

CLINICAL REFERENCE MANUAL VASCULAR TYPE



What Is Vascular Ehlers-Danlos Syndrome?

Ehlers-Danlos syndrome (EDS) is a heterogeneous group of inherited connective tissue disorders. Characterized by articular hypermobility, skin extensibility and tissue fragility, individuals with EDS have a defect in their connective tissue. It is this tissue that provides support to many body parts such as the skin, muscles, ligaments and organs. The fragile skin and unstable joints found in EDS are due to faulty collagen, a protein that acts like glue in the body by adding strength and elasticity to connective tissue.

At least six types of Ehlers-Danlos syndrome have been identified; clinical manifestations vary according to type. Each type is thought to involve a unique defect in connective tissue, although not all of the genes responsible for causing EDS have been found.

Vascular EDS (VEDS) is particularly serious because of possible arterial or organ rupture. VEDS is caused by structural defects in the proa1(III) chain of collagen type III, encoded by the COL3A1 gene; it is inherited in an autosomal dominant manner.

EDS is known to affect men and women of all racial and ethnic backgrounds. Within each family the type of EDS runs true, but individual family members may vary in clinical severity and manifestations. According to current research, the incidence of EDS, as a group of genetic disorders of connective tissue, is 1 in 2,500 to 5,000. The incidence of VEDS is estimated at 1 in 250,000.

The six main types are:

Hypermobility (formerly EDS Type III)

Classical (EDS Types I & II)

Vascular (EDS Type IV)

Kyphoscoliosis (EDS Type VI)

Arthrochalasia (EDS Type VII A&B)

Dermatosparaxis (EDS Type VIIC)

For more information on each EDS type, please see inside the back cover.

Available at EDNF.org:

Understanding Vascular Complications: A Primer of Essential Definitions

By James H. Black III, MD, FACS Illustrations by Jennifer Fairman

Go to www.EDNF.org and click on the red button "Urgent Information on Vascular Complications" for access.

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DIAGNOSIS

CLINICAL SUSPICION

Generally there are three contexts for diagnosing VEDS:

- 1. an individual at 50% (sometimes less) risk in a family with good documentation of a history of VEDS;
- 2. an individual that presents with the characteristic major complications of the disorder in the absence of a family history; *or*
- 3. an individual with enough clinical features (history of bruising, thin appearing skin, *etc.*) to raise concern even with no family history.

AND

TWO MAJOR CRITERIA	OR	ONE MAJOR CRITERION AND TWO MINOR CRITERIA	
 Major criteria: 1. arterial, intestinal, and/or uterine rupture; 2. family history of VEDS, critical in diagnosis: it helps determine if there is a a history of VEDS-congruent complications in the family; it aids identification of individuals who should also be studied; and it provides some perspective on the natural history in the 		 Minor criteria: 1. thin & translucent skin; 2. characteristic facial appearance (large eyes, thin/narrow nose, thin lips, & small chin); 3. extensive bruising; 4. arterial, intestinal, or uterine rupture; 5. aged-appearance of the hands (acrogeria); 6. small joint (finger) hypermobility; 7. congenital dislocation of the hip; 	
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Biochemical and genetic testing are labor and time consuming and thus are not practical in emergencies.

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BIOCHEMICAL AND GENETIC TESTING

A VEDS diagnosis can be confirmed by demonstrating that cultured fibroblasts either:

- make an abnormal type III collagen protein; or
- make clearly less of the protein.

The study of cultured fibroblasts shows abnormal proteins well, but is not entirely reliable for the analysis of quantitative defects (determining if the amount made is low) for a genetic reason. It can be crucial, however, for interpreting some alterations found in genomic DNA.

Direct analysis of genomic DNA from white blood cells or other sources can also be done without the intervening analysis of cultured cells.

All individuals suspected of VEDS should have the mutations identified at the DNA level. This can be done by sequence of the cDNA (made from the messenger RNA) or direct sequence of the COL3A1 gene (which encodes type III collagen).

Sequence of cDNA is a valuable tool and has emerged as the best test available. However, it will generally miss mutations that result in instability of mRNA because of premature termination codons—which would result in only normal product being made from the normal copy of the gene being sequenced. Other limitations include difficulty in determining if some changes are pathological, as well as the inability to identify alterations when there are significant deletions in one copy of the gene. Mosaicism for mutations may be hard to spot.

