips, and attached pinna. **D,** Caucasian woman (c.665G>T, p.G222V) presenting with a long thin nose but otherwise normal facial features. Written consent was obtained at the time of enrollment for clinical photography and use in medical education. *MIN,* Mutations that lead to minimal (10%-15%) normal type III collagen production. Consent to have their images published in JVS was obtained for all patients shown.

the triplets of the helical domain of collagen.[4] One-third of *COL3A1* mutations are caused by "exon skip mutations" that lead to exon splicing errors that cause an in-frame shift in the reading frame for translation.[5] Both types of mutation lead to equal production of abnormal and normal procollagen peptides, but because type III collagen is a homotrimer of three identical procollagen peptides, such mutations lead to production of a seven-to-one ratio of abnormal to normal collagen molecules, thus a minimal (MIN) amount (10%-15%) of normal collagen is produced.[3,6]

The remainder of the *COL3A1* mutations are nonsense mutations or frameshift mutations that lead to the creation of premature termination codons. These premature stops in translation cause rapid degeneration of the mutant messenger RNA by way of non-sense-mediated decay. This causes expression of a single gene, thus termed haploinsufficiency (HI). The end result is production of 50% of the amount of normal type III procollagen. HI mutations are associated with reduced penetrance and delayed onset of arterial pathology compared with MIN mutations.[7]

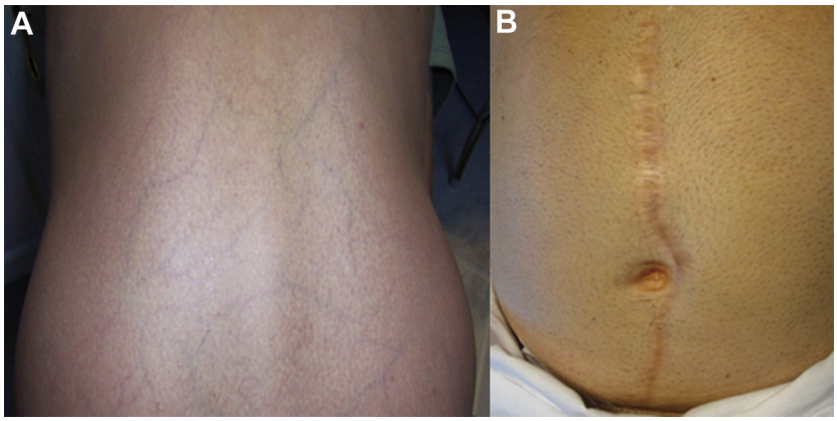

Fig 2. Cutaneous manifestations of vascular Ehlers-Danlos syndrome (vEDS). **A,** Thin, translucent skin with visible venous pattern on the lower back of a patient with vEDS (MIN mutation, exon skip). **B,** Widened atrophic scar in a patient (HI mutation) after open abdominal aortic aneurysm repair. *HI,* Haploinsufficiency mutations that lead to 50% normal type III collagen production; *MIN,* mutations that lead to minimal (10%-15%) normal type III collagen production.

Our aim was to evaluate the current surgical management of vEDS-associated arterial pathology at tertiary referral centers and to correlate presentation and outcome with the underlying type of mutation.

METHODS

Approval by the Institutional Review Board was obtained to enroll individuals with vEDS referred to the University Texas at Houston Medical School, Johns Hopkins Hospital, and the National Institute on Aging (NIA) Studies of Heritable Disorders of Connective Tissue trial (NCT00270686), which was approved by the MedStar Institutional Review Board (#2003-086).

The cohort for this study comprised a subgroup of enrolled individuals with a confirmed molecular diagnosis of vEDS with arterial pathology. Proper consents were obtained from the patients, including written consents for clinical photography and use in medical education. All identifiable photographs in this report are from deceased individuals who provided consents for use of their photographs at the time of enrollment.

Data collected were initially retrospective, and ongoing longitudinal follow-up occurred from the date of enrollment. Data were obtained from study visits, medical records, radiology images, correspondence with referring physicians, and telephone interviews. Abstracted data included demographics, age at diagnosis, family history, reasons for diagnosis, and clinical diagnostic criteria, as defined by the Revised Nosology of Villefranche.[2] Arterial pathology was defined as arterial dissection, aneurysm, and rupture. Data collected included initial age at arterial presentation, surveillance and diagnostic imaging if performed (computed tomography [CT], magnetic resonance imaging, and duplex ultrasound scans), management, morbidity, and mortality.

