

The Canadian Ehlers-Danlos Association

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What Is 'Ehlers-Danlos Syndrome'?

Ehlers-Danlos syndrome (EDS) is a group of hereditary connective tissue disorders characterized by defects of the major structural protein in the body (collagen). Collagen, a tough, fibrous protein, plays an essential role in “holding together,” strengthening, and providing elasticity to bodily cells and tissues. Due to defects of collagen, primary EDS symptoms and findings include abnormally flexible, loose joints (articular hypermobility) that may easily become dislocated; unusually loose, thin, “stretchy” (elastic) skin; and excessive fragility of the skin, blood vessels, and other bodily tissues and membranes.

The different types of EDS were originally categorized in a classification system that used Roman numerals (e.g., EDS I to EDS XI), based upon each form’s associated symptoms and findings (clinical evidence) and underlying cause. A revised, simplified classification system (revised nosology) has since been described in the medical literature that categorizes EDS into six major subtypes, based upon clinical evidence, underlying biochemical defects, and mode of inheritance.

Each subtype of EDS is a distinct hereditary disorder that may affect individuals within certain families (kindreds). In other words, parents with one subtype of EDS will not have children with another EDS subtype. Depending upon the specific subtype present, Ehlers-Danlos syndrome is usually transmitted as an autosomal dominant or autosomal recessive trait.

Symptoms

The symptoms and findings associated with Ehlers-Danlos syndrome (EDS) may vary greatly in range and severity from case to case, depending upon the specific form of the disorder present and other factors. However, the primary findings associated with EDS typically include abnormal “looseness” (laxity) and excessive extension (hyperextension) of joints; susceptibility to partial or complete joint dislocations; chronic joint pain; a tendency to develop degenerative joint disease (osteoarthritis) at an early age; unusually loose, thin, elastic skin; and excessive fragility of the skin, blood vessels, and other bodily tissues and membranes. Due to tissue fragility, affected individuals may easily bruise; experience prolonged bleeding (hemorrhaging) after trauma; have poor wound healing; develop “parchment-like,” thin scarring; and/or have other associated abnormalities.

In many individuals with EDS, associated symptoms and findings may become apparent during childhood. More rarely, depending upon the specific disorder subtype present, certain abnormalities may be apparent beginning at birth (congenital). In addition, in other individuals, such as those with mild disease manifestations, the disorder may not be recognized until adulthood.

The different forms of EDS were formally classified in the 1980s using a Roman numeral system. This categorization identified at least 10 major forms of the disorder based upon genetic and biochemical abnormalities as well as associated symptoms and findings. However, a simplified, revised, updated classification system has since been published in the medical literature that classifies EDS into six primary subtypes as well as some other forms of EDS, based upon the specific underlying biochemical cause, mode of inheritance, major and minor symptoms, and physical findings. The revised classification system serves to further differentiate between the various forms of the disorder as well as some related disorders.

The original classification system differentiates between severe and mild forms of classic EDS (EDS I and II). In the revised categorization, EDS I and II are reclassified as one subtype, known as EDS classical type. According to reports in the medical literature, in individuals with this subtype, associated skin abnormalities may vary greatly, ranging from mild, moderate, to severe in certain affected families (kindreds). EDS classical type may be characterized by excessive laxity and extension of the joints (hypermobility); susceptibility to recurrent sprains and dislocations of certain joints, such as the knees and shoulders; abnormally increased elasticity and extension (hyperextensibility) of the skin; and tissue fragility, potentially leading to degeneration or "splitting" of the skin, abnormal healing of skin wounds, and characteristic, thin, "parchment-" or "paper-like" (papyraceous) scarring that often becomes discolored and widened. Such scarring may occur primarily over certain prominent bony areas (pressure points), such as the shins, knees, elbows, and forehead. In individuals with EDS classical type, additional findings may include the formation of relatively small, fleshy, tumor-like skin growths (molluscoid pseudotumors) and/or hard, round, movable lumps (calcified spheroids) under the skin; unusually "velvety" skin; diminished muscle tone (hypotonia); and/or flat feet (pes planus). EDS classical type may also be characterized by easy bruisability, often occurring in the same areas; abnormal displacement (prolapse) of certain organs due to tissue fragility, such as protrusion of part of the stomach upward through an opening in the diaphragm (hiatal hernia); and/or an increased risk of certain complications after surgical procedures. For example, postsurgical complications may include protrusion of certain organs through weak areas in surrounding membranes, muscles, or other tissues (postsurgical hernias). In addition, some individuals with this subtype may have a deformity of one of the heart valves (mitral valve prolapse), allowing blood to leak backwards into the left upper chamber of the heart (mitral insufficiency), and/or, more rarely, abnormal widening (dilatation) of a region of the aorta, the major blood vessel of the body.