In the end, if clinical confidence in the VEDS diagnosis is high, all approaches may have to be used to identify a mutation.

CLINICAL SIGNS

Many VEDS diagnostic signs are the minor diagnostic criteria:

- thin and translucent skin;
- extensive multiple bruising;
- arterial, intestinal, or uterine rupture;
- aged appearance of the hands (acrogeria);
- small joint (finger) hypermobility;
- congenital dislocation of the hip;
- clubfoot.

People with VEDS often have a very visible venous patterning and a characteristic facial appearance: large eyes that may be prominent or sunken, thin/narrow nose, thin lips, and a small chin.

Prominent varicose veins in young individuals are also common features. Abnormal scar formation after trauma or surgery is often present.

Joint hypermobility is usually limited to the digits. Tendon and muscle rupture can occur.

Other manifestations that may be found in VEDS include: arteriovenous fistula (an opening between an artery and vein); carotid-cavernous fistula; pneumothorax (lung collapse) or pneumohemothorax (lung collapse with collection of air or gas and blood); gingival recession; and complications during and after surgery.

VEDS arteries are notably thin-walled and fragile, and the bowel appears normal but is very fragile. Please see page 9 for surgical recommendations.

NOTE: There are overlapping clinical phenotypes between VEDS and Loeys-Dietz syndrome (LDS), including the velvety and/or hyperlucent skin, easily visible veins, clubfoot, and dural ectasia. However, LDS patients may have hypertelerism, abnormal uvula, arterial tortuosity and bluish sclera. If the individual who is being evaluated for VEDS is not found to have a COL3A1 gene mutation, test for TGFBR1 and 2 gene mutations to diagnose LDS.



TREATMENT

POST-DIAGNOSIS

Once a patient has a positive genetic test for VEDS, there are three goals:

- 1. An integrated care team;
- 2. A clinical and social support network for the individual and the family;
- 3. An environment in which the diagnosis does not unreasonably thwart personal ambitions.

The person and family should meet with a clinician familiar with VEDS, to help the family understand the complications and to discuss the variations among individuals with a mutation.

- All first-degree relatives, particularly children, of the patient diagnosed with VEDS should be screened for the same gene mutation. There may be phenotypic variability in families and normal clinical evaluation may not be sufficient to exclude a gene mutation.
- Counseling must include a frank discussion of the risks of pregnancy because of the potential for catastrophic complications during pregnancy for the woman with VEDS.

Put together a team of clinicians and identify the point person. Having an

expert available to answer questions is critical for the patient and the care team. The team should include a vascular surgeon and a general surgeon, who become familiar with the individual and family and can then devise strategies to deal with complications.

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Write a letter for the individual to carry that contains treatment recommendations, so that any local ER would know how to proceed should a crisis occur.

Consider plans for regular follow-up visits with the geneticist or other knowl-edgeable clinician.

VEDS patients should wear an emergency medical alert bracelet, to call attention to their diagnosis, and blood type for transfusion.

Because these practices are particularly important in emergencies, VEDS patients should educate their health care providers to:

- avoid intramuscular injections;
- perform central vein catheterizations under ultrasound guidance; and
- ensure adequate cross-matched bank blood.

Whatever activities people enjoy should

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be encouraged. It is strongly suggested they avoid collision sports and follow the guidelines generally employed with Marfan syndrome: participation in low impact activities and avoidance of those which involve collision or moderate-tohigh static or dynamic components.

BASELINE TESTING

There are varying opinions about whether or not to survey all arterial segments for asymptomatic aneurysms and/or dissections once the VEDS diagnosis is made. Even more controversial is how often to re-evaluate the person with "whole body" imaging studies.

Many insurance companies argue with clinicians about these screening studies. They are correct in that there are no data to guide clinicians on whether to image or how often to image the asymptomatic VEDS patient; no rigorous data exist that this surveillance results in a better outcome. Moreover, there are no hard guidelines on when to intervene upon asymptomatic arterial aneurysms or dissections in VEDS.

Clearly, though, appropriate baseline imaging is mandatory for accurate future comparison.

Patients with *identified* vascular complications should be followed closely depending on size diameter of aneurysm and symptoms; imaging every six to twelve months is reasonable. If no aneurysm or dissection is present, reevaluate at minimum every two to three years, depending upon the patient's age and family history. MRI/MRA will lessen radiation exposure.

