The Vascular Ehlers-Danlos Syndrome

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Opinion statement

Vascular Ehlers-Danlos syndrome (EDS) is a life-threatening inherited disorder of connective tissue causing severe arterial and gastrointestinal fragility and rupture, as well as complications of surgical and radiologic interventions. The diagnosis should be considered in patients under the age of 45 years who present with arterial tearing or dissection, colonic perforation, or visceral rupture. As for many orphan diseases, delayed diagnosis can lead to inaccurate care. Therefore, vascular EDS is particularly important to surgeons, radiologists, and obstetricians because knowledge of the diagnosis may help in the management of visceral complications. There are currently no specific treatments for this genetic condition, and medical intervention is limited to symptomatic treatment, precautionary measures, genetic counseling, and prenatal diagnosis. A clinical trial is ongoing to study the effectiveness of β blockers with vasodilating properties in vascular EDS. Complications require hospitalization, observation in an intensive care unit, and sometimes emergency surgical intervention. CT, echography, and MRI are the most useful imaging modalities. Arteriography is contraindicated. Whenever possible, a wait-and-see attitude with close surveillance is preferable to unwarranted surgery. Surgical treatment carries a high mortality, whereas the mortality rate associated with endovascular treatment is unknown. To improve the likelihood of good surgical outcome, the surgeon must be informed of the patient’s condition. The intent of surgery is to control hemorrhage if an artery, with or without aneurysm, has ruptured and to reconstruct the arterial vasculature. For vascular repair, simple procedures should be preferred, because more complex techniques can result in further injury and hemorrhage. Postoperative surveillance must be prolonged with close medical follow-up and serial CT scans. Pregnant women with vascular EDS should be considered high-risk cases and be provided special care.

Introduction

Vascular Ehlers-Danlos syndrome (EDS; also known as Ehlers-Danlos syndrome type IV), resulting from mutations in the COL3A1 gene coding for type III collagen, is of particular importance among the heterogeneous group of EDS because this is the only form associated with a high risk of early death due to arterial, intestinal, and uterine ruptures [1••], as well as complications of surgical and radiologic interventions. As for many rare orphan diseases, delayed diagnosis is common, even when the clinical features are typical, leading to inadequate or inappropriate treatment and management. Diagnosis is based initially on clinical findings and is easier for patients presenting with a family history, acrogeria, or a first visceral complication [2].

Vascular complications

Type III collagen is an essential component in the blood vessels and intestinal walls. Quantitative and qualitative defects of type III collagen account for the high propensity to arterial rupture and intestinal perforation observed in vascular EDS. Arterial complications are the leading cause of death in vascular EDS because they are unpredictable and surgical repair is difficult due to tissue fragility [3,4]. Approximately half involve the thoracic or abdominal arteries, and the rest are divided equally between those in the head and neck and those in the limbs [5]. In the thorax and abdomen, any anatomic location can be involved [6,7], with a predilection for middle-sized
arteries. Rupture of an artery into a free space is life-threatening and requires immediate intervention [8], even though the vessels are fragile and surgical repair may be difficult. To maximize the chances of successful outcome, surgeons must be alerted to the patient’s condition so that they can choose optimal precautionary measures [9]. In patients who die during or after surgery, the underlying diagnosis is often not known at the time of intervention [10]. Vascular EDS must also be included in the differential diagnosis of any young patient presenting with cerebrovascular disease [11]. Early diagnosis of stroke in patients with vascular EDS is important because of the potential risk of further examinations and surgical procedures. Conventional arteriography should be avoided because of the high risk of massive hematoma and/or arterial dissection. Surgical treatment of cerebral aneurysm in patients with vascular EDS carries a high morbidity and mortality risk due to tissue fragility. The relatively low prevalence of cerebrovascular complications and the high rate of complications associated with surgery do not support the need for routine screening for cerebral aneurysm in asymptomatic patients with vascular EDS.

Another well-documented complication of vascular EDS is carotid-cavernous fistula [13,14]. In cases that are not life-threatening, conservative treatment is sometimes preferred because postoperative mortality is high. Another classical and extensively documented complication of vascular EDS is dissection of extracranial and intracranial segments of the vertebral and carotid arteries.

GASTROINTESTINAL COMPLICATIONS
Because the walls of the digestive tract are rich in type III collagen, intestinal perforation is another common complication of vascular EDS. Most of the bowel complications affect the colon, commonly the sigmoid colon. Perforation of the small bowel and gastric perforation are far less common. Liver rupture has been reported [15], including during transplantation of a liver from an affected donor [16]. Tissue fragility, poor wound healing, hemorrhage of abdominal vessels, fistulas, and adhesions contribute to surgical complications, death, or both [17]. Recurrent as well as multiple bowel perforations have been documented [18].

OBSTETRICAL COMPLICATIONS
Pregnancy in women affected with vascular EDS should be considered at high risk and should be followed at specialized centers. The reported maternal mortality rate is approximately 12% [19]. Although deaths in several pregnant women due to uterine rupture at term have been reported, it is not known whether the use of elective cesarean section would decrease mortality. However, the risk of complications is highest during labor, delivery, and the immediate postpartum period. MRI is useful in this setting to elucidate complex cases in pregnant women presenting with an increased risk of ischemic or hemorrhagic disorders [20].

LABORATORY DIAGNOSIS
The diagnosis can be confirmed by studies of type III procollagen molecule synthesis by cultured fibroblasts or by the identification of a mutation in the COL3A1 gene coding for type III procollagen [21]. Only a few specialized laboratories are equipped to perform the biochemical assay, whereas the sequencing of the gene is long and difficult [21]. Most mutations are "private" (ie, found in a single family) [2,22].

INDICATIONS FOR HOSPITALIZATION
Vascular or intestinal complications require hospitalization, observation in an intensive care unit, and sometimes emergency surgical intervention. Hospitalization is indicated for any adult, especially under the age of 40 years, who presents with collapse or massive hematoma in which the diagnosis of vascular EDS is suspected [2]. Any patient with an established diagnosis of vascular EDS and thoracic or abdominal pain should also be hospitalized because rapid noninvasive evaluation and diagnosis are required to prevent aneurysm rupture or arterial tearing.

Treatment

**Diet and lifestyle**

- Affected individuals should carry identification cards stating the nature of their condition, level of risk for vascular and gastrointestinal complications, blood group, and contact information for the attending physician [2].
- Strenuous physical exercise and contact sports should be avoided.
- Scuba diving is contraindicated.

**Pharmacologic treatment**

- There are currently no specific treatments, and medical intervention is limited to symptomatic treatment, precautionary measures, and genetic counseling.
- Medications interfering with platelet or coagulation function are contraindicated.