

## Ehlers–Danlos syndromes

The Ehlers–Danlos syndromes (EDS) are a group of heritable, connective tissue disorders characterised by joint hypermobility, skin hyperextensibility and tissue fragility. There is phenotypic and genetic variation among 13 subtypes of EDS<sup>[1]</sup>.

Most types of EDS affect joints and skin and most feature joint hypermobility. Additional features vary by type and include mucocutaneous, vascular, ocular, psychological and systemic manifestations. The clinical spectrum ranges from mild joint hypermobility to severe morbidity and disability, with life-threatening (mainly vascular) complications, particularly in the vascular subtype.

EDS has been classified in a number of different ways in the past. In 2017 a new classification was agreed using evidence-based diagnostic criteria and redefining it as the Ehlers–Danlos syndromes, in recognition of the broad spectrum of types and presentations. It is expected that this classification will be regularly reviewed<sup>[2]</sup>.

The Royal College of General Practitioners (RCGP) has released an Ehlers–Danlos Syndromes Toolkit<sup>[3]</sup>. The toolkit, which has been devised with the help of EDS UK, aims to improve the recognition, response and management of EDS in primary care. It offers a comprehensive guide to approaching the management of people who have EDS in a primary care setting, as well as indications for onward referral.

## Epidemiology of Ehlers–Danlos syndromes

- Overall, EDS has an estimated prevalence<sup>[4]</sup> of 1:5,000 to 1:250,000 births<sup>[4]</sup>.
- The ratio of affected women to men is about 8:1.
- The classical type occurs in 1 in 20,000 to 1 in 40,000 people.
- The vascular type is rare and the estimates of prevalence vary but is thought to affect around 1 in 250,000.
- The arthrochalasia type and the kyphoscoliosis type have each been described in fewer than 100 individuals worldwide.
- Only 10 cases of the dermatosparaxis type have been described.

## Presentation<sup>[4]</sup>

Most types of EDS present with symptoms affecting skin and joints. However, many systems can be affected. This varies with the subtype but clinical features can include:

- Chronic widespread pain is common among EDS patients<sup>[5]</sup> .
- Skin: varying degrees of increased skin elasticity and fragility, bruising easily, scars tending to widen. Splitting may occur easily, particularly on the forehead, knees and elbows.
- Joints: laxity and hypermobility, pes planus. Spontaneous dislocations and subluxations may occur, most often involving the fingers, elbows, shoulders and patellae. Reduction is usually easy and patients can often do it themselves.
- Cardiovascular: dizziness, palpitations, dysautonomia.
- There are occasional heart valve abnormalities; in the rare vascular subtype major vascular rupture is life-threatening.
- Intestinal tract: unexplained abdominal pain, IBS, constipation. In some types diverticulae, constipation or rupture, rectal prolapse. People may be more than usually prone to nausea and to travel sickness.
- Musculoskeletal: in some types herniation, hypotonia, delayed motor development. In some types kyphoscoliosis, dental abnormalities.
- Ocular: in some types abnormalities of the globe and cornea.
- Hearing: tinnitus due to lax support to the ear ossicles.
- Urogynaecological: uterocervical prolapse, obstetric complications – particularly morning sickness, early membrane rupture, precipitate labour, and perineal and vaginal trauma. In the rare vascular type, pregnancy can lead to uterine rupture.
- Systemic: tiredness, fatiguability, sleep disturbance. These symptoms, whilst not required for diagnosis, are often dominant and can be debilitating.
- Psychological: anxiety, depression.
- Dental: chronic temporomandibular dislocation is common.
- Obstetric: premature rupture of membranes.

The specific presentation patterns and their severity vary both between subtypes and within subtypes. They are described in more detail below.

## Investigations<sup>[6]</sup>

In the case of hypermobile EDS (hEDS), diagnosis is normally made on the clinical presentation, by a specialist with expertise in the area.

Molecular genetic testing is now recommended for the definitive diagnosis of the other subtypes, although not all patients with the specific condition will demonstrate the associated mutation. Assays of the enzyme deficiencies resulting from the genetic mutations can also be performed.

## Management<sup>[7]</sup>

Milder presentations are usually managed mainly in primary care. However, specialist involvement is needed for diagnosis, and multidisciplinary teams can contribute to symptom management. Severe forms will need more intense specialist involvement.

