Molecular diagnosis in Vascular Ehlers-Danlos Syndrome Predicts Pattern of Arterial Involvement and Outcomes

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Abstract

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OBJECTIVES—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 based on the type of *COL3A1* mutations and their effect on the amount of normal collagen produced: MIN group had mutations that lead to minimal (10–15%) production of normal type III collagen and HI group had haploinsufficiency mutations that lead to production of half the normal type III collagen.

RESULTS—A cohort of 68 (72%) individuals from 56 families had arterial pathology (44% male, 13% HI). The HI group was older at the time of their first vascular event (mean 42 years, range 26–58 vs. 33 years, range 8–62, P = .016). The HI group had a higher incidence of aortic pathology compared to the MIN group (56% vs. 21%. P = .025). Visceral arterial pathology was seen in 43 arteries in 23 individuals in the MIN group versus only a single artery in 5 individuals in the HI group. Emergent surgical procedures were more likely to be undertaken when vEDS diagnosis was not known (81% vs. 41%, P = .005) and the majority of these procedures were open surgical repair compared to endovascular repair (81% vs. 19%, P = .019). In the elective setting, there was equal use of open and endovascular repair. Post-operative 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). There was no mortality due to arterial complications 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 as diagnosis confirmation, appropriate surveillance, and prophylactic interventions in an elective setting improve surgical outcomes.

Introduction

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 1 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 "missense mutations", which are glycine substitutions in the triplets of the helical domain of collagen. [4] One third of *COL3A1* mutations are caused "exon skip mutations" leading to exon splicing errors causing in-frame shift in the reading frame for translation. [5] Both types of mutations 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 7:1 ratio of abnormal to normal collagen molecules thus there is a minimal amount (MIN) of normal collagen produced (10–15%). [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 mRNA by way of nonsense-mediated decay. This causes expression of a single gene thus termed haploinsufficiency (HI). The end result is production of half the amount of normal type III procollagen. HI mutations are associated with reduced penetrance and delayed onset of arterial pathology compared to MIN mutations. [7] 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 (IRB) was obtained to enroll individuals with vEDS referred to the University Texas at Houston Medical School (UTH), Johns Hopkins Hospital (JHH), and the National Institute on Aging (NIA), (NCT00270686, approved by MedStar IRB #2003-086). The cohort for this study comprised a subgroup of enrolled cases with confirmed molecular diagnosis of vEDS with arterial pathology. Proper consents were obtained from the participants including written consents for clinical photography and use in medical education. All identifiable photographs in this manuscript are from deceased individuals who provided consents for use of their photos 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. Data abstracted included demographics, age at diagnosis, family history, reasons for diagnosis, and clinical diagnostic criteria as defined by the Revised Nosology of Villefranche were collected. [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 (CT, MRI, and duplex ultrasound), management, morbidity, and mortality.

Molecular Diagnosis

COL3A1 mutation detection was performed on a clinical basis in an outside laboratory, or on a research basis at the National Institute on Aging (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 (CLIA) certified laboratory. Results of dermal fibroblasts studies were reviewed and the amount of type III procollagen produced 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 Microsoft Excel 2010 (Microsoft, Redmond, WA) and SPSS 20.0 for Windows (SPSS, Inc., Chicago, IL). Data were 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. Categorical variables were compared using chi-square testing All P values were two-sided and < .05 was considered significant.

Results

Vascular EDS related arterial pathology was documented in 68 cases (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 (35.8%) of the cohort.

Family History

Of the 68 cases, there were reported clinical manifestations of vEDS in 44 (64.7%) cases' family members 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 cases (86.8%) with MIN mutations. MIN mutations included missense (n=42, 61.8%), exon skip (n=12, 17.6%), and unusual mutations (n=5, 7.4%). In addition, one case had biochemical diagnosis of minimal type III procollagen production, thus included in this group. There were 9 cases with HI mutations (13.2%). HI mutations included nonsense (n=5, 55.6%), and frame shift mutations (n=4, 44.4%).

