

VASCULAR EHLERS-DANLOS SYNDROME

Vascular Ehlers-Danlos syndrome (vEDS) is an inherited condition that is quite variable. People are often diagnosed when they have easy and frequent bruising that is not explained by other causes, a spontaneous bowel, or arterial tears, or because other family members are affected. Some people have characteristic facial features, thin skin, and tissue fragility, while in others the diagnosis is only made after the identification of an alteration in the type III collagen gene, COL3A1.

It is estimated that 1 in 40,000–50,000 people have vascular Ehlers-Danlos syndrome.

There are more than a dozen types of Ehlers-Danlos syndrome, each with its own set of features and complications. Vascular Ehlers-Danlos syndrome (vEDS) is a concern because of potentially life-threatening complications.

What other names do people use for vascular Ehlers-Danlos syndrome?

Vascular Ehlers-Danlos syndrome is also referred to as vEDS, Ehlers-Danlos syndrome type IV, Sack-Barabas syndrome, and the arterial form of Ehlers-Danlos syndrome.

How many people are affected with vascular Ehlers-Danlos syndrome?

The exact number of affected people with vEDS is not known. The best estimates, which combine counts of people who have been identified by genetic testing with calculations of how well that number represents all people, suggest that there are probably between 6,000 and 8,000 affected people in the U.S., or about 1/40–50,000 people. For comparison, this is about a quarter of the number who have Marfan syndrome.

What are the clinical characteristics of people that lead to the diagnosis of vascular Ehlers-Danlos syndrome?

The features of vEDS are:

- Spontaneous or easy bruising that is not explained by other causes
- Arterial dissection or rupture
- Gastrointestinal perforation
- Spontaneous pneumothorax
- Rupture of the uterus during pregnancy
- Thin, translucent skin

- Characteristic facial appearance (thin lips and midline groove in the upper lip that runs from the top of the lip to the nose, small chin, thin nose, and large, dark, deep-set eyes).

Among those who have vEDS, about half have other affected people in the family and the remainder are the first in their family to have the condition. When someone is the first affected in their family, vEDS happens spontaneously due to a mutation that arose, usually in the egg or sperm, prior to fertilization.

When there is a spontaneous mutation (the mother does not have vEDS but the baby does), the pregnancy is usually uncomplicated, but delivery may be a few weeks early. About 5% of children with vEDS are born with either unilateral or bilateral club foot deformity. A smaller group may have congenital hip deformity and an even smaller group may have amputation or deformity caused by fibrous strand constriction in utero. Bruising is generally not an issue in the perinatal period (when the baby is an infant), but may become apparent as the child becomes mobile. The usual evaluation for blood issues will fail to identify a cause and testing. Vascular EDS is not in the usual evaluation protocol for bruising in the perinatal and early childhood periods.

Major complications in childhood are very rare and death prior to the age of 10 is even less common. In late childhood, some of the facial features of vEDS become more apparent, bruising may increase because of activity, spontaneous pneumothorax (lung collapse) may develop, and colonic ruptures begin to be seen, usually in the sigmoid colon. By age 20, about a quarter of those with a known vEDS diagnosis have had a significant complication, such as bowel rupture, arterial rupture, or spontaneous pneumothorax. Some of those with vEDS may develop a prematurely aged appearance, especially on the limbs with “acrogeria” or old appearing hands and feet. Even with these outward features, the diagnosis is not commonly considered because vEDS is thought to be a rare condition and most clinicians have only heard about it.

Arterial rupture or dissection generally involves the medium sized arteries (the aorta is occasionally involved) and the person’s outward features reflect the location of arterial involvement. Strokes are rare, but can reflect involvement of cerebral or cervical vessels. Spontaneous coronary artery dissection can lead to symptoms of a heart attack. Bleeding in the chest and abdominal vessels lead to discrete symptoms, but can lead to vascular insufficiency if dissections block blood flow to the bowel, liver, spleen, or brain. Aneurysms are common and can precede dissection and rupture, but spontaneous rupture without enlargement does occur.

About 80% of people with vEDS in whom mutations have been identified have had complications by age 40, but this may over-estimate the frequency because people are often identified when complications occur. As a result, those who have not had major complications are not studied.