Specific management strategies for the subtypes of EDS are described under the relevant subtype heading, below. In general terms:

- Physiotherapy can be very effective. It needs to take a broad view of the issues the patient is dealing with. It is essential for children with hypotonia and useful for adult patients with joint hypermobility problems.
- Cognitive behavioural therapy (CBT) is often recommended. Patients living with chronic, life-changing conditions such as EDS may benefit from talking therapies.
- Symptom relief is important in management. Pain should be managed using the analgesic ladder, always considering the possibility of neuropathic pain.
- Celiprolol – a beta 1-adrenoceptor antagonist with a beta 2-adrenoceptor agonist action – has been used to prevent arterial dissections and ruptures in patients with vascular EDS.
- For patients with skin and soft tissue fragility, extra care (eg, non-tension sutures to skin, deep double sutures to other wounds, leaving stitches in for twice the normal time) should be taken when repairing injuries.
- Ascorbic acid is sometimes recommended to lessen the risk of spontaneous bruising.
- Genetic counselling should be provided.
- Surgical treatment is reserved for complications, or emergencies involving vascular or orthopaedic injury because of the risk of poor wound healing.

## The new classification of the Ehlers–Danlos syndromes<sup>[2]</sup>

The 1988 'Berlin Nosology' recognised 11 subtypes of EDS, defined by Roman numerals, based on clinical findings and mode of inheritance. In 1998 the Villefranche Nosology delineated six subtypes with descriptive names, based on clinical criteria. By 2017 advances in genetics, together with the identification of multiple new EDS subtypes, led to a new classification and the recognition that this is likely to need further revision.

The 2017 classification recognises 13 subtypes of EDS, with significant clinical variability within them and some clinical overlap between them (and with other hereditary connective tissue diseases (HCTDs)). With the exception of the hypermobile type, definite diagnosis relies on genetic testing.

	Clinical EDS subtype	Abbreviation	IP	Genetic basis	Protein
<p>IP: inheritance pattern; AD: autosomal dominant; AR: autosomal recessive, NMD: nonsense-mediated mRNA decay.</p>					
1	Classical EDS	cEDS	AD	Major: <i>COL5A1</i> , ' <i>COL5A1</i>	Type V collagen
Rare: <i>COL1A1</i>	Type I collagen				
c.934C>T, p. (Arg312Cys)					
2	Classical-like EDS	cIEDS	AR	<i>TNXB</i>	Tenascin XB
3	Cardiac-valvular	cvEDS	AR	<i>COL1A2</i> (biallelic mutations that lead to <i>COL1A2</i> NMD and absence of pro $\alpha 2(I)$ collagen chains)	Type I collagen

4	Vascular EDS	vEDS	AD	Major: <i>COL3A1</i>	Type III collagen
Rare: <i>COL1A1</i>	Type I collagen				
c.934C>T, p. (Arg312Cys)					
c.1720C>T, p. (Arg574Cys)					
c.3227C>T, p. (Arg1093Cys)					
5	Hypermobility EDS	hEDS	AD	Unknown	Unknown
6	Arthrochalasia EDS	aEDS	AD	<i>COL1A1</i> , <i>COL1A2</i>	Type I collagen
7	Dermatosparaxis EDS	dEDS	AR	<i>ADAMTS2</i>	ADAMTS-2
8	Kyphoscoliotic EDS	kEDS	AR	<i>PLOD1</i>	LH1
				<i>FKBP14</i>	FKBP22
9	Brittle cornea syndrome	BCS	AR	<i>ZNF469</i>	ZNF469
				<i>PRDM5</i>	PRDM5
10	Spondylodysplastic EDS	spEDS	AR	<i>B4GALT7</i>	$\beta$ 4GalT7
				<i>B3GALT6</i>	$\beta$ 3GalT6
				<i>SLC39A13</i>	ZIP13

11	Musculocontractural EDS	mcEDS	AR	<i>CHST14</i>	D4ST1
				<i>DSE</i>	DSE
12	Myopathic EDS	mEDS	AD or AR	<i>COL12A1</i>	Type XII collagen
13	Periodontal EDS	pEDS	AD	<i>C1R</i>	C1r
				<i>C1S</i>	C1s

There are major and minor clinical criteria for each EDS subtype. A major criterion is present in the vast majority of the affected individuals and/or is characteristic for the disorder. A minor criterion is of lesser diagnostic specificity but its presence supports the diagnosis.

## Hypermobile Ehlers–Danlos syndrome<sup>[1]</sup> [8]

This is the most common form of EDS. The molecular basis is unknown and the diagnosis is clinical. The degree of expression of hEDS varies enormously, and most cases are thought to go undiagnosed. Its presentation lies on a clinical spectrum of joint hypermobility which extends from mild hypermobility without other features, through hypermobility with secondary manifestations, to full hEDS meeting the diagnostic criteria.

There is an unexpected female predominance in hEDS despite suspected autosomal dominant inheritance.

Early diagnosis of hEDS allows for disease monitoring and management. Although there are no therapies approved to treat hEDS, symptoms of hEDS and comorbidities can be managed through physical therapy, exercise, lifestyle modification, medication and when needed, surgical intervention.