For *asymptomatic* VEDS patients, a reasonable annual approach is probably to use duplex ultrasound of carotids/abdomen and echocardiogram to evaluate the aortic root for dilation, with interrogation of the chest and abdomen with using CTA every three years.

LONG-TERM CONSIDERATIONS

At minimum, VEDS patients should be evaluated annually by an internist or cardiologist comfortable with both connective tissue disorders, and titration of medications to monitor regular anti-hypertensive medications should be monitored for a goal blood pressure of <130mmHg systolic.

- During exercise, similar systolic blood pressure should be maintained and heart rate should not increase more than 50% above the resting heart-rate.
- Vascular complications will often occur somewhere apart from the site of an aneurysm that has been followed for years.
- Physicians supervising the care of patients with VEDS should remember how subtly vascular dissection and rupture/bleeding can present, and lower their threshold for imaging with CTA/MRA before assigning an ache or pain to other causes.
- At minimum, image aortic root regularly with echocardiography.

General guidelines for surveillance of unaffected individuals should be followed, and any additional risks for other familial conditions should be considered (*e.g.* breast cancer, other forms of heart disease, *etc.*).

- Patients with VEDS should be seen by an ophthalmologist on an annual basis, even if they appear free of ophthalmologic disease. These appointments should be more frequent if there are *any* ophthalmologic findings.
- Address the possibility of major depression that may be precipitated by the lifespan and lifestyle concerns.

Patients need ongoing, adequate medical management for the fascial pain of the syndrome. Referral and regular evaluation by a pain specialist will be needed.

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Vitamin C is often prescribed, on the theory that Vitamin C is a necessary cofactor in collagen assembly and may reduce bruising. There are no reliable data demonstrating its benefit to date, but it is usually well tolerated.

Orthopedic surgeons: Congenital hip and clubfoot are more frequent in this group.

Pediatricians: There are few complications in childhood except for easy bruising, but bowel rupture and arterial events can occur. Encourage the development of a normal life. For more information, the *EDNF Pediatrics One-Sheet* is available. *Obstetricians/Gynecologists:* Complications of pregnancy include arterial and bowel rupture and uterine rupture during pregnancy for affected women. Affected pregnancies in unaffected women (affected partner) may result in prematurity, and bruising, congenital hips dislocation, and clubfoot may occur.

Ophthalmologists: Keratoconus is a particular risk. See Appendix A and the EDNF *Ophthalmology Medical Resource Guide* for much more information.

Dentists: Gum recession and bleeding are issues. See the *EDNF Dentistry Medical Resource Guide* for more information.



SURGERY AND EMERGENCY MEDICINE

The primary indication for intervention is life-threatening ruptured arterial complications, or secondarily, that nothing else being done has made a difference and there is a potential for benefit. In general, invasive procedures should be avoided in VEDS when possible.

Elective treatment of large aneurysms should be indicated only for excessive large aneurysms with impending signs of rupture after close observation. However, operations should never be withheld until the VEDS patient is unstable, because secondary injury from the borderline blood pressure will cause problems independent of the fragile tissues.

A specific indicator that suggests a procedure can be safely undertaken is a history of good-quality tissue handling, noted in prior operations. Patients with multiple prior vascular or GI catastrophes or multiple vascular dissections can

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be suspected to poorly tolerate surgical intervention, and the threshold for intervention should be more conservative.

- Avoid intramuscular injections.
- Inpatient VEDS patients should not receive intramuscular injections and subcutaneous injections of heparin or heparin substitutes as they can cause massive subcutaneous hematoma and bruising.
- Central lines should be placed only with ultrasound guidance to avoid inadvertent arterial injuries.
- Avoid invasive diagnostic tests and unnecessary diagnostic angiography if CTA or MRA is available and embolization of bleeding vessel is not planned.

The VEDS arteries are notably thinwalled and fragile. The layers of the artery are prone to easily separate and develop hematoma in the wall of the artery. The adventitia often rolls back from the point of division to leave the fragile medial layers.

- Excessive retraction leads to multiple tissue tears, mesenteric hematomas and tears in the small or large bowel. Self-retaining retractors should be used carefully.
- The mean arterial pressure should be reduced to <60mmHg prior to clamping or balloon occlusion of the target vessel.
- The reconstruction should be the simplest possible, using primary ligation or arterial replacement with prosthetic grafts and the anastomosis should be reinforced with felt strips.
- Topical hemostatic agents, bioabsorbable glue, and felt reinforcement should be at hand.
- All members of the medical care team should be aware of the potential for greater than usual harm.