Women with vEDS have a risk of uterine rupture during late pregnancy and delivery, are more likely to have vaginal and cervical tears than unaffected women, and have a small risk of arterial rupture late in pregnancy and in the peripartum period (after the baby is born). Although many medical experts believe that women with vEDS should avoid pregnancy, pregnancy does not appear to shorten the lifespan when compared to women with vEDS who do not become pregnant. A woman with vEDS who becomes pregnant should receive care in a high risk setting and consider delivery by C-section.

What causes vascular Ehlers-Danlos syndrome?

In all but a few instances, people with vEDS have an alteration in one of the two copies of the COL3A1 gene. There are a few people with alterations in both copies of the gene, and there are a few people with changes in COL1A1 that produce vascular aneurysm and rupture, but have features more like classical EDS.

The COL3A1 gene contains the information that directs the cell to make the chains (called pro α 1(III)) of type III procollagen, the molecule that is modified to become type III collagen. Each molecule contains three chains—half are produced from one copy of the gene and half from the second. When we have children, we pass on only one of the two copies of each gene. If the altered copy of the gene is passed on, then the resulting child will resemble the parent who has vEDS and develop features of the condition. This pattern of inheritance is referred to as autosomal dominant— “autosomal” because the COL3A1 gene is on chromosome 2, one of the “autosomes” and not one of the gender related chromosomes (the X and the Y), and “dominant” because it takes only one of the two copies of the gene to be altered to develop the condition. That is, the altered copy “dominates” the playing field.

When the father or mother has vEDS, each offspring has a 50% chance of inheriting the altered copy of the gene. Male and female children will be affected in equal proportion.

About half of people with vEDS inherited the COL3A1 mutation from an affected parent. The others have a spontaneous disease-causing mutation (called a de novo mutation) that occurred in either the egg or the sperm that gave rise to the pregnancy. As a result, they are the first person in their family to have vEDS and, like someone who inherited the condition from a parent, can now pass it on with a 50% chance of transmission with each pregnancy.

How is vascular Ehlers-Danlos syndrome diagnosed?

The diagnosis of vEDS is based on careful assessment of the medical and family history and a physical examination that is designed to determine if the major features are present. The diagnosis is then confirmed (or excluded) by the analysis of the DNA sequence of the COL3A1 gene (both copies), which can be extracted from blood, cells in saliva, or other tissues. This testing may include DNA sequence analysis, deletion/duplication analysis, and biochemical (protein-based) testing.

In many cases, people with vEDS are identified only after a severe complication or death. It is likely that individuals/families with mild outward features do not seek medical attention and thus go undetected. In addition, because of the perceived rarity of the disorder, it is seldom considered and non-vascular complications may not raise a doctor’s suspicion of vEDS.

Genetic testing detects 98% of the changes in the gene for vEDS; the rest require more specialized tests. Genetic testing is strongly recommended to confirm the vEDS diagnosis when a person has a combination of any two of the major features of the condition.

The major features are:

- Family history of vEDS
- Arterial rupture at a young age

- Intestinal rupture in the absence of known diverticular disease or other bowel issues
- Uterine rupture during the third trimester of pregnancy in the absence of previous c-section and/or other severe vaginal tears
- A sudden engorgement and redness of the eye (called arteriovenous carotid cavernous sinus fistula) in the absence of trauma

The minor features are:

- Easy bruising (spontaneous or with minimal trauma) and/or in unusual sites, such as cheeks and back
- Thin, translucent skin with increased visibility of veins
- Characteristic facial appearance (thin lips, small chin, thin nose, large eyes)
- Pneumothorax (collapse of the lung with accumulation of blood and air in the lung cavity)
- An aged appearance to the extremities, particularly the hands (acrogeria)
- Clubfoot (Talipes equinovarus)
- Dislocated hip at birth
- Small joints that move beyond the normal range expected for a joint
- Tendon/muscle rupture
- Early onset varicose veins (under the age of 30)

A family history of the disorder, arterial rupture or dissection in individuals less than 40 years of age, unexplained colon rupture, or spontaneous pneumothorax in the presence of other features consistent with vEDS should all lead to diagnostic studies to determine if the individual has vEDS. Testing for vEDS should also be considered when there is a combination of the other minor clinical features.

If someone is diagnosed with vEDS, the genetic status of relatives should be clarified through clinical evaluation and molecular genetic testing.

What are the recommendations for management of people with vascular Ehlers-Danlos syndrome?

