European Reference Network
for rare or low prevalence complex diseases

Network Vascular Diseases (VASCERN)

VASCERN DO'S AND DON'TS FACTSHEETS FOR RARE VASCULAR DISEASE PATIENTS FACING FREQUENT SITUATIONS

Vascular Ehlers-Danlos syndrome

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VASCERN

VASCERN, the European Reference Network on Rare Multisystemic Vascular Diseases, is dedicated to gathering the best expertise in Europe in order to provide accessible cross-border healthcare to patients with rare vascular diseases (an estimated 1.3 million concerned). These include arterial disease (affecting aorta to small arteries), arterio-venous anomalies, venous malformations, and lymphatic diseases.

VASCERN currently consists of 31 highly specialised multidisciplinary Healthcare Providers (HCPs) from 11 EU Member States and of various European Patient Organisations and is coordinated in Paris, France.

Through our 5 Rare Disease Working Groups (RDWGs) as well as several thematic WGs and the ePAG – European Patient Advocacy Group, we aim to improve care, promote best practices and guidelines, reinforce research, empower patients, provide training for healthcare professionals and realise the full potential of European cooperation for specialised healthcare by exploiting the latest innovations in medical science and health technologies.

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Abbreviations

CTA: Computed tomography angiography
EDS: Ehlers-Danlos syndrome
GPIIβ/IIIα: Glycoprotein II beta/III alpha
LOVD: Leiden Open Variation Database
MRA: Magnetic Resonance Angiography
MSA-WG: Medium-Sized Arteries Working Group
SVI: Superficial venous insufficiency
vEDS: Vascular Ehlers-Danlos syndrome

Introduction

Vascular EDS (OMIM #130050) is a rare disorder that results from heterozygosity for mutations in COL3A1 which encodes the pro-alpha1 chains of the type III procollagen homotrimer. The condition is dominantly inherited but asymptomatic parental mosaicism can result in sib recurrence to normal parents. Arterial fragility, bowel rupture, and pregnancy complications are the major clinical complications and may limit survival to about 50 years.

Molecular diagnostic testing is therefore a key factor in identifying patients for appropriate management. More than 600 COL3A1 genetic variants are registered in the EDS database of the LOVD system, a large majority of them being private (http://www.lovd.nl/). This genetic testing requires having access to a genetic laboratory with experience to test and interpret COL3A1 variants, since not all variants are pathogenic and since those leading to haploinsufficiency result in a better prognosis than those with missense variants at a glycine residue or splice-site variants (Frank et al, 2015).

Clinical evaluation is usually undertaken in expert centres with the involvement of a multidisciplinary team familiar with the clinical features of this condition in probands and their first degree relatives. This rare disease suffers from lack of recognition since the main clinical diagnostic criteria for vEDS are nonspecific (hematomas, skin transparency, arterial events) and it is their association that is suggestive.

Major and minor clinical diagnostic criteria of the 2017 International classification of EDS illustrate the variety of physical signs that may constitute the clinical phenotype, adding to the diversity of arterial and visceral events during the natural course of the disease.

Because of the number of affected tissues, clinical evaluation often involves: cardiologists, clinical geneticists, vascular and interventional radiologists, ophthalmologists, orthopaedicians, physiotherapists, bowel surgeons, and vascular, endovascular and cardiac surgeons. Regular MDT meetings with multiprofessional team involvement will also aid in coordinating care of these patients. Appropriate transition of care of patients from paediatric to adult care is also essential in the care of these patients.

Genetic counselling, pre-pregnancy counselling and management during pregnancy by specialist fetal maternal teams will also be an essential part of the care of pregnant women with this disorder. Provision of appropriate counselling for family planning will also be necessary as pregnancy is associated with death in about 5% of women.

Treatment is largely mechanical, surveillance is not universally adopted, and treatment with antihypertensive agents may provide a measure of protection from arterial rupture. Medical therapy with celiprolol (particular beta-blocker) has shown its efficacy in reducing morbid cardiovascular events in a small group of patients, but there are still unmet medical needs. The need for detailed studies of natural history and mechanistic evaluation of arterial rupture are clear and probably the only way to identify helpful interventions.