The main presenting features of hEDS are joint hypermobility, stretchy (although not fragile) skin, fatigue and musculoskeletal pain, with a positive family history. Although the severity of presenting features can vary, many patients with hEDS have severe widespread symptoms and chronic pain.

Rectal prolapse and genitourinary prolapse are common, and heart valve abnormalities can occur. The diagnostic criteria (given below) are to an extent descriptive of the condition, although the often prominent features of tiredness, fatiguability and disordered sleep are not mentioned there. This is not because they are not recognised, but because they are not specific.

Since the publication of the 2017 criteria, the diagnosis of hEDS is made only in those who meet all of criteria 1, 2 and 3 described below, and should be made by a clinician experienced in EDS. There is currently no 'gold standard' laboratory test to confirm or refute the diagnosis of hEDS.

### **Criterion 1: generalised joint hypermobility (GJH)**

The main tool to assess for GJH is the Beighton score, a nine-point score to assess hypermobility<sup>[9]</sup>. GJH is diagnosed using the Beighton scale; for children with a score of greater than or equal to 6, for adults and up to age 50 years, a score of greater than or equal to 5, and for men and women older than age 50 years, a score of greater than or equal to 4.

If the Beighton score is one point below the cutoff, and the five-point questionnaire (below, regarding joint hypermobility) shows at least two positive items, a diagnosis of joint hypermobility may be made:

The five-point questionnaire asks the following questions:

1. Can you now, or could you ever, place your hands flat on the floor without bending your knees?
2. Can you now, or could you ever bend your thumb to touch your forearm?
3. As a child, did you amuse your friends by contorting your body into strange shapes, or could you do the splits?
4. As a child or teenager, did your shoulder or kneecap dislocate on more than one occasion?
5. Do you consider yourself to be 'double-jointed'?

A 'yes' answer to two or more questions suggests joint hypermobility with 80–85% sensitivity and 80–90% specificity.



The Brighton Score has previously been used to diagnose hEDS. It is a modified version of the Beighton Score which allots points to major and minor criteria, and which requires, for diagnoses, with two major criteria, one major and two minor criteria, four minor criteria or two minor criteria and a first-degree relative diagnosed with hEDS. There will be a few patients who fitted the criteria for hEDS under the previous diagnostic guidelines, but do not meet the criteria for diagnosis under the new criteria. They will keep their diagnosis.

Many factors can influence joint mobility, including gender, age, ethnicity, strength training, stretching exercises and warming up. Muscular overcompensation, injury and surgery can also cause either joint hypermobility or hypomobility.

**Criterion 2: two or more of the following (A-C) MUST be present**

**Feature A:** systemic manifestations of a more generalised connective tissue disorder (a total of FIVE must be present):

- Unusually soft or velvety skin.
- Mild skin hyperextensibility.
- Unexplained striae at the back, groins, thighs, breasts and/or abdomen in adolescents, men or prepubertal women, without a history of significant gain or loss of body fat or weight.
- Bilateral piezogenic papules of the heel.
- Recurrent or multiple abdominal hernia(s) - umbilical, inguinal, crural.
- Atrophic scarring involving at least two sites and without the formation of truly papyraceous and/or hemosideric scars as seen in classical EDS.
- Pelvic floor, rectal and/or uterine prolapse in children, men or nulliparous women, without a known predisposing medical condition.
- Dental crowding and high or narrow palate.
- Arachnodactyly, as defined in one or more of the following: (i) positive wrist sign (Steinberg's sign) on both sides; (ii) positive thumb sign (Walker's sign) on both sides.
- Arm span-to-height ratio  $\geq 1.05$ .
- Mitral valve prolapse (MVP) mild or greater based on strict echocardiographic criteria.
- Aortic root dilatation with Z-score  $> +2$ .

**Feature B:** positive family history, with one or more first-degree relatives independently meeting the current diagnostic criteria for hEDS.

**Feature C:** musculoskeletal complications (must have at least one):

- Musculoskeletal pain in two or more limbs, recurring daily for at least three months
- Chronic, widespread pain for  $\geq 3$  months.
- Recurrent joint dislocations or frank joint instability, in the absence of trauma (a or b):
  - a: three or more atraumatic dislocations in the same joint or two or more atraumatic dislocations in two different joints, occurring at different times.
  - b: joint instability at two or more sites not related to trauma.

**Criterion 3: all the following prerequisites MUST be met**

- No unusual skin fragility, which should prompt consideration of other types of EDS.
- Exclusion of other heritable and acquired connective tissue disorders, including autoimmune rheumatological conditions.
- Exclusion of alternative diagnoses that may also include joint hypermobility by means of hypotonia and/or connective tissue laxity (eg, neuromuscular disorders, other HCTDs such as Marfan's syndrome) and skeletal dysplasias.