In emergency surgery for aortic dissection or vascular rupture, the vascular tissues in the area of the event will not hold sutures (frequently described as "the wet Kleenex look"), and ligation may be only option. Several centimeters above or below will be diseased, but may provide suitable reconstruction zones.

The VEDS bowel appears normal but is very fragile and prone to develop hematoma in the wall during mobilization. Interestingly, prior adhesions from earlier operations may be essentially normal in density and tensile "toughness," and thus lysis of adhesions may be difficult because aggressive traction on the bowel to facilitate adhesion separation will precipitate dramatic hematoma. Surgical staplers often cause significant hematoma due to crush injury.

When VEDS patients are undergoing cardiovascular surgery for other conditions such as valvular disease or coronary artery occlusive disease, bear in mind the principle cardiovascular risks associated with VEDS are arterial rupture or dissection. Stay alert to the possibility of intraoperative complications related to the rupture or dissection of the aorta or major branch vessels. The risk of aortic dissection at the site of aortic cannulation is likely higher than in the normal population.

- When surgery on those vessels is necessary, the tissue are fragile and do not hold sutures well. Therefore complex vascular reconstructions may be deferred in favor of simpler interventions such as simple ligation of aneurysmal vessels when anatomically possible.
- When valve surgery is required, valve replacement rather than repair may be preferable for the same reasons, although successful repair has also been reported. But because operative risks are higher, surgeons will be reluctant to operate unless the indications are pressing and absolutely clear-cut.
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blood should be available for any planned vascular surgical procedure.

- Bleeding, especially into body wall or cavity should be managed conservatively with transfusion and support.
- If intervention is required for ongoing hemorrhage, ligation may be the safest route to stability.
- When ligation is not feasible, appropriate surgical exposure to achieve more proximal and distal access to

uninvolved arteries should be sought so an optimal reconstruction can be performed.

• Rupture of arteries or aortic dissection in VEDS should not be treated with endovascular stent-graft therapy unless the site of rupture is located in a surgically inaccessible area. The available endovascular stent-grafts are not engineered to accommodate the fragile tissue of VEDS.



ADDENDA

A. OPHTHALMOLOGICAL COMPLICATIONS

Patrick Wyse, MD, PhD, FRCS

The principal serious ophthalmologic sequela of VEDS is spontaneous carotid-cavernous fistula and this can be vision and even possibly life threatening.

In my protocol of following a VEDS patient, at their initial assessment I carry out a complete ophthalmologic evaluation including:

- best corrected vision;
- slit lamp examination;
- fundoscopic examination;
- exophthalmometry to establish a baseline of the ocular prominence;
- baseline 30-2 visual field;

- pachymetry to establish corneal thickness;
- fundus photography including stereoscopic views of the optic nerves;
- OCT (optical computed tomography) of the optic nerve heads; and
- auscultation over the globes and temples for bruit.

Corneal thickness as determined by pachymetry is a useful marker in establishing the true intraocular pressure. It is now recognized that a thin cornea in the presence of high normal intraocular pressure is more often associated with progression to glaucoma than is the case with the same intraocular pressures and a thick cornea. The principal colla-

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gen in the cornea is type I collagen with type III collagen and type V collagen being more minor corneal collagens. Significant thinning of the cornea exists in classic EDS, both clinically and in a mouse model with collagen V haploinsufficiency ("Structural Abnormalities of the Cornea and Lid Resulting from Collagen V mutations," Segev *et al.*, *Invest. Ophthal. Vis. Sci.* 2006, 47:565-573).

I have also noted intermediate thinning in my VEDS patients but the numbers are insufficient yet to determine whether this is due to sampling error or is a significant observation.

Apart from the relationship to glaucoma, thin corneas are a factor that must be taken into consideration by photorefractive surgeons. There are some authors who have made the absolute statement that photorefractive surgery should not be done on those with EDS but I am not certain on what evidence that statement is made. I have seen EDS patients who have had photorefractive surgery with stable results and so apart from a strong word of caution I do not believe the evidence is available pro or con with regard to this form of surgery in EDS patients in general and VEDS patients in particular.