Factsheets

These factsheets are based on existing French factsheets which have been reviewed and revised by the VASCERN MSA-WG members.

The MSA-WG wishes to emphasize that these are recommendations made by consensus at expert level. We would recommend that these factsheets be used as a guide to implement locally agreed policies.

These factsheets are meant for patients as well as for caregivers. Implementing these recommendations should go hand in hand with strategies to educate patients about medical situations where specific care is required and about relevant symptoms & how to act when they occur.

Complications in vEDS

Major life limiting complications are due to the increased risk of arterial ruptures. In these cases, urgent repair by any possible means is required. Locations that are commonly symptomatic are iliac and femoral arteries, mesenteric and celiac vessels, renal arteries, aorta (any location), and peripheral arteries of the limbs.

Peripheral arterial dissection

Peripheral arterial dissections, especially those of the medium-sized arteries, are the most frequent complication of vascular Ehlers-Danlos syndrome. They are spontaneous and must be suspected in the presence of an unexplained pain syndrome.

WHAT IS RECOMMENDED

- Call the national centre of reference or the regional centre of competence to seek advice due to the seriousness of the risk of dissection.
- Quickly implement all necessary actions in order to confirm the diagnosis of vascular Ehlers-Danlos Syndrome.
- Preference should be given to non-invasive examinations (such as MRA or CTA) and medical/conservative treatment whenever possible.
- When an arteriography is necessary (rupture, perforation), particular precaution should be taken when the guide is being moved upwards (due to risk of dissection/arterial perforation) and enhanced monitoring of the femoral insertion point is necessary.
- Arterial ruptures should be treated in preference by embolization.
- A protocol of permissive hypotension is recommended without compromise to organ function.
- Caution with use of inotropes is recommended.
- Caution with use of indwelling catheters is advised.

WHAT YOU SHOULD NOT DO

- The insertion of stents (except in the case of a life-threatening emergency) should be avoided.
- Consider surgical treatment, other than as a last resort.
- Systematically initiate treatment with anticoagulation and/or antiplatelet agents.

Abdominal emergencies

Vascular Ehlers-Danlos syndrome predisposes young adults to a high risk of digestive tract events which can be life-threatening. Bowel rupture is uncommon in early childhood, has been described in late childhood, and continues to be a risk into adulthood. Bowel rupture ultimately affects about 25–30% of individuals but rarely leads to death.

The main abdominal emergencies are (in order of severity):

- spontaneous arterial rupture in the peritoneal and/or retroperitoneal cavity,
- spontaneous digestive tract perforation, most often of the sigmoid colon, but also of the rest of the colon, the small intestine, and even the stomach,
- spontaneous rupture of an intra-abdominal organ (spleen, liver).

WHAT IS RECOMMENDED

- Perform an emergency angiography scan in the presence of an acute abdominal syndrome.
- In the event of colonic perforation, a wide colonic resection is the preferred method of treatment (Hartmann type for sigmoid colon).
- In cases of arterial rupture, percutaneous embolization should be preferred over open surgery.
- The use of stents should be limited to life-threatening emergencies, and embolization preferred whenever possible.
- In cases of spontaneous perforation of the digestive tract in a young adult or a child, a diagnosis of vascular Ehlers-Danlos syndrome should be automatically considered.
- A protocol of permissive hypotension is recommended without compromise to organ function.
- Caution with use of inotropes is recommended.
- Caution with use of indwelling catheters is advised.

Abdominal emergencies

WHAT YOU SHOULD NOT DO

- Attempt a minimal repair of a spontaneous perforation of the digestive tract.
- Perform a postoperative follow-up colonoscopy in the event of perforation of the digestive tract.
- Perform open surgery as first-line treatment in cases with arterial rupture.
- Any invasive or semi-invasive examination, particularly when the expected diagnostic rewards are minimal.

Haemoperitoneum

Haemoperitoneum is the cardinal indicator of acute bleeding in the abdominal cavity and requires emergency care.