EDS hypermobility type was formerly classified as EDS III or benign hypermobility syndrome. This form of the disorder is primarily characterized by generalized, excessive extension (hypermobility) of the large and small joints. Additional findings may include abnormally increased skin elasticity, an unusually smooth or "velvet-like" consistency of the skin, and/or easy bruising. Skin abnormalities and bruising susceptibility may be extremely variable from case to case. Some individuals with EDS hypermobility type may develop chronic, potentially disabling joint pain and be prone to recurrent dislocations, particularly of the knee, shoulder, and jaw (i.e., temporomandibular) joints.

EDS vascular type (formerly EDS IV or EDS arterial-ecchymotic type) is primarily characterized by unusually thin, transparent skin with prominent underlying veins, particularly in the chest and abdominal areas; a susceptibility to severe bruising from minor trauma; and tissue fragility, potentially resulting in spontaneous rupture of certain membranes and tissues. For example, affected individuals may be prone to spontaneous rupture of certain mid-sized or large arteries or the intestine (bowel), leading to life-threatening complications. Because acute pain in the abdominal or flank area may indicate possible arterial or intestinal rupture, such symptoms require immediate, emergency medical attention. Individuals with EDS vascular type may also be

prone to developing abnormal channels between certain arteries and veins (arteriovenous fistula, e.g., carotid-cavernous sinus fistula) and have an increased risk of weakening of arterial walls and associated bulging of certain arteries (aneurysms), such as those supplying the head and neck (carotid arteries) and within the skull (intracranial). Aneurysms may be prone to rupturing, potentially resulting in life-threatening complications. Females with EDS vascular type may also be at risk for arterial bleeding and rupture of the uterus during pregnancy as well as vaginal tearing, uterine rupture, and/or other complications during delivery. In addition, affected individuals may be prone to experiencing certain complications during and after surgical procedures, such as separation of the layers of a surgical wound (dehiscence).

Individuals with EDS vascular type may also have abnormally decreased levels of fatty tissue under skin layers (subcutaneous adipose tissue) of the hands, arms, legs, feet, and face. As a result, some affected individuals may have a characteristic facial appearance, including thin lips; a thin, pinched nose; relatively large, prominent eyes; hollow cheeks; and tight, lobeless ears. In addition, skin of the hands and feet may appear prematurely aged (acrogeria). Additional symptoms and findings associated with this EDS subtype may include a deformity in which the foot is twisted out of position at birth (clubfoot); hypermobility that may be limited to joints of the fingers and toes (digits); the early onset of varicose veins, which are unusually widened, twisted veins visible under the skin; and spontaneous rupture of muscles and tendons. In addition, some with this EDS subtype may be susceptible to abnormal accumulations of air and blood in the chest cavity (pneumohemothorax) and/or associated collapse of the lungs (pneumothorax).

In individuals with EDS kyphoscoliosis type (formerly EDS VI), certain symptoms and findings may be apparent at birth (congenital). These include abnormal sideways curvature of the spine (congenital scoliosis) that becomes progressively severe; diminished muscle tone (hypotonia); and generalized, excessive extension and looseness (laxity) of the joints. In children with the disorder, severe hypotonia may cause delays in the acquisition of certain motor skills, and affected adults may lose the ability to walk by the second or third decade of life. Additional findings associated with EDS kyphoscoliosis type may include easy bruising, tissue fragility and associated degenerative (atrophic) scarring of the skin, a risk of spontaneous arterial rupture, abnormally reduced bone mass (osteopenia), and unusually small corneas (microcornea). In addition, because the opaque, inelastic membrane covering the eyeballs (sclera) may be unusually fragile, minor trauma may result in rupture of the sclera, rupture of the transparent region in the front of the eyes (cornea), and/or detachment of the nerve-rich membrane in the back of the eyes (retina).

