

EHLERS-DANLOS SYNDROME: COMPLICATIONS AND SOLUTIONS CONCERNING ANESTHETIC MANAGEMENT

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Introduction

Ehlers-Danlos syndrome (EDS) is a heterogeneous group of connective tissue disorders organized into six clinical subtypes and eleven variants¹. Each subtype is based on the severity of clinical symptoms, the pattern of inheritance and the underlying genetic defect. The complex cascade and the many proteins involved in the synthesis of collagen provide ample opportunity for mutations to occur and generate faulty collagen. All of the gene mutations that have been identified for specific subtypes of EDS involve the synthesis of collagen, collagen-modifying proteins/enzymes and tenascin-X^{2,3}. Consequently, these mutations lead to dysfunctional collagen and cause the classical signs and symptoms of EDS. The most noticeable symptoms are those involving tissues with an abundance of collagen: skin, ligaments, joints, and vessels. The most common clinical symptoms observed in varying degrees in all subtypes of EDS include hyperextensibility and severe fragility of the skin, hypermobile joints, and easy bruising. However, some subtypes have unique signs and symptoms pathognomonic to that subtype and incur their own prognosis. Management of EDS incorporates prevention of complications involving injury to the skin, vessels and joints⁴.

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The anesthesiologist must be extremely careful as there is constant risk of causing preventable injuries. Common, yet necessary, tasks including cannulation of veins, insertion of endotracheal tubes, and intramuscular injections become interventions with exaggerated and unavoidable risks⁵.

Epidemiology

Ehlers-Danlos Syndrome (EDS) is estimated to affect 1 in 5000 people⁶. A higher value has been reported in the black population⁷. It has a polygenic etiology with the most common types being autosomal dominant, but an X-linked recessive and several autosomal recessive patterns have also been identified^{8,9}.

The first clinical description of EDS in 1892 dates back to a Russian dermatologist, Dr. Tschernogobow. Drs. Ehlers and Danlos, Danish and French dermatologists, further expanded on the condition. Later, the genetic heterogeneity of EDS was established in the 1960s, and the first molecular defects in collagen biosynthetic pathways were delineated in 1972¹⁰.

Pathogenesis and Molecular Genetics

Ehlers-Danlos Syndrome is a clinically and genetically heterogeneous group of conditions. Traditionally, it was subdivided into eleven variants. The latest classification of EDS, the Villefranche Nosology, was developed at a consensus conference in 1997¹⁰. Currently six subtypes, based on the severity of the clinical symptoms, the pattern of inheritance and the underlying biochemical and molecular defect are recognized¹¹ [Table 1]⁴. The classical types (EDS I, EDS II) and the hypermobile type (EDS III) are found in 90%. The vascular type (EDS IV) occurs in 3-10%. The kyphoscoliosis, arthrochalasia, and dermatosparaxis types represent very rare conditions¹².

Table 1

Type	Protein	Inheritance	Diagnostic Criteria
Classic (type I/II)	Type V procollagen	AD	<i>Major:</i> hyperextensible skin, widened atrophic scarring, joint hypermobility. <i>Minor:</i> easy bruising, smooth/velvety skin, molluscoid pseudotumors, subcutaneous spheroids, hypotonia, complications of joint hypermobility, surgical complications, positive family history
Hypermobility (type III)	Unknown	AD	<i>Major:</i> generalized joint hypermobility, mild skin involvement. <i>Minor:</i> recurring joint dislocations, chronic joint pain, positive family history
Vascular (type IV)	Type III procollagen	AD	<i>Major:</i> excessive bruising, thin and translucent skin, arterial/intestinal/uterine fragility or rupture, characteristic facial appearance. <i>Minor:</i> acrogeria, early-onset varicose veins, hypermobility of small joints, tendon and muscle rupture, arteriovenous or carotid-cavernous sinus fistula, pneumo(hemo)thorax, positive family history, sudden death in close relative
Kyphoscoliotic (type VI)	Lysyl hydroxylase 1	AR	<i>Major:</i> severe muscular hypotonia at birth, generalized joint laxity, kyphoscoliosis at birth, scleral fragility and rupture of the globe. <i>Minor:</i> tissue fragility, easy bruising, arterial rupture, marfanoid habitus, microcornea, osteopenia, family history
Arthrochalasia (type VIIA/VIIB)	Type I procollagen	AD	<i>Major:</i> severe generalized joint hypermobility with recurrent subluxations, congenital bilateral hip dislocation. <i>Minor:</i> skin hyperextensibility, tissue fragility, easy bruising, muscular hypotonia, kyphoscoliosis, mild osteopenia, occasionally fractures
Dermatosparaxis (type VIIC)	Procollagen-N-proteinase	AR	<i>Major:</i> severe skin fragility, sagging, redundant skin, excessive bruising. <i>Minor:</i> soft, doughy skin texture, premature rupture of membranes,