Molecular diagnosis. *COL3A1* mutation detection was performed on a clinical basis in another laboratory or on a research basis at the NIA. At the NIA, the coding regions and flanking sequences of the *COL3A1* gene were amplified and sequenced. Primers were designed by Primer3 (http://frodo.wi.mit.edu/primer3/) and are available upon request. Mutations were identified by alignment with the reference sequence (ENSG00000168542). Data collected included the *COL3A1* mutation causing vEDS and biochemical analysis of type III procollagen production by dermal fibroblasts performed by a Clinical Laboratory Improvement Amendments-certified laboratory. Results of dermal fibroblasts studies were reviewed, and the amount of type III procollagen produced was verified to correspond with the underlying *COL3A1* mutation. The patients were divided into two groups: MIN and HI based on the predicted effect, and in some cases, proven effect, of *COL3A1* mutations on type III procollagen production.

Statistical analysis. Data were analyzed using Excel 2010 software (Microsoft Corp, Redmond, Wash) and SPSS 20.0 software (IBM Corp, Armonk, NY). Data are presented as mean ± standard error of the mean and ranges or as numbers and percentages. Continuous variables were compared using a two-sample *t*-test, assuming that variance was equal. Categoric variables were compared using χ^2 testing. All P values were two-sided, and $<.05$ was considered significant.

RESULTS

Arterial pathology related to vEDS was documented in 68 individuals (44.1% male). The mean age at diagnosis was 33.0 ± 1.6 years (range, 0.3-63 years). Skin biopsies were performed in 24 of the cohort (35.8%).

Family history. Clinical manifestations of vEDS were reported in the family members of 44 of the 68 individuals

Table I. Demographics, clinical characteristics, and reasons for diagnosis in patients with vascular Ehlers-Danlos syndrome (*vEDS*)

Variables[a]	*All (N = 67)*	*MIN (n = 58)*	*HI (n = 9)*	P[b]
Male	30 (44.1)	23 (39.7)	7 (77.8)	.032
Caucasian	60 (89.6)	51 (87.9)	9 (100.0)	
African American and Hispanic	7 (10.4)	7 (12.1)	0	
Age, years	40.9 (8-70.2)	39.9 (8 -70.2)	47.5 (26-61.6)	.116
Age at				
Diagnosis, years	33 (0.3-63)	31.5 (0.3-63)	42.6 (26-58)	.016
First arterial pathology diagnosis, years	34.2 (8-62)	33.0 (8-62)	41.6 (26-58)	.030
Major and minor criteria				
Family history of vEDS	43 (64.2)	35 (60.3)	8 (88.9)	.097
Easy bruising	51 (76.1)	46 (79.3)	5 (55.6)	.120
Colon perforation	8 (11.9)	8 (13.8)	1 (1.7)	.235
Gravid uterine rupture (females)	1 (2.7)	1	0	
Thin translucent skin	38 (56.7)	36 (62.1)	7 (12.1)	.025
Skin hyperextensibility	7 (10.4)	7 (12.1)	0	.271
Characteristic facial appearance	41 (61.2)	38 (65.5)	3 (33.3)	.065
Carotid-cavernous sinus fistula	4 (6)	4 (6.9)	0	.417
Small joint hypermobility	29 (43.3)	28 (48.3)	1 (11.1)	.036
Tendon or muscle rupture	6 (9)	6 (10.3)	0	.312
Early-onset varicose veins	9 (13.4)	9 (15.5)	0	.204
Pneumothorax/hemothorax	15 (22.4)	14 (24.1)	1 (11.1)	.383
Clubfoot	6 (9)	6 (10.3)	0	.312
Other comorbidities				
Hypertension	15 (22.4)	11 (19)	4 (44.4)	.088
Pyloric stenosis	3 (4.5)	3 (5.2)	0	.485
Shoulder surgery or dislocation	4 (6)	4 (6.9)	0	.417
Migraine headaches	6 (9)	6 (10.3)	0	
Reason for diagnosis				
Personal history of vascular pathology	29 (43.3)	22 (37.9)	7 (77.8)	.025
Family history	21 (31.1)	19 (32.8)	2 (22.2)	
Personal history of colon perforation	5 (7.5)	5 (8.6)	0	
History of excessive bruising	4 (6)	4 (6.9)	0	
Diagnosed at autopsy	2 (3)	2 (3.4)	0	
History of excessive scarring	1 (1.5)	1 (1.7)	0	
History of ruptured spleen	1 (1.5)	1 (1.7)	0	
Strong phenotype	1 (1.5)	1 (1.7)	0	
Unknown reason	2 (3)	2 (3.4)	0	

HI, Haploinsufficiency mutations that lead to 50% normal type III collagen production; *MIN*, mutations that lead to minimal (10%-15%) normal type III collagen production.

[a]Categoric data are presented as number (%) and continuous data as mean (range).

[b]The *P* value was calculated using the Pearson χ^2 test for categoric data and by independent samples *t*-test with equal variances assumed for the continuous variables.

(64.7%), indicating a positive family history. Of those with reported family histories, 15 (22.1%) had a family member with a confirmed molecular diagnosis of vEDS as indicated by the presence of a *COL3A1* mutation.