All VEDS patients need to be made aware of the signs and symptoms of a carotidcavernous fistula and be advised to report to the closest tertiary care hospital should these signs and symptoms develop:

- Increased prominence of an eye;
- Increased inflammation of the conjunctiva;
- Swelling of the eye lid;
- The awareness of an audible bruit;
- Increased blurring of vision; or
- Pain.

Such patients need to be aware of the need for MRA or CTA to evaluate any change in the status of their cavernous sinus. They also need to be aware of the risks posed in an individual with EDS by the normal surgical approach to correcting a carotid-cavernous fistula.

The specific probabilities are difficult to compile but generally, myopia is more common in EDS; and although relatively uncommon, retinal detachment is a possibility. Awareness of the signs and symptoms of retinal detachment is warranted.

One harbinger of retinal detachment is vitreal detachment, the separation of the gel inside the eye from the retinal surface. The symptoms of a vitreal detachment can include a sensation of a transient flashing light in the peripheral field of vision, most typically in the far temporal periphery, followed by floaters in the field of vision which may run the gamut from a spider web like veil to dark spots or blobs of shadow floating across the field of vision. Vitreal detachments in and of themselves are not vision threatening; they are an annoyance and are worrisome, but they do not threaten the vision.

The risk in vitreal detachments relates to the fact that when the vitreous detaches it can induce a tear in the retina which can then lead to a retinal detachment. Empirically that occurs about 1% of the time, so it is not a high risk; but the development of the signs and symptoms of a vitreal detachment warrants a detailed assessment of the peripheral retina to rule out the presence of a retinal tear or detachment.

The cardinal symptom of a retinal detachment is a distinct shadow in the peripheral field of vision which obscures the vision in that area. This symptom warrants an eye examination on an urgent basis.

Without assessment and treatment the area of retinal detachment can extend to the point that it can involve the central retina and then the risk for permanent visual reduction is much greater.



B. A BRIEF PRIMER ON THE VASCULATURE IN VEDS

This appendix is condensed from *Understanding Vascular Complications: A Primer of Essential Definitions*, written by James H. Black, M.D. with illustrations by Jennifer Fairman. Their complete primer is available at www.ednf.org; click on the red button "Urgent Information on Vascular Complications" for access.

BLOOD VESSELS CONSIST OF THREE LAYERS:

- The innermost *intima* is only a few cell layers thick.
- The *media* ("middle") layer is mostly special muscle cells that provide elasticity.
- The outermost layer, the *adventitia*, is primarily connective tissue.



ANEURYSM

True aneurysms occur in arteries and are defined as a dilatation of the blood vessel wall, but with all three layers intact. In EDS aneurysm rupture is unpredictable and may occur at any diameter. While aneurysm rupture is a life-threatening condition, fortunately true aneurysm formation is relatively rare in EDS, occurring in approximately 15% of patients.

DISSECTION

Arterial dissection refers to a tear in the intima; the tear leads to a breach in the three layers of the blood vessel wall, causing two passageways for the flow of the blood. The true lumen is the normal passageway with all three layers intact; the passageway outside the tear is missing the intima.

Aortic dissections are occasionally asymptomatic but more commonly cause an array of symptoms depending on the location and extent of the tear. A dissection may cause pain and may compromise blood flow to the extremities or internal organs. With time the weakened wall may expand to become

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a dissection with an aneurysm component as well.

PSEUDOANEURYSM

Pseudoaneurysms ("false" aneurysms) are a contained rupture of a blood vessel. All three vessel layers are disrupted, so blood pulses into the space outside the vessel. Surrounding hematoma and tissue typically contain the blood flow; but the most dreaded complication remains free rupture of the artery with life-threatening bleeding.

C. GLOSSARY

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- *acrogeria* Reduction or loss of subcutaneous fat and collagen of the hands and feet.
- *aneurysm* Sac formed by localized enlargement of the wall of an artery, a vein, or the heart.
- *arterial rupture* An artery tears open, usually suddenly.
- *arterial tree* Anatomical term used to describe branching pattern of the arteries and/or all of the arteries throughout the body.
- *arteriogram* Uses x-ray to examine the arteries. A dye is injected into the arterial system to make the arteries visible on x-ray. Contraindicated in VEDS patients.
- *arteriovenous fistula* Abnormal connection between an artery and a vein.
- *carotid-cavernous fistula* Cavernous sinus is a venous structure in the head through which the carotid artery travels; if the internal carotid artery ruptures within the cavernous sinus, a *carotid-cavernous fistula* forms.
- *autosomal dominant* Inheritance of an abnormal gene from one parent and a normal gene from the other

parent on non-sex chromosomes.