			large herniae
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Specific mutations of genes for collagen, collagen-modifying enzymes and tenascin have been described in most types¹¹. Collagens are structurally related, extracellular matrix proteins that are essential for development and organogenesis, cell attachment, platelet aggregation and for providing tensile strength to the connective tissues in bone, skin, ligaments and tendon. These collagen proteins are homo-or heterotrimeric molecules that share unique triple-helical domains. The presence of glycine in every third position of each chain is necessary for the formation of a stable collagen helix. The fibrillar collagens are the most widespread and abundant class of collagens and include types I, II, III, V and XI. Precursor molecules, known as procollagens, initiate the biosynthesis of collagen within the fibroblast. These procollagens align and bond from the C- to the N-terminal end of the molecule and, through a series of enzymatic modifications, the triple-helix is formed. Individual collagen molecules then spontaneously assemble into fibrils which are stabilized by covalent cross-linking. A disturbance anywhere along this process can lead to connective tissue instability^{4,10}.

EDS involves collagen types I, III, and V. Type I collagen is the major collagen type in the body and has a wide distribution. A mutation resulting in structural abnormality of type I will result in the arthrochhalasis type of EDS, whereas, a mutation leading to abnormal processing collagen results in the kyphoscoliosis or dermatosparaxis type. In the kyphoscoliotic form, there is a deficient activity in the collagen-modifying enzyme lysyl hydroxylase-1, and, in the dermatosparaxis type, the mutation involves the enzyme procollagen-N-proteinase. Type III collagen is an essential component of many connective tissues found in blood vessels, the gastro-intestinal tract, the uterus and the skin. A mutation in type III collagen, whether structural or haplo-insufficient, results in the vascular type of EDS. Type V collagen is co-expressed with type I in many connective tissues and its mutation results in 50% of classic type of EDS. In rare instances, a mutation causing the substitution of glycine in the procollagen chain of type I collagen has also been identified as a cause of classic EDS⁴.

Previously, EDS has been considered solely as a disease of collagen. Zweers *et al*, however, recently demonstrated that a deficiency of tenascin-X may also contribute to the pathogenesis of EDS. Tenascin-X (TNX) is a large extracellular matrix protein developmentally associated with collagen fibrils and is thought to maintain homeostasis of the extracellular matrix. Its deficiency is associated with fragmentation of elastic fibers, reduction of collagen, failure of fibroblasts to correctly deposit collagen type I, and loose packing of collagen fibrils. It was also determined that an autosomal recessive type of EDS due to TNX deficiency is associated with some cases of dominantly inherited hypermobility type of EDS. Moreover, elastic fiber abnormalities in hypermobility type EDS are specific for TNX-haploinsufficient individuals^{10,11}.

Clinical Features

The diagnosis of Ehlers-Danlos Syndrome is based primarily on clinical criteria. Clinical manifestations are present, to varying degrees, in each subtype of the condition⁴. The principle clinical features include easy bruising and generalized connective tissue fragility, skin hyperextensibility, delayed wound healing with atrophic scarring, and joint hypermobility^{13,14} [Table 2] These features are secondary to the disruption of tissues rich in collagen, such as skin, ligaments, and joints².

Table 2
Characteristics of EDS

Principle Clinical Features
Easy bruising
Joint hypermobility
Skin hyperextensibility
General connective tissue fragility
Delayed wound healing + atrophic scarring

Easy bruising is typically the initial manifestation. Bleeding from the gums following brushing of the teeth, or excessive bleeding after minor

trauma are common presentations^{4,9,15}. Vascular fragility may cause of nonpalpable purpura¹⁶.

Hematological studies such as the platelet count, bleeding time, and coagulation tests are usually normal⁴. However, the Rumpel-Leede (or Hess) test may be positive, indicating capillary fragility. To apply the Rumpel-Leede test, the physician applies a blood-pressure cuff to the upper arm and inflates to a level between the diastolic and systolic pressure values. In a patient whose blood pressure is 120/80, the cuff may be inflated to 100 mmHg, for example. After pressure is maintained for 5 minutes and released, the number of petichiae are counted, with greater than 10 spots recorded as abnormal (positive)^{9,15}.