The HI group was older when the first arterial pathology was diagnosed (mean age 41.6 ± 2.9 years, range 26–58) compared to the MIN group (33.1 ± 1.5 years, range 8–62 years, P = .030). Characteristic facial appearance was common (61.2%) but displayed a wide range of variability (Figure 1). Easy bruising and the characteristic thin translucent skin with visible veins (Figure 2) was seen more commonly in the MIN group than in the HI group (Table 1). Table 1 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 Figure 3.

Aorta involvement was seen in 16 cases. The prevalence of aortic disease was significantly higher in the HI group (55.6%) compared to the MIN group (7%, P < 0.001). Surgical management and outcomes are detailed in Table 2. Non-operative management was undertaken in one case of descending thoracic aorta aneurysm (3.5 cm) that was diagnosed in a patient with MIN mutation without complications.

Brachiocephalic Arteries Pathology

Details of the brachiocephalic arteries involved and management are shown in Table 3. Multi-brachiocephalic arterial involvement was seen in 9 cases, all with MIN mutations.

Visceral Arteries

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

Celiac artery pathology occurred only in individuals with MIN mutation (n=5): three aneurysms (1.5–2 cm in diameter), and two cases of dissection that progressed to aneurysms (1.6–1.8 cm) during one year of follow up. All the cases were managed non-operatively.

Hepatic artery pathology occurred in 10 cases (MIN n=7, 12.1% vs. HI n=3, 33.3%, P = .096). Management was non-operative in aneurysms smaller than 2 cm in diameter (n=6). Two cases had coil embolization: right hepatic artery 2.2 cm in diameter and an intra-parenchymal hepatic artery rupture. One case remains under observation due to high surgical risk for a stable 3 cm proper hepatic artery aneurysm (34 year old female, c.1772G>A, p.Gly591Asp, MIN type mutation).

Splenic artery pathology occurred in 18 cases (MIN n=17, 29.3% vs. HI=1, 11.1%, P = .252). Management was non-operative in isolated dissections or aneurysms smaller than 1.7 cm in diameter (n=6). Coil embolization was performed successfully in 4 cases of aneurysms larger than 2 cm in diameter (one with a contained rupture). Ruptured splenic artery of unknown size with hemodynamic compromise occurred in two female patients requiring operative exploration and splenectomy (62 year old, c.3319G>C, p.Gly1107Arg, and 28 year old, c.3499G>C, p.Gly1000Arg, both MIN type mutations, both diagnosed after the rupture event).

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

Renal artery pathology occurred in 17 cases (MIN n=16, 27.6% vs. HI n=1, 11.1%, P = .291). This involved small aneurysms and dissections (n=14) leading to renal infarcts (n=8), all managed non-operatively. In one case the renal artery had fibromuscular dysplasia type beaded appearance in a patient who had undiagnosed vEDS (41 years old female, c. 766delA, p. Ile256Fx, HI type mutation). The patient underwent an attempted open repair complicated by nephrectomy and subsequent incisional hernia. Coil embolization was performed successfully in one case of an intra-parenchymal renal artery aneurysm and on subsequent follow up was noted to have a dissection treated with non-operative management. Ruptured renal artery with hemodynamic compromise occurred in one case (17 year old female, IVS43+2T>G, MIN type mutation). The patient died intraoperatively due to hemorrhagic shock.

Iliac Arteries

Iliac arteries aneurysms and dissections independent of abdominal aortic involvement occurred in 22 cases (MIN n=20, 34.5% vs. HI n=2, 22.2%, P = .466). Successful non-operative management was utilized in cases of dissection (n=7) aneurysms smaller than 2.5 cm in diameter (n=3). Details of iliac arteries operative management are shown in Table 4. There were two cases of death due to presumed iliac artery rupture: One case with known maximum iliac artery size of 1.4 cm (28 year old female, c.3201+2T>C, MIN type mutation), and the second case had known iliac artery dissection (29 year old female, c. 665G>T, p.Gly222Val, MIN type mutation). Both presented with pain and had cardiac arrest during diagnostic workup.