Mutation types. There were 59 individuals (86.8%) with MIN mutations. MIN mutations included mis-sense in 42 (61.8%), exon skip in 12 (17.6%), and unusual mutations in 5 (7.4%). In addition, one individual had biochemical diagnosis of minimal type III procollagen production and was thus included in this group. There were nine individuals (13.2%) with HI mutations, including non-sense in five (55.6%) and frameshift mutations in four (44.4%).

The HI group was older when the first arterial pathology was diagnosed (mean age, 41.6 ± 2.9; range, 26-58 years) compared with the MIN group (33.1 ± 1.5; range, 8-62 years; $P = .030$). Characteristic facial appearance was common (61.2%) but displayed a wide range of variability (Fig 1). Easy bruising and the characteristic thin translucent skin with visible veins (Fig 2) were seen more commonly in the MIN group than in the HI group (Table I). Table I details the demographics, clinical diagnostic criteria, and reasons for diagnosis of the vEDS cohort.

Arterial pathology. The distribution of arterial pathology based on genotype is illustrated in Fig 3. Aorta involvement was seen in 16 individuals. The prevalence of aortic disease was significantly higher in the HI group (55.6%) than in the MIN group (7%; $P < .001$). Surgical management and outcomes are detailed in Table II. Nonoperative management was undertaken, without complications, in a descending thoracic aorta aneurysm (3.5 cm) that was diagnosed in a patient with MIN mutation.

Pathology of brachiocephalic arteries. Details of the brachiocephalic arteries involved and management are

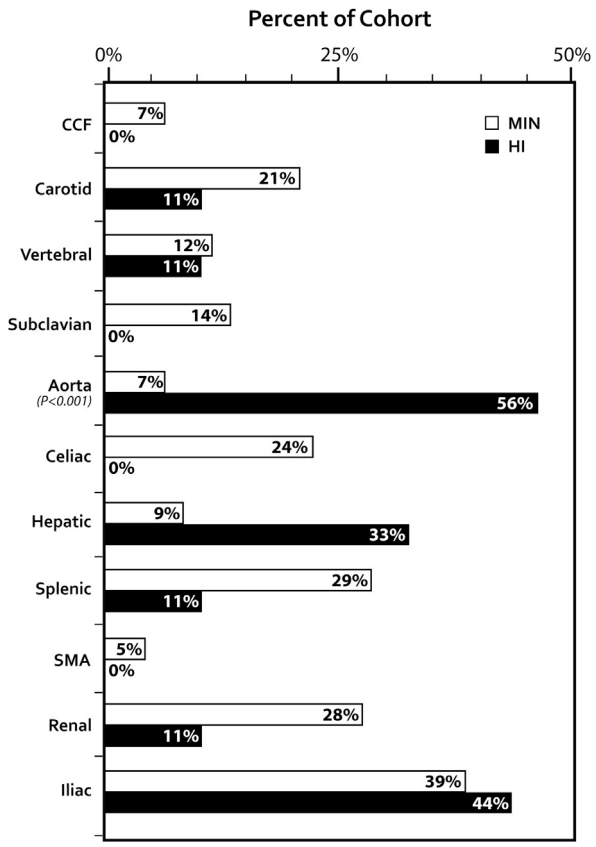

Fig 3. Arterial involvement in vascular Ehlers-Danlos syndrome (vEDS) patients by *COL3A1* mutations. Although vEDS involves medium-sized arteries more commonly, there was an increased prevalence of aortic involvement in the HI cohort compared with the MIN cohort ($P = .025$). *CCF,* Carotid cavernous fistula; *HI,* mutations that lead to 50% normal type III collagen production; *MIN,* mutations that lead to minimal (10%-15%) normal type III collagen production; *SMA,* superior mesenteric artery.

reported in Table III. Multibrachiocephalic arterial involvement was seen in nine individuals, all with MIN mutations.

Visceral arteries. Multivisceral arterial involvement was seen in 23 patients (43 arteries), all in the MIN group. In the HI group, there were five individuals with visceral arterial involvement, all with single-artery pathology.

Celiac artery pathology occurred only in five individuals with MIN mutation: three aneurysms (1.5-2 cm in diameter) and two dissections that progressed to aneurysms (1.6-1.8 cm) during 1 year of follow-up. All of these individuals were managed nonoperatively.

Hepatic artery pathology occurred in 10 individuals (seven MIN [12.1%] vs three HI [33.3%]; $P = .096$). Management was nonoperative in six aneurysms smaller <2 cm in diameter. Two individuals underwent coil embolization to treat a right hepatic artery (2.2 cm in diameter) and an intraparenchymal hepatic artery rupture. One individual, a 34-year-old woman with MIN-type mutation (c.1772G>A, p.Gly591Asp), remains under observation due to high surgical risk for a stable 3-cm proper hepatic artery aneurysm.