EDS arthrochalasia type (formerly EDS VII, Autosomal Dominant [EDS VIIA and VIIB]) is primarily characterized by dislocation of the hips at birth (congenital hip dislocation); severe, generalized, excessive extension of the joints (hypermobility); and recurrent partial dislocations of affected joints (subluxations), such as those of the elbows, knees, hips, and feet. Affected individuals may also have diminished muscle tone (hypotonia), abnormal front-to-back and sideways curvature of the spine (kyphoscoliosis), and mildly reduced bone mass (osteopenia). Additional findings typically include abnormally increased elasticity and extension of the skin (hyperextensibility), easy bruising, and tissue fragility, with associated scarring of the skin.

Primary symptoms and findings associated with EDS dermatosparaxis type (formerly EDS VIII, Autosomal Recessive [EDS VIIC]) include severe skin fragility; soft, sagging, redundant skin; and extensive bruising. In some cases, certain tissues or organs may abnormally protrude through a weak area in a surrounding membrane, muscle, or other tissue (e.g., umbilical hernia, inguinal hernia).

In addition to the six primary EDS subtypes described above, there are some additional, rare forms of EDS. For example, X-linked EDS (formerly EDS Type V) has been described in individuals within at least one family (kindred). Associated symptoms and findings include easy bruising, hyperextensible skin, minor skin fragility, and deformity of one of the heart valves (mitral valve prolapse), allowing blood to leak backwards into the left upper chamber of the heart (mitral insufficiency). Because this form of EDS is transmitted as an X-linked recessive trait, it is fully expressed in males only. (For more information on X-linked inheritance, please see the "Causes" section of this report below.)

The symptoms and findings associated with EDS periodontosis type (formerly EDS Type VIII) are considered similar to those seen in EDS classical type. Additional findings typically include disease of the tissues surrounding and supporting the teeth (periodontal disease), potentially resulting in premature tooth loss.

EDS progeroid form, another rare variant of the disorder, is characterized by loose, elastic skin; hypermobile joints; slow wound healing; degenerative (atrophic) skin scars; and reduced bone mass (osteopenia). Additional findings may include delayed mental development, short stature, and a prematurely aged appearance (progeroid appearance) due to premature wrinkling of facial skin; scanty scalp hair, eyebrows, and eyelashes; and other findings.

According to reports in the literature, some individuals may be affected by additional, rare subtypes of EDS, which are currently referred to as EDS unspecified forms. Such subtypes are characterized by joint hypermobility, loose, elastic skin, and other symptoms and findings commonly seen in individuals with the disorder.

The EDS subtype originally referred to as EDS type X (or EDS dysfibronectinemic type) is extremely rare, affecting only one reported family (kindred). This subtype is characterized by abnormally extensible, loose joints; thin, elastic skin; and abnormalities of the specialized blood cells that play an essential role in blood clotting (platelets). Associated findings typically include the appearance of tiny purplish or reddish spots on the skin due to abnormal bleeding within or under skin layers (petechiae) and/or pinkish, depressed scar-like skin lesions that may later become white (striae distensae). These lesions, which may occur on the thighs, abdomen, buttocks, and breasts, develop due to weakening of elastic tissues.

Some subtypes of EDS included within the original disease classification have been redefined and are no longer part of the original nor the revised EDS categorization. For example, what was previously known as EDS type IX has been redefined and is now termed occipital horn syndrome. In addition, EDS type XI is currently known as familial hypermobility syndrome. For more information on these disorders, please see the "Related Disorders" section of this report below.

Causes

Most forms of Ehlers-Danlos syndrome (EDS) are transmitted as an autosomal dominant or autosomal recessive trait. Each EDS subtype is a distinct hereditary disorder that may affect individuals within certain families (kindreds). In other words, individuals with one subtype of EDS will not have children with another EDS subtype.

The disease genes that cause some forms of EDS have been mapped to particular chromosomes. Although the specific underlying cause of EDS is not known for all EDS subtypes, the disorder is known to result from various defects of collagen, the major structural protein in the body.