- *biochemical testing* Measures the amount or activity of a particular protein or enzyme from a sample of blood, urine, or other tissue from the body.
- *bowel rupture* Hole in the wall of the small or large intestine.
- *cDNA* complementary DNA: a synthesized sequence of DNA that complements an mRNA template.
- *COL3A1 collagen, type III, alpha* – The COL3A1 gene provides instructions for making a component of collagen.
- *colectomy* Surgery during which all or part of the colon (also called the large intestine) is removed.
- *collagen* Main protein in connective tissue and the most abundant in the human

body. There are more than 28 types of collagen in the body. Over 90% of the collagen in the body, however, is of type I, II, III, and IV: Collagen One – skin, tendon, vascular, ligature, organs, main component of bone; Collagen Two – main component of cartilage; Collagen Three – main component of reticular fibers, commonly found alongside type I; Collagen Four – forms bases of cell basement membrane. Collagen diseases are commonly from genetic defects affecting the

defects affecting the biosynthesis, assembly, posttranslational modification, secretion, or other processes in the normal production of collagen. See table at right for notes on collagen disorders by type.

collagen fibrils, fibers – Collagen fibrils are collagen molecules that are organized into an overlapping CLINICAL REFERENCE MANUAL: VASCULAR TYPE EDNF 15

ТҮРЕ	NOTES ON COLLAGEN TYPE	GENE(S)	DISORDERS
Ι	This is the most abundant collagen of the human body. It is present in scar tissue, the end product when tissue heals by repair. It is found in tendons, skin, artery walls, the endomysium of myofibrils, fibrocartilage, and the organic part of bones and teeth.	COL1A1 COL1A2	osteogenesis imperfecta, EDS
II	Hyaline cartilage, makes up 50% of all cartilage protein. Vitreous humour of the eye.	COL2A1	Collagenopathy, types II and XI
III	This is the collagen of granulation tissue, and is produced quickly by young fibroblasts before the tougher type I collagen is synthesized. Reticular fiber. Also found in artery walls, skin, intestines and the uterus	COL3A1	EDS
IV	Basal lamina; eye lens. Also serves as part of the filtration system in capillaries and the glomeruli of nephron in the kidney.	COL4A1 COL4A2 COL4A3 COL4A4 COL4A5 COL4A6	Alport syndrome
V	Most interstitial tissue, assoc. with type I, associated with placenta	COL5A1 COL5A2 COL5A3	EDS Classical

bundle; collagen fibers are bundles of fibrils.

- *colostomy* Surgical procedure that involves connecting a part of the colon to the anterior abdominal wall, leaving an opening on the abdomen called a stoma through which feces leave the body; this procedure may be permanent or temporary.
- *de novo mutation* New gene mutation in a germ cell (egg or sperm) of one of the parents or in the fertilized egg.
- *differential diagnosis* Process that involves making a list of possible diagnoses, then attempting to remove diagnoses from the list until at most one diagnosis remains. Removing diagnoses from the list is done by making observations and using tests that should have different results, depending on which diagnosis is correct.

- *dilatation* Enlargement of a cavity, canal, blood vessel, or opening.
- *dislocation* When bones in a joint become separated or displaced. Ligaments are always damaged in the process.
- *dissection* Tear in the inner lining of an artery that allows blood to leak into the artery wall.
- *DNA bank* Repository of DNA usually used in research.
- *EDS Type IV* Vascular type in older nosology classification; see page 2.
- *Ehlers-Danlos syndrome & types* See inside back cover.
- *fistula* Abnormal passage that occurs between organs, between an organ and the outside of the body, or within the venous system between arteries and veins.
- *gastrointestinal perforation* A hole through the entire wall of the stomach, small intestine or large bowel, that allows intestinal contents to spill into the abdominal cavity.

