Understanding vascular-type Ehlers-Danlos syndrome and avoiding vascular complications

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Vascular-type Ehlers-Danlos syndrome (EDS) is a rare inherited connective tissue disorder caused by a mutation in type III procollagen. It has the highest mortality rate among the six types of EDS. Patients with this syndrome often have typical medical histories and a characteristic physical examination. We present two patients with this rare disorder and highlight the diagnostic and treatment challenges.

Near the turn of the 20th century, Drs. Ehlers and Danlos described individuals with increased skin elasticity, hyperextensible joints, susceptibility to ecchymoses, and cutaneous lesions (1). This description, combined with the initial cases presented by Russian dermatologist Dr. Tschernogobow at the Moscow Venereology and Dermatology Society conference in 1892, added validity to the concept, and wide acceptance of Ehlers-Danlos syndrome (EDS) was garnered by 1936 (2). Six different subtypes of EDS have been described by the Villefranche classification schematic (3). Vascular-type EDS (EDS type 4), a rare inherited connective tissue disorder caused by a mutation in type III procollagen (*Col3A1*), has the highest mortality rate of the six types of EDS (3). It has an autosomal dominant transmission with 100% penetrance and comprises 5% to 10% of all cases of EDS. Vascular-type EDS is often characterized by major and minor criteria including vascular rupture or dissection, narrow facies, hyperpigmentation, pale skin with visible subcutaneous vessels, and easy bruisability. Fatal complications such as arterial dissections, digestive tract rupture, and other organ rupture can occur in up to 80% of affected individuals before the age of 40. The syndrome is linked with genetic abnormalities in types I, III, or V collagen critical to extracellular matrix formation. We present two cases of vascular-type EDS that highlight the diagnostic and treatment challenges encountered with these patients.

PATIENT 1

A 31-year-old man presented with sudden-onset, bilateral upper abdomen pain and several bouts of bilious emesis. His past medical history was notable for bilateral inguinal herniorrhaphies and bilateral shoulder dislocations in high school. His family history was negative. On admission, he had a fever of 101.5°F but was hemodynamically stable. His physical examination was remarkable for pale skin, periorbital hyperpigmentation, talipes equinovarus, and exaggerated joint laxity. His laboratory studies were notable only for a leukocytosis. A computed tomography (CT) scan of the abdomen and pelvis demonstrated a left common and external iliac dissection (with evidence of prior extravasation without active leak) as well as bilateral renal infarcts, a small left common iliac aneurysm (1.7 cm), and a question of bilateral renal artery aneurysms. A renal artery duplex study was inconclusive regarding the presence of renal artery aneurysms, and a renal angiogram was ordered. A CT scan of the head, neck, and chest showed no additional significant vascular changes. Concerns for a connective tissue disease or a genetic syndrome prompted rheumatology and genetics consults. The genetics team suggested vascular-type EDS as the most likely diagnosis. The renal angiogram was then cancelled due to the potential risk of renal dissection or obliteration. Rheumatological markers and hypercoagulability testing all returned negative. An angiotensin-converting enzyme inhibitor was started as standard therapy. Genetic testing later confirmed a diagnosis of vascular-type EDS with a *Gly981Arg* mutation.

PATIENT 2

A 69-year-old man presented to the hospital with urinary frequency. He developed pelvic discomfort, and a subsequent CT with intravenous contrast revealed a 6×6 mm renal stone at the right ureterovesicular junction with right-sided hydronephrosis. Important incidental findings on this scan were bilateral iliac aneurysms and focal dissections and pseudoaneurysms of the celiac, distal mesenteric, left gastric, superior mesenteric, and superior left renal arteries. The patient's past medical history included the presence of hypertension, previous kidney stones, and two previous cerebrovascular accidents. A recent admission for a transient ischemic attack prompted a cerebral contrast CT angiogram showing large aneurysms with a clot at the base of the right vertebral artery and an arteriovenous shunt in the distal right vertebral artery segment. The patient also had a history of inguinal and ventral hernia repairs. The patient's family history

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was notable for a brother who had an unexplained spontaneous bowel rupture requiring urgent surgical repair at age 60. His physical examination was notable for decreased strength in the right upper and lower extremities. A renal angiogram was scheduled to further evaluate the renal vasculature.