Many other features are described in hEDS but most are not specific or sensitive enough to form part of the formal diagnostic criteria. These include:

- Sleep disturbance and fatigue.
- Postural tachycardia syndrome (causing fast heart rate, dizziness and fainting).
- Gastrointestinal disorders (unexplained abdominal pain, IBS, constipation).
- Anxiety, depression, panic disorder.
- Urinary dysfunction.
- Tendency to nausea.
- Generalised pain.
- Headaches.

These manifestations may be more debilitating than the joint symptoms and often impair functionality and quality of life.

## Management of hEDS

- Regular gentle exercise and maintenance of BMI within the recommended range is encouraged to maintain cardiovascular and muscular fitness and to keep joints mobilised and healthy.
- Pilates can be beneficial in helping maintain core stability and maintaining good posture.
- Contact team sports, such as rugby and football, increase the risk of injury and it is better to choose less high-risk activities such as tennis or swimming.
- Some individuals benefit from referral to medical specialities such as: pain management, rheumatology, physiotherapy or occupational therapy.
- Periodic echocardiography is considered advisable, to look for 'floppy' mitral valve or aortic regurgitation.
- Joint hypermobility tends to increase during pregnancy, which may result in further instability and joint pain. There is an increased chance of early rupture of the membranes, of rapid labour and of breech presentation.

## Classical Ehlers–Danlos syndrome<sup>[2]</sup> <sup>[6]</sup> <sup>[8]</sup>

Classical EDS (cEDS) affects 1 in 20,000–50,000 people. It is an autosomal dominant condition, which may be inherited from either parent or may arise through new mutation.

The main issue for people with cEDS is skin being usually fragile. The skin is prone to splitting, particularly over the forehead, elbows, knees and chin; scars often widen over time. Other skin sequelae include molluscoid pseudotumours (rolled-up skin around joints vulnerable to damage), subcutaneous spheroids (mobile nodules under the skin) and easy bruising. Muscle hypotonia in children with cEDS may lead to delayed gross motor development. Other manifestations of tissue extensibility include hiatus hernia, childhood anal prolapse, cervical incompetence and postoperative hernias.

Diagnosis of cEDS requires skin hyperextensibility and atrophic scarring PLUS either GJH or at least three minor criteria. The severity of the skin involvement is variable.

### Major criteria

- Skin hyperextensibility and atrophic scarring.
- GJH.

## Minor criteria

- Easy bruising.
- Soft, doughy skin.
- Skin fragility (or traumatic splitting).
- Molluscoid pseudotumours.
- Subcutaneous spheroids.
- Hernia (or history thereof).
- Epicanthal folds.
- Complications of joint hypermobility (eg, sprains, subluxation, pain, pes planus).
- Family history of a first-degree relative who meets clinical criteria.

The inheritance is usually autosomal dominant. Most cEDS patients have a mutation in one of the genes encoding type V collagen, although there are other rare variants. Molecular testing is needed to reach a final diagnosis.

## Management of cEDS

- Management of fragile skin aims at protecting the skin to minimise injuries, with clothing and, particularly when engaging in activities which risk injury, appropriate, protective pads and helmets. Wounds should be sutured in layers, ideally by a plastic surgeon. Many affected patients will be known to local plastic surgery teams. Stitches need to be left in place for longer than usual and wounds need extra support, with Steri-strips® or bandaging.
- Children with cEDS may need to find a balance between restrictions and risks. Contact sports such as rugby, ice hockey, boxing and martial arts are particularly high-risk and may need to be avoided. Less impactful physical activities such as badminton, table tennis, bowling and swimming are better alternatives. Joint dislocations can occur and may limit particular activities such as trampolining.
- Regular gentle exercise is appropriate. Fatigue and joint pain can be features of cEDS and regular gentle exercise helps to reduce these effects.
- Adults with cEDS may benefit from Pilates to build core strength and help protect joints.
- Physiotherapy is helpful in significant joint hypermobility.

- Occupational therapy can suggest aids to daily living, and advise on pacing activities to avoid the 'boom and bust' phenomenon and extreme fatigue that can follow a period of over-activity.
- There is an increased risk of vaginal and perineal tearing in labour, and particular care is needed to slow delivery.
- There is an increased risk of early rupture of membranes and premature delivery if either parent has cEDS.
- Both mitral regurgitation and (more rarely) aortic root dilatation are sometimes seen in cEDS.