Collagen is the tough, fibrous protein that serves to provide elasticity to and strengthen bodily cells and tissues.

EDS classical type is inherited as an autosomal dominant trait. Human traits including the classic genetic diseases, are the product of the interaction of two genes for that condition, one received from the father and one from the mother.

In dominant disorders, a single copy of the disease gene (received from either the mother or father) will be expressed "dominating" the other normal gene and resulting in the appearance of the disease. The risk of transmitting the disorder from affected parent to offspring is 50 percent for each pregnancy regardless of the sex of the resulting child.

According to researchers, in at least some affected individuals, EDS classical type may result from abnormal changes (mutations) in the gene known as collagen type V, alpha-1 (COL5A1), which has been mapped to the long arm (q) of chromosome 9 (9q34.2-q34.3), or the gene collagen type V, alpha-2 (COL5A2), located on the long arm of chromosome 2 (2q31). Chromosomes are found in the nucleus of all body cells. They carry the genetic characteristics of each individual. Pairs of human chromosomes are numbered from 1 through 22, with an unequal 23rd pair of X and Y chromosomes for males and two X chromosomes for females. Each chromosome has a short arm designated as "p" and a long arm identified by the letter "q." Chromosomes are further subdivided into bands that are numbered.

EDS hypermobility type is transmitted as an autosomal dominant trait. A specific underlying collagen defect responsible for this form of the disorder has not been identified. EDS vascular type is also inherited as an autosomal dominant trait. This subtype is caused by abnormal changes (mutations) of the gene known as collagen type III, alpha-1 (COL3A1), which is located on the long arm of chromosome 2 (2q31).

EDS kyphoscoliosis type is inherited as an autosomal recessive trait. In recessive disorders, the condition does not appear unless a person inherits the same defective gene for the same trait from each parent. If an individual receives one normal gene and one gene for the disease, the person will be a carrier for the disease, but usually will not show symptoms. The risk of transmitting the disease to the children of a couple, both of whom are carriers for a recessive disorder, is 25 percent. Fifty percent of their children risk being carriers of the disease, but generally will not show symptoms of the disorder. Twenty-five percent of their children may receive both normal genes, one from each parent, and will be genetically normal (for that particular trait). The risk is the same for each pregnancy.

In some affected individuals, the kyphoscoliosis subtype is thought to result from mutations of a gene (called "procollagen-lysine, 2-oxoglutarate 5-dioxygenase" [PLOD]) that encodes a collagen-modifying enzyme known as lysyl hydroxylase. Deficiency of this enzyme may result in the symptoms and findings associated with this form of EDS. The PLOD gene has been mapped to the short arm of chromosome 1 (1p36.3-p36.2).

EDS arthrochalasia type is transmitted as an autosomal dominant trait. This subtype may result from mutations of the gene known as collagen type I, alpha-1 (COL1A1), which has been mapped to the long arm of chromosome 17 (17q21.31-q22.05), or the gene called collagen type I, alpha-2 (COL1A2), located on the long arm of chromosome 7 (7q22.1).

EDS dermatosparaxis type has autosomal recessive inheritance. This EDS subtype is thought to be caused by mutations of a gene or genes that encode a collagen-modifying enzyme known as procollagen I N-terminal peptidase.

As discussed above (see "Symptoms"), in addition to the six primary EDS subtypes, there are some other, rare forms of EDS. The rare subtype known as X-linked EDS is, as its name indicates, transmitted as an X-linked trait. X-linked recessive disorders are conditions that are coded on the X chromosome. Females have two X chromosomes, but males have one X chromosome and one Y chromosome. Therefore, in females, disease traits on the X chromosome may be masked by the normal gene on the other X chromosome. Since males only have one X chromosome, if they inherit a gene for a disease present on the X, it will be expressed. Males with X-linked disorders transmit the gene to all their daughters, who are carriers, but never to their sons. Females who are carriers of an X-linked disorder have a 50 percent risk of transmitting the carrier condition to their daughters and a 50 percent risk of transmitting the disease to their sons. In some females who inherit a single copy of a disease gene for an X-linked recessive trait (heterozygotes), disease traits on the X chromosome may not always be masked by the normal gene on the other X chromosome. Therefore, it is possible that some female carriers of the disease gene may exhibit some of the symptoms associated with the disorder; however, according to reports in the medical literature, to date, no female carriers of the disease gene for X-linked EDS have experienced symptoms (asymptomatic carriers).