Skin hyperextensibility should be tested at a neutral site such as the volar surface of the forearm as it less subjected to mechanical forces or scarring. To determine the amount of hyperextensibility, the skin is pulled up until the clinician feels resistance. It may be difficult to assess hyperextensibility in the skin of young children due to large amounts of subcutaneous fat⁴.

Tissue fragility results in splitting of the skin following relatively minor trauma. Areas particularly at risk are the knees, elbows, shins, forehead and chin. Lacerations and incisions heal slowly. Widened atrophic scars, "cigarette-paper scars", are also a manifestation of tissue fragility^{7,8,9}. Additionally, in areas of repetitive trauma, hemosiderin deposition may lead to dark discoloration of the skin⁴.

Table 3

The nine-point Beighton hypermobility score (Ref. 9) One point may be gained for each side for maneuvers 1-4 so that the hypermobility score will have maximum of nine points if all are positive. A score of 4/9 indicates widespread hypermobility.

Ability	Left	Right
Passively dorsiflex the fifth metacarpopharlangeal joint to 90°	1	1
Oppose the thumb to the volar aspect of the ipsilateral forearm	1	1
Hyperextend the elbow to 10°	1	1
Hyperextend the knee to 10°	1	1
Place hands flat on the floor without bending knees	1	

Max possible score:	9
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Joint hypermobility often affects large and small joints and can be assessed using the Beighton scale [Table 3]. A score of $\geq 4/9$ defines widespread joint hypermobility.

The Beighton criteria can also be used to diagnose joint hypermobility syndrome [Table 4]. Hypermobility may lead to occasional or frequent dislocations of joints. Those most commonly involved are the shoulder, hip and patella⁴. Joint hypermobility also leads to chronic musculoskeletal pain and possibly premature degenerative joint disease¹⁷.

Table 4

Beighton criteria for joint hypermobility syndrome (JHS) (Ref. 8) JHS is diagnosed in the presence of two major criteria, or one major and two minor criteria, or four minor criteria. Two minor criteria will suffice where there is an unequivocally affected first-degree relative.

<p>Major</p> <ul style="list-style-type: none"> • Beighton score of $\geq 4/9$, or more (either currently or historically). • Arthralgia for longer than 3 months in four or more joints. <p>Minor</p> <ul style="list-style-type: none"> • A Beighton score of 1-3 out of 9 (0-3 if aged 50+). • Arthralgia in 1-3 joints, or back pain or spondylosis, spondylolysis/spondylolisthesis. • Dislocation in more than one joint, or in one joint on more than one occasion. • Three or more soft tissue lesions (e.g. epicondylitis, tenosynovitis or bursitis). • Marfanoid habitus (tall, slim, arm span > height, arachnodactyly). • Skin striae, hyperextensibility, thin skin or abnormal scarring. • Eye signs: drooping eyelids, or myopia, or anti-mongoloid slant. • Varicose veins, or hernia, or uterine/rectal prolapse.

Cardiovascular manifestations range from no apparent lesion to arterial aneurysms, arterial rupture without aneurysm, varicose veins, aortic regurgitation, mitral valve prolapse and conduction disturbances^{8,9}. Floppy mitral valve syndrome and the combination of mitral and tricuspid insufficiency due to redundant chordae tendinae or valve cusps have been reported^{9,15}. There does not seem to be a particular succession of

cardiovascular lesions^{8,9}.

Other common manifestations to all types of EDS are a result of the deficiency in collagen, such as spontaneous pneumothorax, diverticula of the intestine or bladder, measophagus, megatrachea, and megacolon. Diaphragmatic, umbilical and inguinal hernias are common^{9,15}.

Some signs and symptoms are more characteristic of certain subtypes based on the specific deficiency present [Table 1]⁴. In classic EDS (type I/II), the skin is described as very soft and “velvety”^{8,9}. Molluscoid pseudotumors and subcutaneous spheroids are present. Also, prematurity due to premature rupture of the membranes is more frequent than in the general population. In severe cases, aortic and bowel rupture may occur. In the hypermobility type of EDS (type III), joint hypermobility with recurrent dislocations is a much more prominent feature than skin changes⁴.