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- *genetic counseling* Process by which patients or relatives who are at risk of an inherited disorder are advised of the consequences and nature of the disorder, the probability of developing or transmitting it, and the options open to them in management and family planning in order to prevent, avoid or manage it.
- *genomic DNA* Full complement of DNA contained in the genome of a cell or organism.
- *gingival recession* Loss of gum tissue leading to exposure of the roots of teeth.
- *hemorrhage* A rapid and uncontrollable loss of blood.
- *hypertension* A condition where blood pressure is elevated; hypertension should be closely monitored in EDS patients.
- *inguinal hernia* Occurs when soft tissue (such as the intestines) bulges through a weak point or tear in lower abdominal wall.
- *medical alert service* Medical alert jewelry combined with telephone emergency support for complex information; some offer mini computer drives which can hold complete medical histories.
- *molecular genetic testing* Examination of blood, other body fluid, or tissue samples for biochemical, chromosomal, or genetic markers that indicate the presence or absence of genetic disease.
- mosaicism the property or state of being composed of cells of two genetically different types; the presence of two populations of cells with different genotypes in one individual, who has developed from a single fertilized egg.
- *nosology* Nosology deals with classification of diseases by *etiology* (cause), *pathogenesis* (mechanism by which the disease is caused), or by *symptomology*. Diseases often

cannot be defined or classified clearly, especially when etiology or pathogenesis are unknown; thus diagnostic terms often only reflect a symptom or set of symptoms (syndrome).

- *peripartum arterial rupture* Rupture of an artery in a woman during the last month of pregnancy or the first few months after delivery.
- *pneumohemothorax* Accumulation of blood and gas in the pleural cavity (space around the lungs).
- *pneumothorax* The collection of air or gas in the space around the lungs.
- *retroperitoneal bleeding* Bleeding of organs and structures that lie behind the peritoneum; can be caused by ruptured aortic aneurysm.
- *somatic cells* Any cells forming the body of an organism, as opposed to germline cells. Mammalian germline cells (or *gametes*) are the spermatozoa and ova which fuse during fertilization to produce a zygote, from which the embryo develops. Every other cell type, apart from the sperm and ova, the cells from which they are made (gametocytes) and undifferentiated stem cells, is a somatic cell: internal organs, skin, bones, blood, and connective tissue.
- *stroke* A stroke occurs when a blood clot blocks an artery or a blood vessel breaks, interrupting blood flow to an area of the brain; when either of these things happen, brain cells begin to die and brain damage occurs.
- *suture dehiscence* Splitting open of a surgical wound.
- *talipes equinovarus* Club foot, a deformity marked by a plantarflexed, inverted, and adducted foot.
- *tissue and vessel friability* Fragile, easily damaged tissues and vessels. *uterine rupture* – Tearing open of the

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uterus; during pregnancy, the fetus, placenta and blood can flood the mother's abdomen if the uterus ruptures.

venous subtraction angiography –

Imaging technique used to see inside blood vessels and organs; performed by injecting a radioopaque contrast agent into the blood vessel and imaging it with X-ray based techniques like fluoroscopy. Images are usually taken at two to three frames per second, which allows the radiologist to evaluate the real-time flow of the blood through the vessel(s). This technique visually removes the bones and other organs so that only the vessels, filled with contrast agent, can be seen.

- *venous varicosity* Occurs when valves in the veins fail or are damaged and cannot keep the flow of blood from moving in the wrong direction; circulation of blood is impaired and can then pool in the area, forming twists and bulges in the veins.
- Villefranche 1997 Revision of the traditional classifications of Ehlers-Danlos syndrome (nosology); simplified the numbering system to a name-based system based on the cause of each type. The complete nosology can be read at http://www.ednf.org/index. php?option=com_content&task= view&id=1352&Itemid=88888970.





What Are the EDS Types?

Dn-line

HYPERMOBILITY (FORMERLY EDS TYPE III)

Joint hypermobility is the dominant clinical manifestation. Generalized joint hypermobility that affects large (elbows, knees) and small (fingers and toes) joints is evident in the Hypermobility Type. Recurring joint subluxations and dislocations are common occurrences. Certain joints, such as the shoulder, patella, and temporomandibular joint dislocate frequently. The skin involvement (hvperextensibility and/or smooth velvety skin) as well as bruising tendencies in the Hypermobility Type are present but variable in severity. Chronic joint and limb pain is a common complaint amongst individuals with the Hypermobility Type. Skeletal X-rays are normal. Musculoskeletal pain is early onset, chronic and may be debilitating. The anatomical distribution is wide and tender points can sometimes be elicited.

Clinical Testing – To date, no distinctive biochemical collagen finding has been identified by researchers. The Hypermobility Type of EDS is inherited in an autosomal dominant manner.