Splenic artery pathology occurred in 18 individuals (17 MIN [29.3%] vs one HI [11.1%]; $P = .252$). Management was nonoperative in isolated dissections or in aneurysms <1.7 cm in diameter (n = six). Coil embolization was performed successfully in four aneurysms >2 cm in diameter (one with a contained rupture). A ruptured splenic artery of unknown size with hemodynamic compromise occurred in two female patients who required operative exploration and splenectomy. One was 62 years old (c.3319G>C, p.Gly1107Arg), the other was 28 years old (c.3499G>C, p.Gly1000Arg), and both had MIN-type mutations and were diagnosed after the rupture event.

Superior mesenteric artery (SMA) pathology occurred only in individuals with the MIN mutation. One patient, a 20-year-old man (c.2482G>T, p. Gly828Trp), presented with rupture not amenable to repair, thus necessitating ligation and right hemicolectomy. One patient with SMA dissection was managed nonoperatively, and another SMA dissection in a 39-year-old woman (c.2356G>A, p.Gly786Arg) was managed by placement of a 6-mm ×18-mm bare metal stent. Initial attempt at access through the brachial artery for intended embolization was complicated by brachial artery dissection, necessitating transfer to a tertiary center (Johns Hopkins Hospital). The case was then performed through a femoral artery access, with manual compression for 5F sheath removal, and no adverse events.

Renal artery pathology occurred in 17 individuals (16 MIN [27.6%] vs one HI [11.1%]; $P = .291$). This involved small aneurysms and dissections in 14, leading to renal infarcts in eight, all managed nonoperatively. The renal artery in a 41-year-old female patient who had undiagnosed vEDS (c.766delA, p. Ile256Fx, HI type mutation) had fibromuscular dysplasia-type beaded appearance. She underwent an attempted open repair, complicated by nephrectomy and a subsequent incisional hernia. Coil embolization was performed successfully in one patient with an intra-parenchymal renal artery aneurysm, and on subsequent follow-up was noted to have a dissection that was treated with nonoperative management. A ruptured renal artery with hemodynamic compromise occurred in a 17-year-old female patient (IVS43+2T>G, MIN-type mutation), who died intraoperatively of hemorrhagic shock.

Iliac arteries. Iliac arteries aneurysms and dissections independent of abdominal aortic involvement occurred in 22 individuals (22 MIN [34.5%] vs two HI [22.2%]; $P = .466$). Successful nonoperative management was used in cases of dissection (n = seven) aneurysms <2.5 cm in diameter (n = three). Details of iliac arteries operative management are reported in Table IV. Two patients died of presumed iliac artery rupture: one was a 28-year-old woman (c.3201+2T>C, MIN-type mutation) with a known maximum iliac artery size of 1.4 cm, and the second was a 29-year-old woman (c.665G>T, p.Gly222Val, MIN-type mutation) with known iliac artery dissection. Both

Table II. Surgical management and outcomes of aortic pathology in patients with vascular Ehlers-Danlos syndrome (vEDS)

Aortic pathology	*Age, years*	*Sex*	*Mutation*	*Operation*	*Outcome*
Thoracic aorta					
Type A aortic dissection	40	M	HI	Interposition graft, fem-fem bypass ATA and arch homograft	Graft infection
Type B aortic dissection with extension into iliacs	35	M	HI	Endovascular stent graft	Renal infarcts due to embolization, alive at age 42
Chronic type B dissection with 6 cm DTA aneurysm	19	M	MIN	Reversed elephant trunk (Dacron)[a]	Enlargement of intercostals patch 2 years later
				Interposition Dacron graft, bypass to celiac, SMA, and renal arteries	Alive at age 25
Abdominal aorta					
AAA	40	M	HI	Aortobiiliac repair	Iliac limb thrombosis, IH
				Redo aortobiiliac bypass, Incisional hernia repair	Abdominal wound dehiscence. (Fig 2, *B*). Alive at age 52
AAA saccular (4 cm), bilateral CIAA with dissection	58	M	HI	Aortobiiliac repair, jump graft to RIIA	Alive at age 61
AAA, dissection, rupture	51	M	HI	Aortobiiliac repair; "buttery" aorta	Alive at age 57
Abdominal aortic dissection (trauma related) to RCFA with RLE ischemia	24	M	HI	Fem-fem bypass	Abdominal aorta at 3 cm. Alive at age 32
AAA (4.6 cm)	41	M	HI	Interposition graft	Alive at age 47
AAA, bilateral CIAA	21	F	MIN	Aortobiiliac repair, fragile tissue	Abdominal wound dehiscence. Died 10 years later
AAA (4.5 cm), bilateral CIAA due to aortic dissection (trauma related)	27	M	MIN	Aortobiiliac repair	Alive at age 27

AAA, Abdominal aortic aneurysm; *ATA,* ascending thoracic aorta; *CIAA,* common iliac artery aneurysm; *DTA,* descending thoracic aorta; *F,* female; *fem-fem,* femorofemoral; *HI,* haploinsufficiency mutations that lead to 50% normal type III collagen production; *IH,* intimal hyperplasia; *M,* male; *MIN,* mutations that lead to minimal (10%-15%) normal type III collagen production; *RCFA,* right common femoral artery; *RIIA,* right internal iliac artery; *RLE,* right lower extremity; *SMA,* superior mesenteric artery.
[a]DuPont, Wilmington, Del.

presented with pain and had cardiac arrest during the diagnostic workup.