It is recommended that those with vEDS:

- Wear an identifying medical alert bracelet or necklace and carry an information card for emergency care.
- Establish an organized care team. In general, medical care for people with vEDS occurs in their local community and requires a primary care physician who can coordinate needs with other specialists. The specialists should include a vascular medicine doctor (often a cardiologist), vascular surgeon, general surgeon, and a geneticist. The cooperation among these doctors should create emergency preparedness and assurance that ordinary care proceeds.

- Have ongoing monitoring. Many people with vEDS wish to have regular monitoring of their vascular tree (entire vascular system). When abnormalities are identified, monitoring is often important to determine if treatment is appropriate. Doctors may recommend an annual physical examination, including a carotid and abdominal ultrasound. People with known artery problems may need an evaluation by computerized tomography angiography or magnetic resonance angiography every six to 12 months.
- Follow their doctors' recommendations for taking medications. It is important to take blood pressure medication to assure that blood pressure is maintained in the normal range. Treatment may also include pain medication for joints and muscles. .
- Have surgery when recommended. In general, surgical procedures are more likely to be successful when the treating physician is aware of the diagnosis of vEDS and its associated tissue fragility. In some instances, surgery to repair blood vessels or damaged joints may be necessary before an emergency occurs. Having an operation in a controlled setting is preferable to emergency surgery. Because blood vessels and other hollow organs are fragile and subject to rupture in people with vEDS, doctors recommend surgery only when there is a risk of life-threatening bleeding.
- Manage pregnancy appropriately. Pregnant women with vEDS should be followed in a high-risk obstetric program. Prenatal testing is available for pregnancies that are at an increased risk of passing the COL3A1 mutation to offspring because of a known disease-causing mutation in one of the parents. Genetic counseling is an important aspect of care and generally includes discussions prior to becoming pregnant. Pre-implantation genetic diagnosis, in which unaffected embryos are selected for implantation, can eliminate the risk of transmission from an affected parent.
- Pursue physical therapy, when appropriate. Some people with vEDS benefit from strengthening their muscles. A physical or occupational therapist can provide exercises to strengthen muscles without causing injury.
- Avoid circumstances that can cause medical problems. People with vEDS should avoid contact sports, heavy lifting, weight training, and activities that may include sudden impact or jarring of the body.
- Modify exercise, according to your doctor's recommendations. Children with vEDS may need a modified exercise plan at school. It is essential to discuss physical activities and specific activity levels with a knowledgeable physician so that exercise can be incorporated safely into the regular healthcare routine. This should be an ongoing conversation because, as children age, their medical status and desires can change. Anyone with vEDS should favor a non-competitive activity performed at a pace that permits conversation, such as brisk walking, leisurely bicycling, slow jogging, shooting baskets, leisurely tennis or swimming, and use of light weights without straining. Some children with mild forms of vEDS have been successful in competitive environments in "non-collision" sports.
- Take care with routine colonoscopy and arteriography. These should be performed with great caution and only to identify life-threatening sources of bleeding prior to facilitate treatment.

- Be prepared for an emergency situation. vEDS is considered the most serious form of Ehlers-Danlos syndrome due to the possibility of arterial or organ rupture. If you experience sudden chest or abdominal pain, go to a hospital emergency department immediately. Tests, such as MRA, MRI, and CT, can identify arterial or bowel complications, such as a rupture, that require surgery. Individuals should have emergency instructions from their personal physician to provide EMS workers in case of emergency. Families should also be proactive and alert local first responders to their diagnosis.

What is the expected lifespan for people with vascular Ehlers-Danlos syndrome?

The currently available estimate of lifespan for people with vEDS is based on histories of people who have been tested genetically and confirmed to be affected. This probably represents a population biased toward the more affected end of the clinical spectrum because those with mild features are often not diagnosed. In this population, the median life span is about 51 years, but there are considerable differences based on the class of the genetic mutation. For example, individuals who have a “null” mutation—meaning that one copy of the COL3A1 gene is non-functional and about half the usual amount of normal type III collagen is made—appear to have a near average lifespan, similar to the expected lifespan in the US. Lifespan is typically lower for those with mutations that result in glycine substitutions, and for those with mutations that interfere with the normal protein production. It is important to note that the estimates are based on populations and there are people who have lived longer and shorter than the median. The data is not necessarily useful for the predictions for an individual.

Do you have questions? Would you like more information?

- Contact our Help & Resource Center, through our website (marfan.org/secure/ask) or call 800-862-7326, ext. 126, to speak with a nurse who can answer your questions and send you additional information.
- Visit our website at marfan.org. You can print information that interests you.