Impact of preoperative diagnosis of vEDS on operative outcomes

Fifty procedures (29 emergent, 21 elective) were performed in 35 patients (9 HI, 25.7%) and involved the brachiocephalic arteries (n=9), coronary arteries (n=3), aorta (n=12), iliac arteries (n=8), visceral arteries (n=14), tibial arteries (n=2), inferior epigastric artery (n=1), and ruptured chordae tendineae (n=1). Emergent procedures were performed in 62.2% and 46.2% of the MIN and HI groups respectively. Post-operative complications were not different between the MIN and HI groups (MIN=13, 35.1%, vs. HI=4, 30.7%, P = .775)

Diagnosis of vEDS was known in 42% cases prior to surgical intervention. In these cases, arterial repairs 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 (Figure 4). In the cases requiring emergency interventions, surgical technique was altered to accommodate the fragility of tissues (Figure 5).

The undiagnosed vEDS cases were significantly more likely to present in an emergent 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 cases (P < 0.001, Table 5). All intraoperative deaths (n=3) occurred in cases with MIN type mutation who presented in an emergent fashion requiring management without the benefit of 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 of death was 31.4 ± 2.6 years (range 17–45 years). Causes of death were the following: intraoperative deaths during attempts to repair ruptured iliac (n=2) and renal artery (n=1), stroke post carotid cavernous fistula embolization (n=1), mesenteric arterial thrombosis and necrosis after admission for small bowel obstruction (n=1) (Figure 1A), central line insertion complication (n =1) (Figure 1B), rapid aneurysmal degeneration of iliac and gluteal arteries complicated by retroperitoneum and spontaneous hemothorax post colostomy take down (n=1) (Figure 1C), presumed iliac artery rupture (n=2) (Figure 1D), 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 pursued when the diagnosis is suspected.[8] Confirmation of the underlying molecular diagnosis and classifying the mutation based on the impact on type III collagen production are important elements in the counseling and management of vEDS patients. Furthermore, it differentiates the vEDS from other syndromes such as Loeys-Dietz syndrome (LDS) which has 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 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 cases in which 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 outcomes when compared to cases repaired in an emergent fashion and when the diagnosis is not known. We have shown that open repairs of the aorta are well tolerated in the elective setting, and endovascular repairs of the 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 as it allows for careful intubation, use of ultrasound guided vascular access, and stringent blood pressure control. Indeed one case survived an abdominal aortic aneurysm repair, only to die at a separate hospitalization ten years later due to a central line complication. Intraoperatively, the surgeon should be prepared to deal with the fragile tissues. Clamping techniques are modified, this includes a more proximal "fall-back position" to avoid placing vascular

clamps on the same location, avoiding Rommel tourniquet use as they tend to create circumferential adventitial hematoma, and external pneumatic tourniquets are used to control limbs proximally. In the case of aortic repairs, buttressing the sutures lines with circumferential individual felt pledgets to promote hemostasis 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] During the post-operative period, there should be specific attention to blood pressure control. We have used a stepwise increase in allowed-systolic pressure (SBP) in aortic patients with SBP maintained at <90mmHg for the first 24–48 hours postoperatively, gradually increasing to normotension on postoperative days 3–5. Since treatment with beta-adrenergic blocking agents has been shown to decreased 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 since 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 as to the extent these patients should have ongoing surveillance for vascular diseases, a topic that is controversial.[8] We recommend surveillance with carotid artery ultrasound, 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 computed tomography as needed based on vascular pathology identified. The young age of most patients makes routine use of computed tomography as a surveillance method problematic due to lifetime radiation exposure issues. Since rare vascular complications have occurred in patients in their teenage years, it is reasonable to obtain a baseline study before the age of 20 years. Patients with a known vascular lesion can be followed in a manner tailored to the lesion and the patient. However, further data regarding intensity of surveillance is needed. In patients without 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 were generally 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 surgical repair of this arterial pathology can be done. Further research regarding these asymptomatic vascular anatomical 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, translucent or thin skin should be examined, and history should be elicited to note club foot, dislocations or pneumothorax. However, the absence of the facial appearance or suspicious clinical history does not rule out the disease, since there are a considerable number of patients without major features (Figure 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. Correct diagnosis also allows for the first degree relatives to undergo counseling and testing, thus identifying asymptomatic vEDS individuals prior to experiencing 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 is significant and warrants 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.