## Classical-like Ehlers-Danlos syndrome<sup>[8]</sup>

*Also called tenascin-X deficient Ehlers-Danlos syndrome*

This very rare condition is similar to cEDS (but it is autosomal recessive and it lacks the characteristic scarring). Some carriers may have mild signs or symptoms of hypermobility.

Diagnosis of classical-like EDS (clEDS) requires all three major criteria AND a family history compatible with autosomal recessive transmission. Confirmatory molecular testing is needed to reach a final diagnosis.

### Major criteria

- Skin hyperextensibility with velvety skin texture and absence of atrophic scarring.
- GJH with or without recurrent dislocations (most commonly shoulder and ankle).
- Easily bruised skin/spontaneous ecchymoses.

### Minor criteria

- Foot deformities: broad/plump forefoot, brachydactyly with excessive skin; pes planus; hallux valgus; piezogenic papules.
- Leg oedema in the legs in absence of cardiac failure.
- Mild proximal and distal muscle weakness.
- Axonal polyneuropathy.
- Atrophy of muscles in hands and feet.
- Acrogeric hands, mallet finger(s), clinodactyly, brachydactyly.

- Vaginal/uterine/rectal prolapse.

cIEDS is caused by a lack of tenascin XB (TNXB), which is a glycoprotein expressed in connective tissues including skin, joints and muscles, where it binds collagen.

### **Management of cIEDS**

- The Ehlers–Danlos Society suggests that individuals should have an echocardiogram to check the heart valves, and a baseline pulmonary function test in adulthood.
- It is thought that individuals with cIEDS may be at increased risk of diverticulitis.
- Whilst it is always important to maintain a healthy lifestyle, for individuals with cIEDS it is specifically recommended to avoid smoking.

## **Cardiac–valvular Ehlers–Danlos syndrome<sup>[8]</sup>**

Cardiac–valvular EDS (cvEDS) is a severe, autosomal recessive EDS affecting type 1 collagen, characterised by severe, progressive cardio–valvular problems. Diagnosis is based on severe progressive cardiac–valvular problems and a family history compatible with autosomal recessive inheritance, PLUS one other major criterion or at least two minor criteria. Confirmatory molecular testing is needed for a final diagnosis.

### **Major criteria**

- Severe progressive cardiac–valvular problems (aortic valve, mitral valve).
- Skin involvement: skin hyperextensibility, atrophic scars, thin skin, easy bruising.
- Joint hypermobility (generalised or restricted to small joints).

### **Minor criteria**

- Inguinal hernia.
- Pectus deformity (especially excavatum).
- Joint dislocations.
- Foot deformities: pes planus, pes planovalgus, hallux valgus.

# Vascular Ehlers–Danlos syndrome<sup>[4]</sup> <sup>[8]</sup> <sup>[10]</sup>

Vascular EDS (vEDS) is an autosomal dominant EDS caused by mutations in the genes coding for type III collagen. Some people with vEDS have a de novo mutation and therefore no family history. vEDS is rare and is estimated to occur in 1 in 50,000–200,000 people.

Its consequences are often catastrophic, with life-threatening medical emergencies. vEDS may not be suspected until sudden death occurs at a young age.

Disorders in the metabolism of fibrillary collagen affect the soft connective tissues, resulting in abnormalities in the skin, joints, hollow organs, and blood vessels.

The main risk people with vEDS face is life-threatening spontaneous rupture of medium/large arteries at any age from mid-adolescence to late adult life. Arterial aneurysms, and rupture of the sigmoid colon are also common. The maternal mortality during pregnancy has been quoted at 15%. Other features include early varicose veins, premature skin ageing on the hands and feet, and fine, thinning hair.

Because of the fragility of the soft tissue, surgical and endovascular interventions have high complication rates.

Diagnosis is based on a positive family history arterial rupture or dissection before the age of 40 years, unexplained sigmoid colon rupture, or spontaneous pneumothorax, in the presence of other features consistent with vEDS. Testing should also be considered in the presence of a combination of the other 'minor' clinical features listed below. The diagnosis rests on the identification of a causative variant in one allele of COL3A1.

## Major criteria

- Family history of vEDS with documented causative variant in COL3A1.
- Arterial rupture at a young age.
- Spontaneous sigmoid colon perforation in the absence of known diverticular disease or other bowel pathology.
- Uterine rupture during the third trimester in the absence of previous caesarean section and/or severe peripartum perineum tears.
- Carotid-cavernous sinus fistula (CCSF) formation in the absence of trauma.