WHAT IS RECOMMENDED

- Perform an emergency abdominal angiography scan to look for an arterial rupture, a digestive tract perforation or an intra-abdominal organ rupture.
- In the event of an arterial rupture, selective embolization should be preferred over open surgery.
- A protocol of permissive hypotension is recommended without compromise to organ function.
- Caution with use of inotropes is recommended.
- Caution with use of indwelling catheters is advised.

WHAT YOU SHOULD NOT DO

- Anticoagulant and antiplatelet treatments are associated with the occurrence of haemoperitoneum, in particular in the post-operative digestive period. In order to limit the risk of complications, these treatments should be taken for the shortest duration possible.
- Avoid unnecessary arterial puncture.

Arterial revascularisation

Arterial events (dissections, aneurysms) are the most frequent complications of vascular Ehlers-Danlos syndrome. Most often, the arterial events are treated medically and therefore do not require intervention, such as surgery.

WHAT IS RECOMMENDED

- Give preference to medical management and treatment for arterial events whenever possible.
- In the event of arterial rupture, emergency arteriography with embolization should be preferred, ideally in a specialised centre with prior experience in dealing with patients with vascular EDS.
- A protocol of permissive hypotension is recommended without compromise to organ function.
- Caution with use of inotropes is recommended.
- Caution with use of indwelling catheters is advised.

WHAT YOU SHOULD NOT DO

- Treat an arterial rupture by surgical means in an emergency context, except in the case of salvage surgery. In this case, special precautions with vascular clamping and sutures are required.
- In the event of an emergency surgical procedure, simple procedures (ligatures) are to be preferred over complex vascular reconstruction.

Aortic dissection

Taking into account the arterial fragility which is characteristic of the disease, the occurrence of a dissection and, rarely, the rupture of the aorta are the possible complications. However, these arterial accidents occur in the abdominal aorta more often than the thoracic aorta.

WHAT IS RECOMMENDED

- If an acute chest and/or abdominal pain syndrome is present, it is imperative to urgently check for the presence of a dissection or rupture of the aorta.
- Give preference to non-invasive examinations (such as MRA or CTA) and medical treatment whenever possible.
- For type A aortic dissections, surgical treatment is indicated as the primary option.
- A protocol of permissive hypotension is recommended without compromise to organ function.
- Caution with use of inotropes is recommended.
- Caution with use of indwelling catheters is advised.

WHAT YOU SHOULD NOT DO

- Use a stent as a first option in the presence of a dissection of the descending aorta; unless there is no other therapeutic alternative.

Acute coronary syndrome

There does appear to be a slightly increased risk of acute coronary syndrome in vascular Ehlers-Danlos syndrome. Given the arterial fragility, dissection of a coronary artery may result in an acute coronary syndrome (non-atheromatous).

WHAT IS RECOMMENDED

- Rule out an aortic dissection in the presence of an acute coronary syndrome in a patient with vascular Ehlers-Danlos syndrome.
- Give preference to non-invasive examinations (coronary scan) and medical treatment whenever possible.
- When a coronary angiography is necessary, particular caution should be taken when moving the guide upwards (due to risk of dissection/arterial perforation) and enhanced monitoring of the femoral insertion point is necessary.

WHAT YOU SHOULD NOT DO

- Use fibrinolytic or anti GPIIβ/IIIα agents as first-line treatments.
- Insertion of stents requiring dual or prolonged antiplatelet therapy should be avoided whenever possible.
- Radial coronary angiography (risk of dissection and ischemia of the hand).

Carotid-cavernous fistulas

Carotid-cavernous fistula is a possible complication of vascular Ehlers-Danlos syndrome. It affects around 10-15% of patients with the syndrome, and consists of a rupture of the intracranial carotid artery into the main collection site of venous blood in the brain. Its spontaneous character is pathognomonic for vascular EDS.