Acknowledgments

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Figure 1.
Spectrum of facial features in individuals with vEDS: variability among patients and does not necessarily correlate with the severity of the underlying arterial pathology. All four individuals here died from vascular complications **(A)** Caucasian male (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 female (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 male (MIN mutation, c.2870G>T, p.G957D) with down slanting palpebral fissures, long and thin nose, thin lips and attached pinna. **(D)** Caucasian female (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.
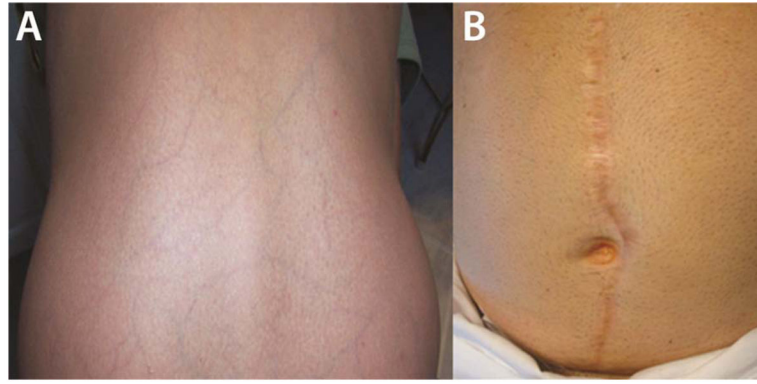
Figure 2.
Cutaneous manifestations of vEDS. **(A)** Thin translucent skin with visible venous pattern on the lower back of a patient with vEDS (MIN mutation, exon skip). **(B)** Widened atrophic scar in patient following open abdominal aortic aneurysm repair (HI mutation)