Effect preoperative diagnosis of vEDS on operative outcomes. Fifty procedures (29 emergency, 21 elective) were performed in 35 patients (nine HI [25.7%]) and involved the brachiocephalic arteries in 9, coronary arteries in 3, aorta in 12, iliac arteries in 8, visceral arteries in 14, tibial arteries in 2, inferior epigastric artery in 1, and ruptured chordae tendineae in 1. Emergency procedures were performed in 62.2% of the MIN group and in 46.2% of the HI group. Postoperative complications were similar between the MIN (13 [35.1%]) and HI (four [30.7%]) groups ($P = .775$)

Diagnosis of vEDS was known in 42% of individuals before surgical intervention. Arterial repairs in these patients were approached in an elective manner with an equal mix of open and endovascular repair, 48.4% and 51.7%, respectively, as necessitated by the underlying arterial pathology (Fig 4). In patients who required emergency interventions, the surgical technique was altered to accommodate the fragility of tissues.

The patients with undiagnosed vEDS were significantly more likely to present in an emergency fashion (80.9% vs 41.3%; $P = .005$) and undergo open surgical repair (81% vs 48.3%; $P = .019$). Postoperative complications were substantially increased in these individuals ($P < .001$; Table V). All intraoperative deaths (n = 3) occurred in individuals with the MIN-type mutation who presented in an emergency fashion and required management without the benefit of a preoperative vEDS diagnosis.

Mortality. Mean follow-up from the time of diagnosis was 8 ± 0.82 years (range, 1-26 years). There were 12 deaths, all occurring in the MIN group (21%), with mean age at death of 31.4 ± 2.6 years (range, 17-45 years). Causes of death were intraoperative deaths during attempts to repair ruptured iliac arteries (n = 2) and a renal artery (n = 1), stroke after carotid cavernous fistula embolization (n = 1), mesenteric arterial thrombosis and necrosis after admission for small-bowel obstruction (n = 1; Fig 1, *A*), central catheter insertion complication (n = 1; Fig 1, *B*), rapid aneurysmal degeneration of iliac and gluteal arteries complicated by retroperitoneum and spontaneous hemothorax after colostomy take down (n = 1; Fig 1, *C*), presumed iliac artery rupture (n = 2; Fig 1, *D*), and unexpected death of unknown causes (n = 3).

DISCUSSION

Management of vascular pathology associated with vEDS remains a clinical challenge. This report highlights the importance of establishing the molecular diagnosis in cases of vEDS. Although clinical findings can offer a suggestion of the diagnosis, molecular testing should be

Table III. Presentation, management, and complications of brachiocephalic arteries pathology in patients with vascular Ehlers-Danlos syndrome (vEDS)

Artery	*Arterial pathology*	*No.*	*Mutation (No.)*	*Age range, years*	*Presentation (No.)*	*Management*	*Complications/comments*
Carotid	Dissection	5	MIN (4), HI (1)	26-51	Surveillance (2), symptomatic (1), trauma (2)	Nonoperative	None
	Stenosis	2	MIN (1), HI (1)	36-41	Surveillance	Nonoperative	FMD appearance (HI)
	Ectasia	3	MIN (2), HI (1)	36-63	Surveillance	Nonoperative	None
	Aneurysm	7	MIN	22-56	Surveillance (6), Symptomatic (1)	Nonoperative (6), coiling & stenting (1)	TIA after coiling
	CCF	5	MIN	25-46	Symptomatic	Endovascular	One required repeat embolization 2 years later
Vertebral	Dissection	6	MIN (5), HI (1)	22-52	Surveillance (3), symptomatic (3)	Nonoperative	PCA infarct (age 52), stenosis on F/U (n = 2)
	Ectasia	1	MIN	36	Surveillance	Nonoperative	None
	Aneurysm	1	MIN	29	Surveillance	Nonoperative	0.5 cm at V2
	Dissection	2	MIN	41	Surveillance	Nonoperative	Bilateral in same case
Subclavian	Ectasia	1	MIN	52	Surveillance	Nonoperative	None
	Aneurysm	3	MIN	26-34	Surveillance	Nonoperative (3)	None
	Aneurysm	1	MIN	26	Symptomatic	R SCA ligation, L axillary to R SCA bypass	Bypass thrombosis, reintervention, alive at age 27
	Aneurysm	1	MIN	18-32	Rupture (R SCA)	Endovascular stenting R CCA/R SCA	No complications
	Aneurysm	1	MIN	32	Rupture (L SCA)	Carotid subclavian bypass	Post-op infarcts, prolonged ventilator dependence, tracheostomy