## Minor criteria

- Bruising without identified trauma and/or in unusual sites such as cheeks and back.
- Thin, translucent skin with increased venous visibility.
- Characteristic facial appearance, sometimes called the 'Madonna face', including lobeless ears, thick nose and lips, and prominent eyes.
- Spontaneous pneumothorax.
- Acrogeria.
- Talipes equinovarus.
- Congenital hip dislocation.
- Hypermobility of small joints.
- Tendon and muscle rupture.
- Keratoconus.
- Gingival recession and gingival fragility.
- Early-onset varicose veins (under age 30 years and nulliparous if female).

### **Management of vEDS**

vEDS is associated with a shortened overall survival due to the risk of arterial rupture. The traditional approach was to treat such complications conservatively until life-threatening.

- More recently, treatment with the beta-blocker celiprolol has been shown to result in a three-fold decrease in arterial rupture in vEDS patients.
- Observational studies suggest elective surgical repair of blood vessels at risk of rupture, undertaken at tertiary referral centres that have expertise in managing connective tissue disorders, may be protective.

vEDS patients are best managed by multidisciplinary teams with expertise in managing connective tissue disorders. They should wear a medical alert bracelet, necklace or similar. The EDS National Diagnostic Service has produced a medic alert sheet for professionals, with the information that may be needed in case of an emergency. They should avoid invasive tests or invasive treatments unless strictly necessary.

This is a challenging condition to come to terms with. Specialist counselling sessions may be needed to help patients adjust to the inherent risks.



# Arthrochalasia Ehlers–Danlos syndrome<sup>[8]</sup> <sup>[11]</sup>

Arthrochalasia EDS (aEDS) is an autosomal dominant EDS. It is a very rare, severe subtype in which congenital bilateral hip dislocation is a major feature, and joints are much looser than in the hypermobile type. Muscular hypotonia and mild dysmorphic features may be present. Only around 30 cases have been described. Diagnosis requires this, together with skin hyperextensibility OR severe GJH with multiple dislocations/subluxations, PLUS at least two other minor criteria. Confirmatory testing is needed for a final diagnosis.

## Major criteria

- Congenital bilateral hip dislocation.
- Severe GJH, with multiple dislocations/subluxations.
- Skin hyperextensibility.

## Minor criteria

- Muscle hypotonia.
- Kyphoscoliosis.
- Radiologically mild osteopenia.
- Tissue fragility, including atrophic scars.
- Easily bruised skin.

A rare (but more common than aEDS) differential diagnosis is Larsen syndrome, a congenital disorder caused by a defect in the gene encoding filamin B, a cytoplasmic protein important in the cytoskeleton. It causes dislocation of the large joints, facial anomalies and a variety of cardiovascular and orthopaedic abnormalities.

## Management of aEDS

Although no curative treatments exist, a prenatal or postnatal early diagnosis and appropriate early intervention can alleviate physical and psychological distress.

The most important problems for children with aEDS are orthopaedic, in particular the bilateral congenital hip dislocation, since this severely affects mobility. Neither stable reduction by a closed method, such as a Pavlik harness, orthosis, or cast, nor operative procedures involving only the joint capsule tend to be successful. Iliac osteotomy with or without femoral osteotomy may improve stability of the hips.

The recurrent or persistent dislocation of other joints can cause severe delay in motor development. Generalised hypermobility and muscular hypotonia are worst in infancy and tend to improve with age, making the application of orthoses to stabilise the lower extremities more successful later in childhood. Orthoses can occasionally cause skin injury, but if skin problems are mild, the use of orthoses to stabilise knee, ankle and foot joints can improve motor development.

## **Dermatosparaxis Ehlers–Danlos syndrome**<sup>[8]</sup>

Dermatosparaxis EDS (dEDS) is an extremely rare autosomal recessive EDS subtype which has been described only around 10 times. It is characterised by extremely fragile, sagging skin, and is usually diagnosed before the age of 2 years. Fragility, bruising and sagging are severe, but healing is not impaired.

Diagnosis requires extreme skin fragility and the characteristic craniofacial features, plus either one other major criterion or three minor criteria. Confirmatory testing is needed for diagnosis.

### **Major criteria**

- Extreme skin fragility with congenital or postnatal skin tears.
- Characteristic craniofacial features.
- Redundant, almost lax skin, with excessive skin folds at wrists and ankles.
- Increased palmar wrinkling.
- Severe tendency to bruising with subcutaneous haematomas and haemorrhage.
- Umbilical hernia.
- Postnatal growth restriction.
- Short limbs, hands and feet.
- Perinatal complications due to connective tissue fragility.

### **Minor criteria**

- Soft, doughy skin texture.
- Skin hyperextensibility.
- Atrophic scars.
- GJH.

- Visceral fragility (eg, bladder rupture, diaphragmatic rupture, rectal prolapse).
- Delayed motor development.
- Osteopenia.
- Hirsutism.
- Tooth abnormalities.
- Refractive errors (myopia, astigmatism).
- Strabismus.