Percent of Cohort
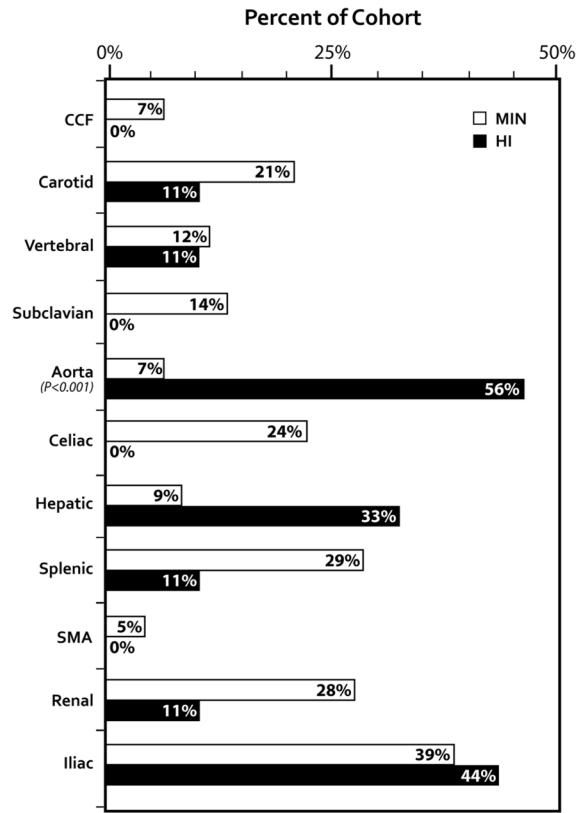
Figure 3.
Arterial involvement in vEDS cases by COL3A1 mutations. Though vEDS involves medium sized arteries more commonly, there was an increased prevalence of aortic involvement in the HI cohort compared to the MIN cohort (P = .025)
MIN: mutations that lead to minimal normal type III collagen production. HI: mutations that lead to 50% normal type III collagen production. CCF: Carotid Cavernous Fistula.
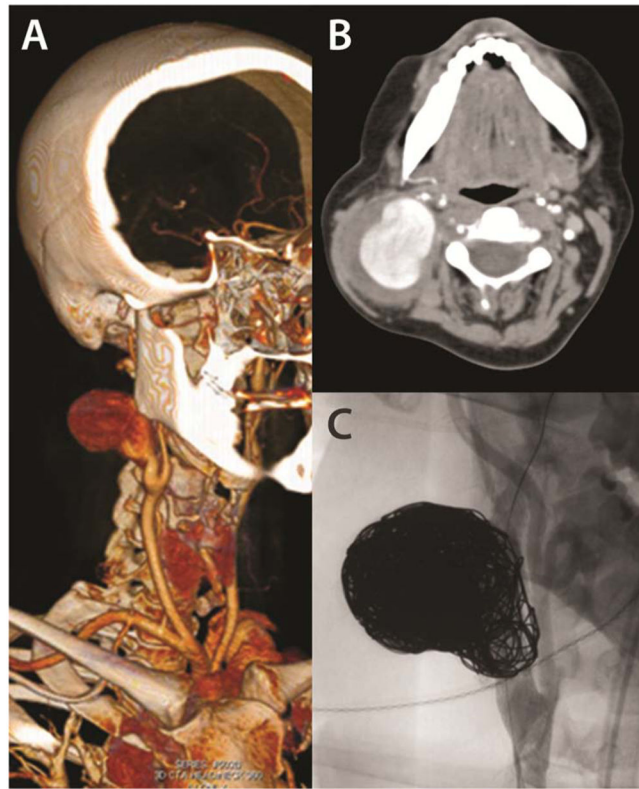
Figure 4.
A 6 cm carotid artery aneurysm which developed in a 34 year old woman acutely in the post-partum period. **(A, B)** 3-D reconstruction and representative axial image of a computed tomography scan demonstrating the large right internal carotid artery aneurysm. Her arterial pathology led to vEDS diagnosis (MIN mutation, c.1772G>A, p.Gly591Asp) and preoperative multidisciplinary planning accordingly. She was successfully treated with stent-assisted coil embolization of the ICA aneurysm **(C)**. *Images courtesy of Johns Hopkins/NIH*
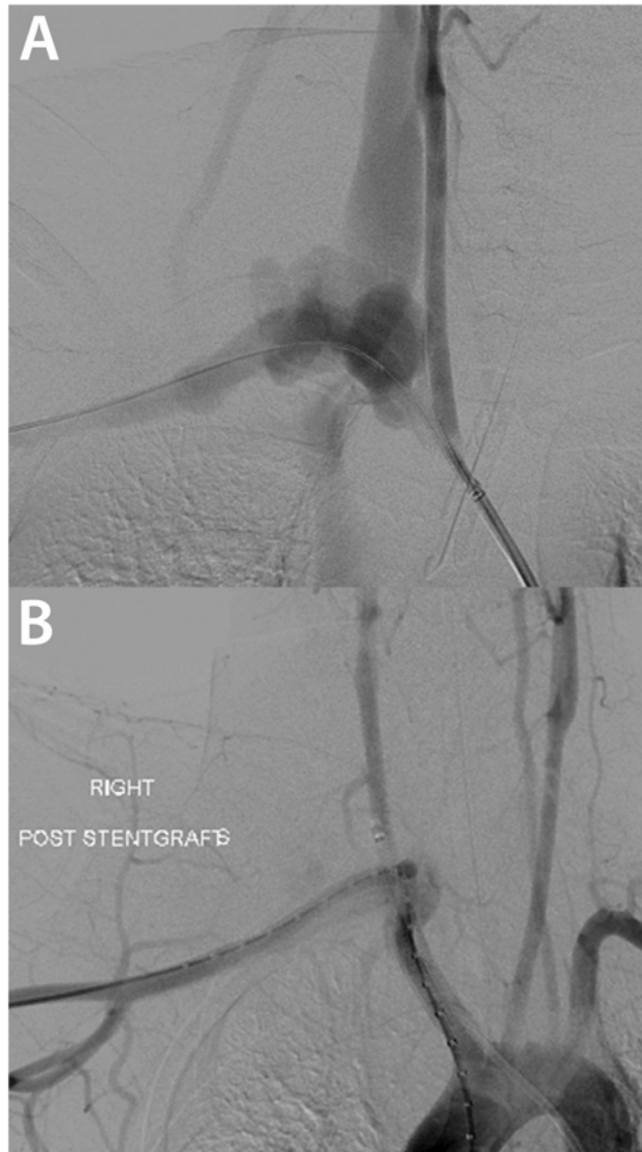
Figure 5.
Endovascular repair of a right subclavian artery rupture presenting with sudden onset of left shoulder pain radiating to the neck in an 18 year old man with known vEDS (MIN mutation, (c.3847C>T). **(A)** Arteriogram demonstrating the rupture site and arteriovenous fistula to right internal jugular vein. **(B)** Knowledge of his diagnosis allowed for the surgical treatment to be tailored to his diagnosis with 7 mm Self expanding covered stents in the common carotid and subclavian arteries without complications. *Images courtesy of Dr. Ali Azizzadeh, MD (UT Houston).*