EDS periodontosis type, another rare subtype, has autosomal dominant inheritance. EDS progeroid form, which is thought to be inherited as an autosomal dominant trait, may be caused by gene mutations that result in deficiency of a particular enzyme (XGPT deficiency). The subtype known as EDS type X (or EDS dysfibronectinemic type), which has been described in several siblings in one affected family (kindred), is thought to have autosomal recessive inheritance.

According to reports in the medical literature, there appear to be additional, rare subtypes of EDS that may have autosomal dominant or autosomal recessive inheritance (e.g., EDS, autosomal dominant, unspecified type; EDS, autosomal recessive, unspecified type).

Affected Populations

Males and females are equally affected by autosomal dominant and autosomal recessive forms of Ehlers-Danlos syndrome (EDS). The X-linked subtype of EDS is fully expressed in males only. It is possible that some females who carry a single copy of the disease gene (heterozygotes) for X-linked EDS may develop some symptoms; however, according to the medical literature, reports indicate that no female carriers have developed associated symptoms (asymptomatic).

In many individuals with EDS, associated symptoms and findings may become apparent during childhood. However, depending upon the form of the disorder present, some abnormalities may be apparent at birth. In other cases, such as those with relatively mild disease manifestations, EDS may not be recognized until adulthood.

Reported estimates concerning the disorder's overall frequency have varied, ranging from one in 5,000 to 10,000 births. However, because those with mild joint and skin manifestations may not seek medical attention or remain undiagnosed, it is difficult to determine the true frequency of EDS in the general population. EDS classical, hypermobility, and vascular types account for most reported cases of the disorder. EDS kyphoscoliosis, arthrochalasia, dermatosparaxis, and other subtypes are considered much less common. For example, some forms of EDS (e.g., EDS type X

or EDS dysfibronectinemic type) may have only been reported in individuals within one affected family (kindred).

The first published accounts of Ehlers-Danlos syndrome occurred in 1892. The syndrome was furthered clarified by Ehlers in 1901 and Danlos in 1908.

Related Disorders

Some of the symptoms of the following disorders may be similar to those seen in Ehlers-Danlos syndrome (EDS). Comparisons may be useful for a differential diagnosis:

Occipital horn syndrome (OHS), also known as X-linked cutis laxa, is a rare disorder that was formerly classified as a subtype of EDS (EDS type IX). The disorder has been recategorized with other connective tissue diseases that result from defects of copper metabolism. OHS is characterized by abnormally loose skin that tends to hang in folds (cutis laxa); abnormalities of the muscular organ that stores urine (bladder); the formation of "horn-like" bony protuberances on both sides of the back of the skull (occipital horns) and other skeletal abnormalities; excessive extension (hypermobility) of the fingers and toes; and limited extension of the elbows and knees. In some cases, affected individuals may have a prematurely aged facial appearance, a hooked nose, sagging cheeks, downwardly slanting eyelid folds (palpebral fissures), and/or other facial abnormalities. The disorder may also be characterized by mild mental retardation. OHS is transmitted as an X-linked recessive trait and is caused by deficiency of an enzyme (lysyl oxidase deficiency) that results in abnormalities of copper metabolism.

Familial hypermobility syndrome was also formerly categorized as a subtype of EDS (EDS type XI). However, researchers since suggested that the designation of EDS be reserved for the association of joint hypermobility with distinctive skin changes, resulting in the disorder's separate categorization. Familial hypermobility syndrome is characterized by looseness (laxity) and excessive extension of the joints; recurrent dislocation of certain joints, such as those of the shoulders and knees; and, in some cases, dislocation of the hip joints at birth (congenital). This disorder is transmitted as an autosomal dominant trait.

There are additional disorders that may be characterized by joint hypermobility, skin changes, and/or other abnormalities similar to those associated with EDS, such as other forms of cutis laxa or other related disorders. (For more information on these disorders, please choose "cutis laxa" or other specific disease names as your search term in the Rare Disease Database.)