The vascular type of EDS (type IV) is the most clinically significant since it has the most severe presentation and is the only form with an increased risk of death. Complications are relatively rare in childhood, but 25% of these patients have some type of complication by age 20 and greater than 80% have some form of complication by age 40¹⁹. Some manifestations early in life may include premature rupture of membranes in the mother, congenital clubfoot, or congenital hip dislocation. Furthermore, the median lifespan is 48 years²⁰. This type of EDS is the result of mutations in type III collagen which is abundant in major blood vessels, skin, and hollow viscera. Diagnosis is based on presence of two of the following: thin, translucent skin, arterial/intestinal/uterine rupture, easy bruising, and characteristic facial appearance²¹. The typical features of joint hypermobility and skin hyperextensibility seen in most forms of EDS are relatively unusual in type IV. The connective tissue matrix of major vessels and viscera is more likely to be affected. In fact, 70% of arterial collagen is composed of type III collagen²⁰. Arterial rupture may take the form of tears, dissection or fistula formation. Medium-sized arteries of the thorax and abdomen are the most commonly involved¹⁹. Cystic medial necrosis of the proximal aorta is prevalent⁷. Hollow viscera

rupture is also a complication of this form of EDS. There are reports of gastric, small intestine, and large intestine perforation/rupture, with the sigmoid colon at particular risk¹⁹. Facial dysmorphism consists of a slender face, with prominent bones, sunken cheeks, a thin nose, thin lips, eyelid telangiectasia, periorbital pigmentation, lobeless ears and possible bulging eyes^{4,19}. The skin is not hyperelastic but thin and translucent, showing a visible pattern over the chest, abdomen, and extremities. Other skin changes may include acrogeria or an excessive wrinkling and thinness of the skin over the hands and feet. Less usual skin manifestations include keloid formation, Raynaud phenomenon and elastosis perforans serpiginosa, which is seen as keratotic plugs within an annular lesion particularly on the neck and antecubital fossae^{4,16}. Obstetrical complications are frequent and these patients should be considered high-risk^{8,9}. Some of these complications include uterine rupture usually in the third trimester, vaginal lacerations, prolapse of uterus and bladder, premature delivery because of cervical insufficiency or fragility of membranes^{4,19}.

The kyphoscoliotic form of EDS (type VI) can be recognized by severe muscle hypotonia and joint hypermobility at birth. Severe, progressive kyphoscoliosis is usually present. These patients may also demonstrate ocular fragility that may lead to retinal detachment, bleeding and rupture of the ocular globe, and microcomea⁴.

In the arthrochalasia type of EDS (type VIIA/B), severe joint hypermobility and congenital bilateral hip dislocation is frequently present. The skin is only moderately hyperextensible and there is usually only mild to moderate bruising. This presentation is in sharp contrast to the dermatosparaxis type of EDS (type VIIC), where severe bruising and extreme fragility and laxity of the skin are present during childhood. Other characteristic features include large fontanels, short stature, typical facies with epicanthic folds, downslanting palpebral fissures, puffy eyelids, blue sclera, and micrognathia⁴.

Therapy

There is no causal therapy available for EDS, however, a series of preventative guidelines based on common sense and clinical experience can be applied to all forms. For example, patients with skin fragility should wear protective pads or bandages over the forehead, knees, and shins, to minimize skin lacerations. In the instance that dermal wounds do occur, these should be closed without tension and preferably in two layers. Subcutaneous stitches should be applied generously and cutaneous stitches should be left in place twice as long as usual. Additional use of adhesive tape to adjacent skin can help prevent stretching and dehiscence of the scar. Currently, no cases of adverse outcomes with removal of the tape have been reported⁴.

Protective pads and bandages can help prevent bruises and hematomas. Patients with pronounced bruising should avoid contact sports and heavy exercise. In addition, supplementation with ascorbic acid, a cofactor for cross-linking of collagen fibrils, may decrease the tendency of bruising. DDAVP (vasopressin) has also been found to be useful in those with chronic bruising and epistaxis by normalizing the bleeding time⁴.

Cardiac abnormalities should be considered in EDS patients. Patients with mitral valve prolapse and regurgitation require antibiotic prophylaxis for bacterial endocarditis^{4,21}. Because patients with EDS are prone to cardiac conduction abnormalities and aortic dilatation and dissection, a baseline echocardiogram with aortic diameter measurement is recommended prior to the age of 10 years. Follow-up studies can then be performed in those with abnormal findings⁴.

Prophylactic measures are of special importance for patients with the vascular type of EDS. Drugs that interfere with platelet function should be avoided. Invasive vascular procedures, such as arteriography and catheterization, should be replaced by ultrasonography and/or subtraction angiography due to the risk of vascular rupture. Surgical interventions are generally discouraged; if unavoidable, careful manipulation of vascular and other tissues is imperative. Moreover, women with type IV EDS should be counseled about the increased risk of uterine rupture, bleeding, and other complications of pregnancy⁴.