Table 1

Demographics, clinical characteristics, and reasons for diagnosis in patients with vEDS

N (%), Mean (range)	All (N=67)	MIN (N=58)	HI (N=9)	P*
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	40.9 (8–70.2)	39.9 (8–70.2)	47.5 (26–61.6)	.116
Age at diagnosis	33 (0.3–63)	31.5 (0.3–63)	42.6 (26–58)	.016
Age at first arterial pathology diagnosis	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 hyperextensibilty	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	

MIN: mutations that lead to minimal normal type III collagen production. HI: mutations that lead to 50% normal type III collagen production.

*
P value calculated using the Pearson Chi-square test for categorical data and independent samples t-test with equal variances assumed for the continuous variables.

Table 2

Surgical management and outcomes of aortic pathology in patients with vEDS

Aortic Pathology Age/Sex	Mutation	Operation		Outcome
Thoracic Aorta				
Type A aortic dissection 40M	HI	**1**	Interposition graft, fem-fem bypass	Graft infection
		2	ATA & arch Homograft	
Type B aortic dissection with extension into iliacs 35M	HI	Endovascular Stent Graft		Renal Infarcts due to embolization, alive at age 42
Chronic type B dissection with 6 cm DTA aneurysm 19M	MIN	**1**	Reversed Elephant trunk (Dacron)	Enlargement of intercostals patch 2 years later Alive at age 25
		2	Interposition Dacron graft, bypass to celiac, SMA, and renal arteries	
Abdominal Aorta				
AAA (40M)	HI	**1**	Aortobiiliac repair	Iliac limb thrombosis, IH Abdominal wound dehiscence. (Figure 2B). Alive at age 52
		2	Redo aortobiiliac bypass, Incisional hernia repair	
AAA saccular (4 cm), bilateral CIAA with dissection (58M)	HI	Aortobiiliac repair, jump graft to RIIA		Alive at age 61
AAA, dissection, rupture (51M)	HI	Aortobiiliac repair. "Buttery" Aorta		Alive at age 57
Abdominal aortic dissection (trauma related) to R CFA with RLE ischemia (24M)	HI	Fem-Fem bypass		Abdominal aorta is at 3 cm. Alive at age 32
AAA (4.6 cm) (41M)	HI	Interposition graft		Alive at age 47
AAA, bilateral CIAA (21F)	MIN	Aortobiiliac repair, fragile tissue		Abdominal wound dehiscence. Died 10 years later
AAA (4.5 cm), bilateral CIAA due to aortic dissection(trauma related) (27M)	MIN	Aortobiiliac repair		Alive at age 27