WHAT IS RECOMMENDED

- The appearance of a pulsating murmur in the auscultation of the skull or the eye will suggest the presence of a carotid-cavernous fistula. This suspicion is increased when the eye on the same side as the murmur becomes red and/ or painful. Swelling around the eye may also be present.
- If a carotid-cavernous fistula is suspected, an angiography /cerebral MRI scan is recommended.
- Management and care in a neurovascular unit is required. Therapeutic occlusion of the fistula is often necessary, in spite of the inherent risk of the procedure. This procedure must be carried out in a specialist centre with the greatest possible level of experience.
- Blood pressure in particular should be closely monitored. Maintain a blood pressure target <130/80 mmHg. A protocol of permissive hypotension is recommended without compromise to organ function.
- Caution with use of inotropes is recommended.
- Caution with use of indwelling catheters is advised.

WHAT YOU SHOULD NOT DO

- Delay imaging procedures which alone determine the diagnosis.
- Delay embolization when it is absolutely necessary, as it is a source of significant functional sequelae.

Pneumothorax

Pneumothorax is frequently associated with vascular Ehlers-Danlos syndrome and is the most frequent respiratory manifestation of the disease. It can occur from adolescence onwards and sometimes precedes genetic diagnosis. Treatment usually involves the insertion of a chest tube (complete pneumothorax).

WHAT IS RECOMMENDED

- In the event of a failure to remove the chest tube, a mechanical pleurodesis should be discussed at the time of the first occurrence.

WHAT YOU SHOULD NOT DO

- Pleurodesis in the event of first episode without a failure to remove the chest tube.
- Pleurodesis in cases of partial or prophylactic pneumothorax with asymptomatic bullous lesions in a patient without pneumothorax.

Stroke

Due to the vascular fragility which is characteristic of vascular Ehlers-Danlos syndrome, the cerebral arteries are often affected by complications, most commonly at the cervical level. The latter often present in the form of spontaneous dissections, which can obstruct the affected artery to varying degrees.

WHAT IS RECOMMENDED

- In the event of clinical signs that may suggest a stroke, urgently carry out an imaging scan of the brain and of the cerebral arteries (angiography scan or MRI).
- Discuss with the referring team any indication of revascularisation (thrombolysis, salvage arteriography), arteriography presents a particular risk.
- Search specifically for a carotid-cavernous fistula in the event of pulsatile tinnitus, associated or not with exophthalmos.

WHAT YOU SHOULD NOT DO

- An angioplasty (salvage) with stenting at the level of the arteries of the supra-aortic trunks.

Pregnancy, Delivery and Postpartum care

Pregnancy

Pregnancy presents a particular risk in female patients with vascular Ehlers-Danlos syndrome. It is associated with an increased risk of pregnancy-related complications, directly related to the tissue fragility which is characteristic of the disease. Complications occur in about half the pregnancies and include premature rupture of membranes with preterm delivery, rare uterine rupture during labor, severe perineal tears, and antepartum and post-partum hemorrhage.

WHAT IS RECOMMENDED

- Discuss any planned pregnancy with the medical and obstetrics referral team prior to conception,
- The occurrence of arterial or digestive system incidents may contraindicate a pregnancy.
- Discuss and suggest the possibility of performing prenatal diagnosis.
- Perform a complete arterial lesion assessment before or in early pregnancy.
- Arrange for increased monitoring of the uterine cervix, especially from the 28th week onwards.
- Maintain treatment with celiprolol, or introduce it if the pregnancy started without treatment.

WHAT YOU SHOULD NOT DO

- Interrupt treatment with beta-blockers during pregnancy and the peripartum period.

Delivery

There are no formal recommendations regarding the best method of delivery for patients with vascular Ehlers-Danlos syndrome. A caesarean section between 35 and 37 weeks of gestation is the approach adopted by the reference centre for rare vascular diseases, especially for primiparous patients with a known diagnosis.

WHAT IS RECOMMENDED

- Schedule the delivery due to the elevated risk of maternal complications.
- Always recommend carrying out a caesarean section between 35 and 37 weeks of gestation.
- Plan for the birth to take place in a level 3 maternity unit.

WHAT YOU SHOULD NOT DO

- Delivery at home or in a level 1-2 maternity unit.
- Vaginal delivery without prior multidisciplinary consultation.