## Kyphoscoliotic Ehlers–Danlos syndrome<sup>[8]</sup> <sup>[12]</sup>

Kyphoscoliotic EDS (kEDS) is a rare, autosomal recessive EDS which has been described only around 60 times. It is caused by deficiency of lysyl hydroxylase which is used in collagen formation, and is characterised by progressive kyphoscoliosis. Babies are very floppy, with late motor milestones. Young children are often investigated for neuromuscular disease because of the severity of floppiness. In older children there may be difficulties with walking. There is a thin conjunctiva with blue appearing sclera (eyes) and hypotonia with muscle weakness. The cornea may be smaller than usual – very rarely, the globe may rupture.

Joints are very hypermobile and there may be frequent dislocations. Skin may be stretchy, soft, and fragile, bruise easily and form widened, atrophic scars. Vascular fragility has been reported.

Diagnosis requires congenital muscle hypotonia and congenital or early-onset kyphoscoliosis, plus either GJH or three minor criteria. Confirmatory testing is needed for a final diagnosis.

### Major criteria

- Congenital muscle hypotonia.
- Congenital or early-onset kyphoscoliosis (progressive or non–progressive).
- GJH with dislocations/subluxations (shoulders, hips and knees in particular).

### Minor criteria

- Skin hyperextensibility.
- Easily bruised skin.

- Rupture/aneurysm of a medium-sized artery.
- Osteopenia/osteoporosis.
- Blue sclerae.
- Hernia (umbilical or inguinal).
- Pectus deformity.
- Marfanoid habitus.
- Talipes equinovarus.
- Refractive errors (myopia, hypermetropia).
- Skin fragility (easy bruising, friable skin, poor wound healing), widened atrophic scarring.
- Scleral and ocular fragility/rupture.
- Microcornea.
- Facial dysmorphism.
- Congenital hearing impairment (sensorineural, conductive, or mixed).
- Follicular hyperkeratosis.
- Muscle atrophy.
- Bladder diverticula.

## **Brittle cornea syndrome**<sup>[8]</sup>

This autosomal recessive EDS subtype predominantly affects the eye, causing a thin cornea (which may rupture), with progressive keratoconus and keratoglobus, and blue sclerae. High myopia and retinal detachment are common.

Affected individuals also typically have some of the skin and joint features of classical and hypermobility types of EDS.

## **Spondylodysplastic Ehlers–Danlos syndrome**<sup>[8]</sup>

Spondylodysplastic EDS (spEDS) is an autosomal recessive EDS type, particularly characterised by short stature and muscle hypotonia. Bowing of limbs is common.

This is a severe EDS. Unlike other types, there may be a delay in cognitive development. Ocular, skeletal, joint, vascular and lung features may be present and there are characteristic facial features.

## Musculocontractural Ehlers–Danlos syndrome<sup>[8]</sup>

Musculocontractural EDS (mcEDS) is an autosomal recessive type, characterised by severe muscle contractures, severe skin laxity, fragility and bruisability, and atrophic scars. There may be skeletal, ocular, colonic and renal features.

## Myopathic Ehlers–Danlos syndrome<sup>[8]</sup>

Myopathic EDS (mEDS) is an EDS subtype which may be autosomal dominant or autosomal recessive. It causes congenital muscle hypotonia, and/or muscle atrophy, that improves with age. There may be joint contractures or hypermobility.

## Periodontal Ehlers–Danlos syndrome<sup>[8]</sup>

Periodontal EDS (pEDS) is an autosomal dominant EDS subtype, causing predominantly dental problems. There may be severe and intractable periodontitis from childhood, and/or a lack of attached gingiva, with a positive family history. Skin and joint features typical of other forms of EDS are commonly seen.

## Genetic basis of Ehlers–Danlos syndrome<sup>[8]</sup> <sup>[13]</sup>

Mutations in a number of different genes underlie the different types of EDS. Some of these genes provide instructions for the building blocks of collagen. Others provide instructions for making proteins that interact with collagen.

- Mutations in the COL5A1 gene or the COL5A2 gene cause the classical type.
- The cause of the hypermobility type has not been identified, although mutations in the TNXB gene are present in a tiny percentage of cases.
- Mutations in the COL3A1 gene lead to the vascular type.
- Mutations in the PLOD1 gene cause the kyphoscoliosis type.
- Mutations in the COL1A1 or COL1A2 genes cause the arthrochalasia type.
- Mutations in the ADAMTS2 gene cause the dermatosparaxis type.
- Other forms result from mutations in other genes; some of these have not been identified.

## Differential diagnosis<sup>[5]</sup>

The differential diagnosis of EDS includes:

- [Hypermobility spectrum disorders](#).