After an extensive negative rheumatologic evaluation, vascular surgery, rheumatology, and the genetics services suggested a diagnosis of vascular-type EDH, despite the lack of classical skin findings or facial appearance. Accordingly, vascular surgery cancelled the patient's renal artery angiogram in fear of a high risk for potential arterial dissection. The patient subsequently had a genetic analysis in the 12 genes known to be associated with genetic forms of thoracic aortic aneurysms, including vascular-type EDS, Marfan syndrome, and related disorders. This panel was negative in this patient. However, given possible variations in disease-associated mutations, additional genetics testing was pursued. Deletion or duplication of one or more of the 12 exons in the thoracic aortic aneurysms and dissections panel was suspected, and the diagnosis of vascular-type EDS was maintained. Treatment with daily aspirin, losartan, simvastatin, and amlodipine was initiated.

DISCUSSION

In vascular-type EDS, vascular dissection or organ rupture may occur in the thorax and abdomen (50%), head and neck area (25%), or extremities (25%). This pathophysiology results from an identified collagen type III gene mutation (substitution of glycine) known as *COL3A1* that results in decreased thermal stability and proteolytic processing in the proA1 chain of collagen type III (4). These defects lead to devastating complications, including vascular dissection (aneurysmal formation, arteriovenous fistulae, or dissection), gastrointestinal perforation, or uterine rupture (4). Common childhood occurrences in those affected by vascular-type EDS may include talipes equinovarus, inguinal hernia, pneumothorax, and recurrent joint subluxation or dislocation (4). Cerebrovascular complications may also occur, including intracranial hemorrhage due to carotid cavernous sinus fistulae or cervical artery aneurysmal rupture (4). Historically, 25% of those with genetic testing confirming vascular-type EDS experience a significant medical problem requiring hospitalization by age 20 (~75% by age 40), and the median life expectancy for those with vascular-type EDS is 48 years (4).

Sequence analysis of *COL3A1* confirms the clinical diagnosis of vascular-type EDS in over 95% of the cases. Most mutations are point (missense or skipping) mutations that lead to substitutions for glycine (substitution of glycine by glutamic acid driven by a mutation in exon 46 *COL3A1*) in the triple helical region of the collagen molecule. Other types of mutations have also been identified, such as splice site mutations, partial gene deletions, and rarely tested mutations resulting in *COL3A1* haploinsufficiency (5). The types of mutations are thought to be relevant since missense and exon-skipping mutations of *COL3A1* seem to be associated with a higher risk of vascular or organ rupture prior to the age of 23 years. Alternatively, individuals with haploinsufficiency mutations tend to have a lower risk of vascular or organ rupture, with major complications occurring before the age of 37 years (5). For these reasons, haploinsufficiency mutations have become of increasing interest, and some postulate that presentations of vascular-type EDS at older ages is a result of this type of mutation.

Table. Certain clinical, morphological, and genetic characteristics in two patients with Ehlers-Danlos syndrome

Variable	Case 1	Case 2
Age (years) on case presentation	31	69
Age (years) of symptom onset	13	40
Arterial, intestinal/uterine rupture or dissection	+	+
Thin translucent skin	+	0
Easy bruising	0	0
Extensive scarring and hyperpigmentation	+	0
Characteristic facies	+	0
Small joint hypermobility	+	0
Tendon/muscle rupture	0	0
Joint subluxations or dislocations	+	0
Talipes equinovarus	+	0
COL3A4 mutation	+	0
Cerebrovascular accident	0	+
Hernia/hernia repair	+	+
Multiple aneurysms	+	+
Family history of vascular rupture	Unknown	+

Characteristics associated with the two patients are listed in the *Table*. While Patient 1 had confirmed genetic testing and fit a number of major/minor criteria, Patient 2 was older and had a number of vascular findings (aneurysms, pseudoaneurysms, hernias, cerebrovascular events) that are suggestive of EDS type 4. Although genetic testing could not be confirmed, patients presenting at older ages with milder forms of disease have been noted due to haploinsufficiency mutations that are not commonly tested for.

Despite these differences, recognizing basic variations in presentations will allow clinicians to consider a diagnosis of EDS type 4. Although it is a rare disease, the inability to recognize the pertinent medical history, key physical findings, and potential risks of elective procedures in this population may have devastating consequences. Being familiar with these domains is paramount to delivering optimal treatment and avoiding undesirable outcomes.

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