Finally, in order to cope with the limitations of the disorder, emotional support and psychological therapy may be indicated for all types of EDS⁴. Approximately 36% of patients with EDS were found to have a decline in psychological well-being compared to 14% in healthy controls¹². For this reason, support groups are available and can be beneficial to all those affected by the illness, including families.

Anesthetic Management

Because of the many clinical manifestations of EDS, patients with the condition must be held in special consideration when requiring any anesthetic procedure throughout the perioperative period.

Pre-operatively the patient's EDS subtype should be determined as each hold different challenges. For example, type III patients will be much more prone to joint dislocations, whereas, type IV patients can have deadly vascular complications. All patients should be typed, cross-matched and evaluated for clotting abnormalities due to the propensity to bleed. The anesthesiologist must be prepared for a rapid transfusion. EDS may also predispose to certain cardiac abnormalities. While most are thought to be relatively mild, a detailed cardiac evaluation should be completed prior to any surgical procedure²². Particular attention must be paid to conduction abnormalities, most commonly atrial fibrillation secondary to mitral regurgitation and atrial enlargement, which can be continually assessed intra-operatively with ECG monitoring. Furthermore, prophylactic antibiotics may be dispensed to guard against subacute bacterial endocarditis if mitral valve disease is detected. Finally, the cervical spine is evaluated for any atlantoaxial instability due to a laxity in the ligaments⁷.

Peri-operatively many problems arise due to tissue fragility and the propensity for hemorrhage and hematoma formation, therefore, the number of needle sticks should be minimized²². According to the National Institute for Clinical Excellence, all central monitoring devices should be inserted under ultrasound guidance to safeguard against rupturing an underlying aneurysm, dissection and rupture. Additionally, these monitors

should be used for the minimum amount of time necessary. Anesthetic technique should avoid hypertension since arterial walls are already weakened. Tissue fragility may also pose a problem with intubation. Any instrumentation of the nose, mouth, or esophagus must be carefully performed with awareness of the patients increased susceptibility to bleeding which may potentially lead to a compromised airway. In fact, simple laryngoscopy may damage the gums, mucosa, and airway. Appropriate assessment of endotracheal tube placement should be performed immediately by chest auscultation, CO₂ and O₂ saturation monitoring, and possibly chest x-ray. Fiberoptic intubation should be considered to minimize trauma and to insure proper placement. Airway and dental conditions (i.e loose teeth) should be evaluated for any defects that may cause intubation difficulties or trauma. If the use of a mask is necessary, the pressure applied to it should be closely monitored to avoid excessive bruising on the face. Vaseline may be considered in this case for protection. Low airway pressures with assisted or controlled ventilation should be maintained due to a higher risk of pneumothoraces.

Skin hyperextensibility is yet another feature that poses a problem for the anesthesiologist. Increased skin laxity impedes vessel fixation for inserting catheters. Furthermore, it may interfere with IV and ET tube placement. Moreover, when taping the IV or ET tube, extra care should be taken to insure proper fixation and to protect against the increased fragility of the skin. Skin hyperelasticity can hide significant vessel trauma and extravasation. Finally, care must be taken with movement and positioning of the patient due to bruising and joint dislocations⁷.

Post-operatively, the same considerations apply. There is an 8-60% chance of pleural effusion experienced by EDS patients in the ICU. There is also a high incidence of surgical emphysema due to accidental tracheal puncture in the peri-operative period. As previously mentioned, all cannulae should be removed as soon as possible. Central venous catheter erosions can result in pleural effusion and pericardial tamponade. These consequences have a 74% incidence of mortality²⁰.

All intramuscular and subcutaneous injections, including use of local anesthesia, should be avoided due to the propensity for hematoma

formation and bleeding. Also, it has been found that people with EDS may be less likely to gain analgesia from the use of regional anesthetics¹⁷. However, use of epidural blocks in obstetric patients has been found to be safe and efficacious²³.

Summary

Ehlers-Danlos syndrome is an inherited disorder that results in dysfunctional collagen bundles. These dysfunctional collagen bundles are most noticeable in tissues rich with collagen fibers-skin, vessels, GI, and ligaments. Until gene therapy advancements can correct the underlying gene mutations causing faulty collagen, the mainstay of treatment is prevention of traumatic injury. The success of anesthetic management in patients with EDS requires understanding of the role of collagen in the various tissues of the body. Collagen-rich tissue fragility, skin hyperextensibility, joint hypermobility, hematoma formation and cardiovascular disease are just some of the complications that need to be accounted for before every anesthetic procedure involving EDS patients. Anesthesiologists should be keenly that any physical manipulation of EDS patients incurs risks of trauma.

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