- [Marfan's syndrome.](#)
- [Loey-Dietz syndrome.](#)
- [Cutis laxa syndromes.](#)
- [Autosomal dominant polycystic kidney disease.](#)
- [Osteogenesis imperfecta type 1.](#)
- [Fibromyalgia.](#)
- [Depression.](#)
- [Chronic fatigue syndrome.](#)

## **Ehlers-Danlos syndromes and surgery**<sup>[14]</sup>

EDS raises three major issues for surgeons:

- Tissue strength is decreased, which makes the tissue less suitable for surgery.
- The fragility of the blood vessels can cause problems during surgery.
- Wound healing is often delayed or incomplete.

Orthodontic surgery is also complicated by the high rate of chronic temporomandibular dislocation in EDS.

Local anaesthetics, arterial catheters and central venous catheters carry a higher risk of haematoma formation in patients with EDS.

Surgery requires careful tissue handling and a longer immobilisation afterwards.

## **Ehlers-Danlos syndromes and pregnancy**<sup>[14]</sup>

### **Antenatal problems**

- Varicose veins, haemorrhoids and the vulval varicosities are more common in EDS.
- Reflux tends to get worse: many people with EDS have ongoing reflux and symptoms may worsen during pregnancy.
- Oedema is common in pregnancy, but the additional laxity of blood vessels in EDS may exacerbate symptoms. Women with EDS may experience an earlier onset and more severe symptoms of carpal tunnel syndrome.

- Women with EDS may be more than usually prone to nausea, vomiting and vertigo. Most suggested treatments have not been shown in studies to be useful.
- Many people with EDS experience regular headaches, which tend to get worse in early pregnancy.
- Many people with EDS have tinnitus due to instability of the bones in the middle ear. Pregnancy may exacerbate this condition.
- Women with EDS need to take care to protect their joints throughout pregnancy. Musculoskeletal symptoms which are more common in pregnancy in EDS include:
  - Pelvic girdle pain (symphysis pubis dysfunction).
  - Back pain.
  - Generalised musculoskeletal pain. The increased laxity in the EDS joints and tissues can lead to the initiation or increase in pain.
- Proprioception is often poor in people with EDS and may lead to loss of balance in pregnancy.
- Palpitations and ectopic beats are common in EDS and may increase in pregnancy.
- Breast changes occur in most pregnant women. The hyperelastic skin in a woman with EDS means that extra support is important.
- People with EDS are more prone to stretchmarks generally.
- People with EDS have an increased susceptibility to anxiety and depression. It is essential that mental health be addressed in pregnancy, to reduce the likelihood of postnatal depression.

### **Problems during delivery**

- Due to the fragility of connective tissue, those with EDS are more prone to prelabour spontaneous rupture of membranes (SROM), including preterm SROM. If a baby has EDS the likelihood of prelabour rupture of membranes is increased.
- In patients with vEDS, pregnancy may be dangerous. Obstetric complications include risk of uterine rupture during labour, and bleeding and rupture of blood vessels and the colon during the puerperium<sup>[6]</sup>.
- Although not fully understood, it is not uncommon for those with EDS to have a poor response to lidocaine (used in epidurals). Antenatal anaesthetist assessment should be offered.

- Due to the dysautonomia apparent in many people with EDS, general anaesthetics can cause a significant drop in blood pressure.
- Women with EDS are more prone to a precipitate birth, with the associated risk of tissue damage.
- Fetal malposition is more common, particularly persistent occipito-posterior or even occipito-transverse presentations. However, whereas women without EDS may have a difficult second stage with these presentations, women with EDS may have no problem, and it is important for caregivers not to move too soon to assisted delivery.
- Women with EDS can be more prone to postpartum haemorrhage.
- Women with EDS have fragile skin that is more prone to tearing and may take longer to heal. Extra care should be taken during birth to prevent vaginal and perineal damage.
- EDS skin takes longer to heal than normal skin, and dissolvable stitches may dissolve too early. Silk sutures are recommended for perineal repair.

## Prognosis in the Ehlers Danlos syndromes<sup>[8]</sup>

- Prognosis will vary with the type and the severity.
- Lifespan is usually normal, with the exception of the vascular type.
- In milder cases there may be no major effect on life, but many patients with EDS have significant or severe disability.
- Some families experience EDS with high prevalence of severe complications.

*Dr Mary Lowth is an author or the original author of this leaflet.*

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## Further reading

- [Ehlers-Danlos Syndrome, Classic Type, Type 1](#); Online Mendelian Inheritance in Man (OMIM)
- [The 2017 EDS International Classification: Your Questions Answered](#); The Ehlers Danlos Society

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