ATA: Ascending Thoracic Aorta. DTA: Descending Thoracic Aorta. AAA: Abdominal Aortic Aneurysm. M: Male. F: Female. MIN: mutations that lead to minimal normal type III collagen production. HI: mutations that lead to 50% normal type III collagen production.

Table 3

Presentation, management, and complications of brachiocephalic arteries pathology in patients with vEDS.

Arterial Pathology	N	Mutation	Age range	Presentation	Management	Complications/Comments
Carotid Artery						
Dissection	5	MIN (4), HI (1)	26–51	Surveillance (2), Symptomatic (1), Trauma (2)	Non-operative	None
Stenosis	2	MIN (1), HI (1)	36–41	Surveillance	Non-operative	FMD appearance (HI)
Ectasia	3	MIN (2), HI (1)	36–63	Surveillance	Non-operative	None
Aneurysm	7	MIN	22–56	Surveillance (6), Symptomatic (1)	Non-operative (6), Coiling & stenting (1)	TIA post coiling (case in Figure 5)
CCF	5	MIN	25–46	Symptomatic	Endovascular	One required repeat embolization 2 years later
Vertebral Artery						
Dissection	6	MIN (5), HI (1)	22–52	Surveillance (3), Symptomatic (3)	Non-operative	PCA infarct (age 52), Stenosis on F/U (n=2)
Ectasia	1	MIN	36	Surveillance	Non-operative	None
Aneurysm	1	MIN	29	Surveillance	Non-operative	0.5 cm at V2
Subclavian Artery						
Dissection	2	MIN	41	Surveillance	Non-operative	Bilateral in same case
Ectasia	1	MIN	52	Surveillance	Non-operative	None
Aneurysm	3	MIN	26–34	Surveillance	Non-operative (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 (case in Figure 7)
Aneurysm	1	MIN	32	Rupture (L SCA)	Carotid Subclavian bypass	Post op infarcts, prolonged vent dependence, tracheostomy

CCF: Carotid-Cavernous fistula, CCA: Common Carotid Artery. SCA: Subclavian artery, Op: Operative, F/U: Follow-up, R: right, L: Left, MIN: mutations that lead to minimal normal type III collagen production. HI: mutations that lead to 50% normal type III collagen production.

Table 4

Iliac artery interventions and complications in cases of vEDS

Pathology	Mutation	Age	Management	Complications
AVF/ symptomatic	MIN	28	Elective Endovascular repair	Alive at age 34
AVF/ rupture	MIN	28	Emergent 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 (case in figure 6)
Dissection/ rupture	MIN	42	Emergent open repair	Wound infection, alive at age 50
Aneurysm/ rupture	MIN	22	Emergent open repair	Intraoperative death

AVF: Arteriovenous fistula. MIN: mutations that lead to minimal normal type III collagen production. HI: mutations that lead to 50% normal type III collagen production.

Table 5

Fifty Operative procedures classified according to preoperative knowledge of vEDS diagnosis

N=50 (%)	Diagnosis Known N=29	Diagnosis not known N=21	P[*]
Family History	13 (44.8)	9 (42.9)	.890
Haploinsufficiency 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
Emergent Repairs	12 (41.3)	17 (80.9)	.005
Intraoperative Death	0	3 (14.2)	.036
Post-operative complications	4 (13.7)	13 (61.9)	<.001

[*] P value calculated using the Pearson Chi-square test for categorical data