CCA, Common carotid artery; *CCF,* carotid-cavernous fistula; *FMD,* fibromuscular dysplasia; *F/U,* follow-up; *HI,* haploinsufficiency mutations that lead to 50% normal type III collagen production; *L,* left; *MIN,* mutations that lead to minimal (10%-15%) normal type III collagen production; *PCA,* posterior cerebral artery; *R,* right; *TIA,* transient ischemic attack; *SCA,* subclavian artery.

Table IV. Iliac artery interventions and complications in cases of vascular Ehlers-Danlos syndrome (vEDS)

Pathology	*Mutation*	*Age, years*	*Management*	*Complications*
AVF/symptomatic	MIN	28	Elective endovascular repair	Alive at age 34
AVF/rupture	MIN	28	Emergency open repair	Intraoperative death
Dissection	MIN	55	Elective prophylactic iliofemoral bypass	Alive at age 59
Dissection	MIN	43	Elective prophylactic iliofemoral bypass	Alive at age 48
Aneurysm/dissection	HI	27	Elective prophylactic aortobiiliac repair	Alive at age 26
Dissection/rupture	MIN	42	Emergency open repair	Wound infection, alive at age 50
Aneurysm/rupture	MIN	22	Emergency open repair	Intraoperative death

AVF, Arteriovenous fistula; *HI,* haploinsufficiency mutations that lead to 50% normal type III collagen production; *MIN,* mutations that lead to minimal (10%-15%) normal type III collagen production.

pursued when the diagnosis is suspected.[8] Confirmation of the underlying molecular diagnosis and classifying the mutation by the effect on type III collagen production are important elements in the counseling and care of vEDS patients. Furthermore, it differentiates vEDS from other syndromes such as Loeys-Dietz syndrome, which has a similar age at presentation and features that overlap with vEDS patients.[9] Molecular testing allows for critical genotype-phenotype correlations to be identified, such as the fact that patients with HI mutations present at an older age, have milder arterial disease than those with MIN mutations,[7] and have a high prevalence of aortic disease.

Our data support that elective repair for arterial complications can be performed with acceptable morbidity. Given the small cohort size, it is difficult to set absolute guidelines beyond what is currently recommended for patients without vEDS. We propose elective interventions in when rapid change, such as growth or dissection, occurs in a previously stable aneurysm, and we individualize the recommendations to the patient based on the risk/benefit profile for each patient. Knowledge of the molecular diagnosis allows preoperative counseling and modification of the surgical techniques, which are critical to successful outcomes. Patients with an established preoperative diagnosis treated in an elective setting have significantly improved