CLASSICAL (FORMERLY EDS TYPES I AND II)

Marked skin hyperextensibility (stretchy) with widened atrophic scars and joint hypermobility are found in the Classical Type of EDS. The skin manifestations range in severity from mild to severe expression. The skin is smooth and velvety with the evidence of tissue fragility and easy bruisability. Examples of tissue extensibility and fragility include hiatal hernia, anal prolapse in childhood and cervical insufficiency. Hernias may be a

post-operative complication. Scars are found mostly over pressure points such as the knees, elbows, forehead and chin. Molluscoid pseudo tumors (calcified hematomas) associated with scars are frequently found over pressure points such as the elbows, and spheroids (fat containing cysts) are usually found the on the forearms and shins. Complications of joint hypermobility include sprains, dislocations/subluxations and pes planus (flat foot) to name a few. Recurrent joint subluxations are common in the shoulder, patella and temporomandibular joints. Muscle hypotonia and delayed gross motor development may also be evident.

Clinical Testing – Abnormal electrophoretic mobility of the proa1(V) or proa2(V) chains of collagen type V has been detected in several but not all families with the Classical Type. The Classical Type of EDS is inherited in an autosomal dominant manner.

VASCULAR (FORMERLY EDS TYPE IV)

See inside front cover.

KYPHOSCOLIOSIS (FORMERLY EDS TYPE VI)

Generalized joint laxity and severe muscle hypotonia (weak muscle tone) at birth are seen in this type of EDS. The muscular hypotonia can be very pronounced and leads to delayed gross motor development. Individuals with the Kyphoscoliosis Type present with scoliosis at birth that is progressive. The phenotype is most often severe, frequently resulting in the loss of ambulation in the second





or third decade. Scleral fragility may lead to rupture of the ocular globe after minor trauma. Tissue fragility including atrophic scars and easy bruising may be seen in the Kyphoscoliosis Type. Spontaneous arterial rupture can occur. Other findings may include: marfanoid habitus (Marfan like features); micro cornea (abnormally small cornea); and radiologically considerable osteopenia (diminished amount of bone tissue).

Clinical Testing – Kyphoscoliosis Type EDS is the result of a deficiency of lysyl hydroxylase (procollagen-lysine 5-dioxygenase, or PLOD), which is a collagen-modifying enzyme. This type of EDS is inherited in an autosomal recessive manner. Kyphoscoliosis Type can be diagnosed through a urine test.

ARTHROCHALASIA (FORMERLY EDS TYPE VII A & B)

Congenital hip dislocation has been present in all biochemically proven individuals with this type of EDS. Severe generalized joint hypermobility with recurrent subluxations are seen in individuals with this type of EDS. Other manifestations of this type may include: skin hyperextensibility with easy bruising; tissue fragility including atrophic scars; muscle hypotonia; Kyphoscoliosis and radiologically mild osteopenia.

Clinical Testing – The Arthrochalasia Type is caused by mutations leading to deficient processing of the amino-terminal end of proa1(I) [type A] or proa2(I)[type B] chains of collagen type I. It is inherited in an autosomal dominant manner. A skin biopsy can also diagnose this type of EDS.

DERMATOSPARAXIS (FORMERLY EDS TYPE VIIC)

Individuals with Dermatosparaxis Type EDS have severe skin fragility and substantial bruising. Wound healing is not impaired and the scars are not atrophic. The skin texture is soft and doughy. Sagging, redundant skin is evident. The redundancy of facial skin results in an appearance resembling cutis laxa. Large hernias (umbilical, inguinal) may also be seen. The number of patients reported with this type of EDS is small.

Clinical Testing – Dermatosparaxis Type EDS is caused by a deficiency of procollagen I N-terminal peptidase. It is inherited in an autosomal recessive manner. A skin biopsy can diagnose this type of EDS.

OTHER

EDS type V (X-linked) has been described in a single family. It is a rare variant and the molecular basis of which remains unknown.

EDS type VIII is similar to the Classical Type except that in addition it presents with periodontal friability. This is a rare type of EDS. The existence of this syndrome as an autonomous entity is uncertain.

EDS type IX was previously redefined as "Occipital Horn syndrome", an X-linked recessive condition allelic to Menkes syndrome. This was previously removed from the EDS classification.

EDS type X has been described in only one family.

EDS type XI termed "Familial Joint Hypermobility syndrome" was previously removed from the EDS classification. Its relationship to EDS is not yet defined.



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