Standard Therapies

Diagnosis

Ehlers-Danlos syndrome (EDS) is diagnosed based upon a thorough clinical evaluation, characteristic physical findings, a careful patient and family history, and specialized tests.

Specialized diagnostic laboratory tests may be available for certain EDS subtypes in which the specific underlying biochemical defect has been identified and characterized. In addition, in some families (kindreds) affected by a particular EDS subtype who have identified gene mutations, precise genetic testing may be available that enables diagnosis before or after birth (prenatal or postnatal diagnosis). However, it is possible that such testing may only be accessible through research laboratories with a special interest in EDS.

In addition, in some cases, diagnostic testing includes the removal (biopsy) and microscopic examination (e.g., electron microscopy) of small samples of skin tissue. Such examination may reveal characteristic abnormalities in collagen structure seen in certain EDS subtypes.

The clinical evaluation of individuals with suspected or diagnosed EDS typically includes assessments to detect and determine the extent of skin and joint hyperextensibility. For example, physicians may measure skin hyperextensibility by carefully pulling up skin at a neutral site until the point of resistance, and joint hyperextensibility may be evaluated using a clinical rating scale (i.e., Beighton scale). In addition, in some cases, specialized imaging tests, such as computerized tomography (CT) scanning, magnetic resonance imaging (MRI), and echocardiography, are used to detect and characterize mitral valve prolapse and aortic dilatation. During a CT scan, a computer and x-rays create a film showing cross-sectional images of certain bodily structures. MRI uses a magnetic field to create cross-sectional images of particular organs and tissues. During an echocardiogram, sound waves are directed toward the heart, enabling physicians to study cardiac function and motion.

In addition, in some individuals with EDS, specialized x-ray studies may be used to characterize round, movable lumps (calcified spheroids) under the skin; to detect and determine the extent of abnormal spinal curvature (scoliosis and/or kyphosis) and/or reduced bone mass (osteopenia) (e.g., in those with EDS kyphoscoliosis or arthrochalasia types); and/or to confirm and characterize certain other abnormalities.

In some cases, physicians may recommend that individuals with EDS vascular type be monitored with appropriate noninvasive imaging techniques (e.g., CT scanning, MRI, ultrasonography) to ensure early detection of arterial changes (e.g., aneurysms) that may result in spontaneous arterial rupture and potentially life-threatening complications. Angiography, a diagnostic test that is often used to detect aneurysms, must be avoided, since this technique may be hazardous to individuals with EDS, particularly those with EDS vascular type. During angiography, a substance that is impenetrable by x-rays (contrast medium) is injected into an artery via a flexible plastic tube (catheter) and an x-ray series is taken that visualizes blood flow through certain blood vessels.

Treatment

The treatment of individuals with EDS is directed toward the specific symptoms that are apparent in each individual. Treatment may require the coordinated efforts of a team of specialists who may need to systematically and comprehensively plan an affected individual's treatment. Such specialists may include pediatricians or internists; specialists who diagnose and treat disorders of the skeleton, joints, muscles, and related tissues (orthopedists); physicians who diagnose and treatment skin disorders (dermatologists); specialists who diagnose and treat connective tissue diseases (rheumatologists); surgeons; physical and occupational therapists; and other health care professionals.

In individuals with EDS, the use of special braces may help to stabilize affected joints. In addition, specialized physical and occupational therapy techniques may help to preserve the joints and strengthen muscles. Parents of young children with the disorder and affected individuals should also take necessary precautions to prevent injuries and trauma, such as may occur during contact sports. Wearing protective clothing and special padding over pressure points (e.g., shins, knees, elbows) may be beneficial.

Females with EDS vascular type should be counseled concerning the increased risk of certain complications during pregnancy and delivery and the need for meticulous obstetric care. In

addition, appropriate precautions and careful monitoring are essential before, during, and after dental or surgical procedures. Because fragile tissues and stitched (i.e., sutured) incisions or wounds may easily tear during or after surgery, unnecessary surgical procedures should be avoided. Accordingly, when surgery is necessary in individuals with EDS, specific surgical approaches require careful evaluation.

Genetic counseling will be of benefit for affected individuals and family members. Other treatment for individuals with EDS is symptomatic and supportive.

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