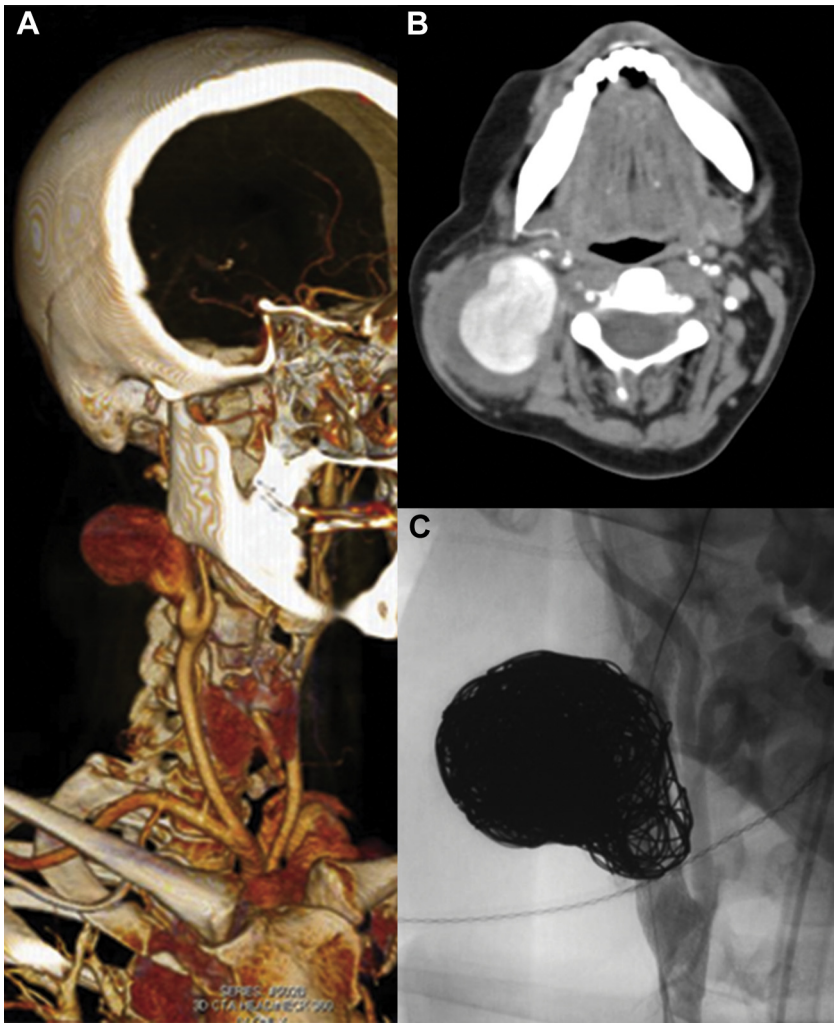

Fig 4. A 6-cm carotid artery aneurysm developed in a 34-year-old woman acutely in the postpartum period. **A,** A three-dimensional computed tomography (CT) reconstruction and **(B)** representative axial image of a CT scan demonstrate the large right internal carotid artery aneurysm. Her arterial pathology led to vascular Ehlers-Danlos syndrome (vEDS) diagnosis (MIN mutation, c.1772G>A, p.Gly591Asp) and preoperative multidisciplinary planning accordingly. **C,** She was successfully treated with stent-assisted coil embolization of the internal carotid artery aneurysm. *MIN*, mutations that lead to minimal (10%-15%) normal type III collagen production. Images courtesy of Johns Hopkins Hospital/National Institutes of Health.

outcomes compared with patients who undergo emergency repair and when the diagnosis is not known.

We have shown that open repairs of the aorta are well tolerated in the elective setting and that endovascular repairs of medium-sized arteries are also well tolerated.[10] The preoperative diagnosis allows the surgeon to prepare for perioperative and intraoperative management. In the perioperative setting, communication with the anesthesiologists is a key element in management because it allows for careful intubation, use of ultrasound-guided vascular access, and stringent blood pressure control. Indeed, one individual survived an abdominal aortic aneurysm repair, only to die of a central catheter complication during another hospitalization 10 years later.

Intraoperatively, the surgeon should be prepared to deal with the fragile tissues. Clamping techniques are modified, including a more proximal "fall-back position" to avoid placing vascular clamps on the same location, avoiding a Rommel tourniquet because it tends to create circumferential adventitial hematoma, and using external pneumatic tourniquets to control limbs proximally. Buttressing the sutures lines with circumferential individual felt pledgets to promote hemostasis in aortic repairs has been described.[11]

In the endovascular setting for arterial embolization in medium-sized arteries, the surgeon can apply these same principles of access vessel management with open exposure for large diameter sheaths, minimal sheath exchanges, and circumferential individual pledget reinforcement for closure.[10]

Table V. Fifty operative procedures classified according to preoperative knowledge of vascular Ehlers-Danlos syndrome (vEDS) diagnosis

Variable	*Diagnosis known (n = 29), No. (%)*	*Diagnosis not known (n = 21), No. (%)*	P[a]
Family history	13 (44.8)	9 (42.9)	.890
HI mutation	6 (20.7)	7 (33.3)	.314
Open surgical repair	14 (48.3)	17 (81.0)	.019
Endovascular procedures	15 (51.7)	4 (19.0)	.019
Emergency repairs	12 (41.3)	17 (80.9)	.005
Intraoperative death	0	3 (14.2)	.036
Postoperative complications	4 (13.7)	13 (61.9)	<.001

HI, Haploinsufficiency mutations that lead to 50% normal type III collagen production.
[a]*P* value calculated using the Pearson χ^2 test for categoric data.

During the postoperative period, there should be specific attention to blood pressure control. We have used a stepwise increase in allowed systolic pressure in aortic patients, with systolic blood pressure maintained at <90 mm Hg for the first 24 to 48 hours postoperatively, gradually increasing to normotension on postoperative days 3 to 5. Because treatment with β-adrenergic blocking agents has been shown to decrease vascular events in vEDS patients,[12] these agents should be considered for blood pressure control. Other postoperative considerations include adequate pain management and diligent monitoring and immediate treatment of constipation because it may lead to bowel rupture.