Breastfeeding

Vascular Ehlers-Danlos syndrome in itself is not a contraindication to breastfeeding. Nonetheless, the beta-blocker treatment prescribed to prevent the vascular complications of the disease in the mother is not generally recommended during breastfeeding as it is transmitted to the newborn through breast milk.

WHAT IS RECOMMENDED

- Discuss breastfeeding on a case-by-case basis with the attending obstetric and paediatric teams.

WHAT YOU SHOULD NOT DO

- Interrupt the mother's beta-blocker treatment with celiprolol in order to allow for breastfeeding.
- Consider breastfeeding when the newborn has displayed side-effects of beta-blocker use (including bradycardia, respiratory distress and/or hypoglycemia).
- Consider breastfeeding when maternal complications, related to vascular Ehlers-Danlos syndrome, have been reported in the peripartum period.

Invasive investigations and treatment of common medical emergencies in vEDS

Colonoscopy

Colonoscopy is an invasive examination of the colon frequently performed in routine medical practice. Patients with vascular Ehlers-Danlos syndrome have a fragility of the colon which can make this examination dangerous. It is therefore in principle avoided, in order to prevent potentially serious complications.

WHAT IS RECOMMENDED

- Colonoscopy screening for common diseases of the colon should be avoided.
- Colonic video capsule should be the preferred examination whenever possible over invasive exploration of the colon.

WHAT YOU SHOULD NOT DO

- Perform a colonoscopy after an episode of spontaneous perforation of the colon, particularly in a patient who has previously experienced a colonic perforation.

Pulmonary embolism

There is no particular risk of pulmonary embolism associated with vascular Ehlers-Danlos syndrome.

WHAT IS RECOMMENDED

- Follow standard treatment protocols for pulmonary embolisms (anticoagulant treatment).

WHAT YOU SHOULD NOT DO

- Fibrinolysis should be avoided whenever possible due to the increased risk of haemorrhage over the course of the disease.

Venous Thrombosis

There is no particular risk of venous thrombosis associated with vascular Ehlers-Danlos syndrome. In contrast, superficial venous insufficiency (SVI) of the lower limbs is common (varicose veins), which may be a risk factor for venous thrombosis. SVI in vEDS is characterized by its onset of venous disease before the age of 20 years and the early presence of significant (>3 mm) varicose veins.

WHAT IS RECOMMENDED

- Carry out a venous assessment if there are functional or physical symptoms of superficial venous insufficiency of the lower limbs.

WHAT YOU SHOULD NOT DO

- Treat saphenous insufficiency by vein stripping (risk of arterial or femoral venous rupture).

Antiplatelet agents and anticoagulants

The fragility of patients with vascular Ehlers-Danlos syndrome is not conducive to the prescription of antiplatelet and anticoagulant treatments.

WHAT IS RECOMMENDED

- Discuss the prescription of antiplatelet agents / anticoagulants on a case-by-case basis.
- In all cases limit the prescription to the minimum duration necessary.
- Limit the prescription of NSAIDs and if they are necessary use only on an infrequent basis.

WHAT YOU SHOULD NOT DO

- Continue antiplatelet / anticoagulant treatment over the long term, unless otherwise indicated.
- Combine anticoagulants with antiplatelets, and/or several antiplatelet agents.

Exercise

Most of the usual aspects of daily living and recreational activities are not restricted in vEDS. The major concerns associated with high level sports activities are the risk of vascular rupture with the trauma of collisions and the change in blood pressure during these activities.

WHAT IS RECOMMENDED

- Mild to moderate aerobic physical activity, where there is the capacity to converse with partner, is thought to be beneficial.
- Use of equipment such as stationary bicycles, elliptical trainers or well cushioned treadmills could be encouraged.
- Light weights to retain tone and strength and good breath control while using weights.

WHAT YOU SHOULD NOT DO

- Collision sports and isometric activities are generally discouraged.
- Running on hard surfaces and for long distances may exacerbate foot, ankle, knee, and hip pain.
- Activities with rapid acceleration/deceleration should be discouraged as these may increase the risk of vessel dissection.

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