With the understanding that diagnosed vEDS patients can do well with elective surgical repair of arterial pathology, it raises the question about the extent these patients should have ongoing surveillance for vascular diseases, a topic that is controversial.[8] We recommend surveillance with carotid artery ultrasound scans and noninvasive imaging of the thoracic and abdominal aorta, visceral arteries, and iliac arteries by using magnetic resonance angiography (MRA) during the initial evaluation of these patients, followed by targeted CT as needed based on vascular pathology identified. The young age of most patients makes routine use of CT as a surveillance method problematic due to lifetime radiation exposure issues. Because rare vascular complications have occurred in patients in their teenaged years, it is reasonable to obtain a baseline study before the age of 20 years. Patients with a known vascular lesion can be monitored in a manner tailored to the lesion and the patient. However, further data regarding intensity of surveillance is needed.

In patients without a vascular manifestation, periodic arterial screening is recommended; however, frequency is not known, and further data regarding intensity of surveillance is needed.[2] Without ongoing surveillance, vascular complications have generally been described as sudden and catastrophic, and our data support this statement. It was generally believed that gradual vascular dilatation, such as seen in Marfan syndrome, was not a feature of vEDS.[13] With surveillance, asymptomatic dissections and aneurysms can be identified in vEDS patients, and our data suggest that this arterial pathology can be surgically repaired. Further research regarding these asymptomatic vascular anatomic events is needed to determine natural history and morphology changes that may motivate surgical or endovascular intervention.

It is imperative that the disease be properly diagnosed when encountering peripheral arterial aneurysms or dissections in a young patient. Features of vEDS, such as facial characteristics, unexplained bruises, and translucent or thin skin should be examined, and a history should be elicited to note clubfoot, dislocations, or pneumothorax. However, the absence of the facial appearance or a clinical history suggestive of vEDS does not rule out the disease, because there are a considerable number of patients without major features (Fig 1). Obtaining a family history of sudden death due to unknown causes at a young age or arterial complications is important for identifying possible cases of vEDS, and referral to a medical geneticist for counseling and diagnosis is appropriate. Establishing the diagnosis allows for genetic counseling, proper surveillance to detect the arterial pathology, and for elective repair planning by a multidisciplinary team involving vascular surgeons, cardiac surgeons, interventionists, and medical geneticists. The correct diagnosis also allows for the first-degree relatives to undergo counseling and testing, thus identifying asymptomatic vEDS individuals before they experience a potentially catastrophic event.

The development of medical treatment options, such as the use of celiprolol,[12,14] as well as growing experience with prophylactic endovascular and open procedures, stand to improve the prognosis for vEDS. Although the disease is rare, the morbidity and mortality are significant and warrant the study of long-term outcomes with contemporary surgical and medical interventions.

CONCLUSIONS

Establishing the molecular diagnosis of vEDS is imperative to disease management. When surgical repair is indicated, elective repairs offered by a multidisciplinary team and using surgical techniques applied to address the fragile tissues are associated with favorable outcomes. This approach is expected to improve the overall prognosis of patients with vEDS.

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AUTHOR CONTRIBUTIONS

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Final approval of the article: SS, JB, AC, BG, NM, DM, HS, ZX
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DM and NM contributed equally as senior authors to this report.

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DISCUSSION

Dr R. Clement Darling (*Albany, NY*). The haploinsufficiency type, are you still comfortable doing endovascular repair? Classically we are taught not to. We actually just did one right before we came here, and we had to do a type A repair and then we fixed the secondary part with an endograft. But the question is: Is that a durable procedure? Is that something that is just temporary and then you have to go back in to do a more definitive procedure?

Dr Sherene Shalhub. The short answer is we don't know. Current recommendations argue against the use of aortic endovascular stent grafts, which is different from angioembolizations. Thoracic aortic endografts exert external radial force and push on the abnormal aortic walls; thus, they are not recommended in the collagen disorders. However, having said that, reviewing the literature, there are quite a few cases that are reported with successful repair, but their genotype data are not always provided; thus, it is difficult to extrapolate based on these case reports.

Dr Darling. And a lot of those reports don't have long-term results.

Dr Shalhub. That is true.

Dr B. Timothy Baxter (*Omaha, Neb*). You talked about the surveillance. I wondered what your recommendations are in terms of interval of surveillance and type of studies to do in these patients?

Dr Shalhub. The current recommendations have been established where they are recommending follow-up for these. Magnetic resonance imaging is a perfectly fine modality of surveillance. In terms of how frequently to surveil them, we do not know, but are recommending starting at age 20 and surveilling every 2 to 3 years. If they have abnormalities that are new, they may warrant closer follow-up to look for interval enlargement or changes.

Dr Manish Mehta. (*Albany, NY*). Does the presence of the haploinsufficiency mutation change your management regardless of the indication that the patient is presenting with?

Dr Shalhub. I would still approach them the same way, but it may make me feel more comfortable doing an open operation, for example, as opposed to using an endovascular approach. Our hypothesis was that it makes a difference because the amount of type III collagen in the tissue is more than the patients with minimal mutations. But again, the numbers are small at this stage, so it is hard to generalize. I am hoping that as we continue to enroll more patients, we will obtain more information and be able to make better recommendations.