

Ehlers–Danlos syndrome – a commonly misunderstood group of conditions

Author: Glenda Sobey^A

Ehlers–Danlos syndrome (EDS) is a heterogeneous group of inherited connective tissue disorders. These are separate and specific conditions that are distinct in features and, where it is known, genetic basis. The skin, joints, blood vessels and internal organs are variably affected (Table 1).

Presentation

With various organ systems potentially affected, the initial presentation can be to one or more medical specialties (Table 2).

Classification

The 1997 Villefranche classification of EDS was based on the identification of genetic alterations affecting the synthesis and structure of type I, III and V collagen.¹ Since then, the molecular genetic basis of other types of EDS has been delineated and a further classification is due. Aside from genetic alterations in collagen, genetic defects affecting the biosynthesis of other components of the extracellular matrix, as well as signalling pathways and intracellular trafficking, can contribute to EDS pathogenesis.²

The Villefranche nomenclature with six subtypes is still widely used. Of these, the classical, vascular and hypermobility types are most commonly seen and are discussed in this review. The arthrochalasic, dermatosparactic and kyphoscoliotic types are rare. Modern molecular techniques have identified specific genes relating to most of the Villefranche subtypes (Table 3).

Classical Ehlers–Danlos syndrome

The triad of joint hypermobility, marked skin hyperextensibility (Fig 1a) and widened atrophic scars (Fig 1b) is the hallmark of this condition. Further cutaneous signs include easy bruising with staining from haemosiderin deposition, subcutaneous spheroids (subcutaneous fat lobules that have lost blood supply and calcified), molluscoid pseudotumours (thickened fleshy lesions particularly over elbows and knees associated with scars) and the absence of stretch marks (striae).

Electron microscopy of the skin shows typical ‘collagen flowers’ or ‘cauliflowers’ (Fig 2), which result from abnormal

Key points

The different types of Ehlers–Danlos syndrome (EDS) are separate conditions with monogenic inheritance

Accurate molecular genetic testing is available for many types of EDS

Vascular EDS is potentially life threatening with a risk of sudden death

There is a UK National Specialist Diagnostic Service for complex EDS

EDS is a group of conditions with multisystem involvement and it can present to all specialties

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fibrillogenesis of the collagen fibrils comprising type I and V collagen. Mutations in type V collagen are known to cause classical EDS.³ Many different mutations in type V collagen have been identified. However, there is as yet no obvious genotype–phenotype correlation. Classical EDS is a dominantly inherited condition, although the severity can vary significantly within the same family. A clinical cameo is presented in Box 1.

Cardiology assessment, including echocardiography, is recommended for classical EDS specifically assessing for aortic root dilatation and mitral valve prolapse.⁴ Joint hypermobility in classical EDS is best managed by rheumatologists together with physiotherapy and occupational therapy. Shin pads can be helpful to reduce injury, particularly during childhood, and can be custom-made through local appliance departments.

Patients with classical EDS should be known to the plastic surgeons at their local hospital so that any wounds can be expertly sutured in the first instance. They should wear a medical warning bracelet inscribed ‘classical EDS’.

Vascular Ehlers–Danlos syndrome

The potential for arterial and hollow organ rupture at a young age with the risk of sudden death makes this the most

Author: ^Ahead of EDS National Diagnostic Service, Sheffield Children’s NHS Foundation Trust, Sheffield, UK

Box 1. Clinical cameo – classical Ehlers–Danlos syndrome.

Alice, a 4-year-old girl, is referred to haematology with severe bruising after minor falls. These falls also lead to lacerations that require suturing under general anaesthetic by plastic surgery. She is prone to falling because of joint hypermobility. No bleeding disorder is identified despite extensive investigation. Therefore, Alice is referred to clinical genetics querying a diagnosis of vascular EDS. A skin biopsy shows multiple collagen flowers. This informs the choice of molecular genetic testing and a mutation in type V collagen is found, confirming a diagnosis of classical EDS. Custom-made shin pads protect against further lacerations and bruising. Specialised physiotherapy improves her muscle tone and proprioception, reducing fall frequency.

EDS = Ehlers–Danlos syndrome.

anxiety-provoking form of EDS for patients, their families and physicians. Easy bruising, which can be at sites not prone to trauma, is often the presenting feature, particularly in childhood. It is not uncommon for these families to have had contact with child protection agencies because of such bruising. Congenital talipes can also be a feature.

The skin is thin and translucent with visible underlying vessels and, although it is not hyperextensible, can be fragile. Some patients with vascular EDS have a typical facial appearance with a thin, pinched nose, prominent eyes and lobeless ears (Fig 3). Joint hypermobility associated with vascular EDS is usually limited to the small joints of the hands. It is important to note that these typical clinical features can be subtle or absent, thus making clinical diagnosis difficult, particularly when there is no contributory family history.

Where an unexplained arterial rupture or bowel rupture has occurred, the diagnosis of vascular EDS needs to be excluded. Some patients with vascular EDS also present initially with repeated pneumothoraces. Sudden death during the third or fourth decade of life can be the presenting feature.

Arterial (including aortic) dissection, rupture and aneurysm represent the major risks for individuals with vascular EDS. The sigmoid colon is the most common site for bowel rupture. Obstetric complications include uterine and arterial rupture as well as severe lacerations from vaginal delivery.

Vascular EDS is caused by mutation in the *COL3A1* gene, which encodes type III collagen. Molecular genetic testing is highly sensitive and specific for this condition. Genotype–phenotype correlations do not yet allow for accurate prognostication.

The optimal ongoing care of patients with vascular EDS is challenging. Surgical interventions are discouraged and, where possible, conservative medical management is preferred. When essential, surgical procedures should be performed by a highly experienced surgical team. It is thought that open surgery is safer than laparoscopic procedures. Good supplies of cross-matched blood should be readily available. A clinical cameo is presented in Box 2.

Table 1. Clinical presentations that suggest Ehlers–Danlos syndrome as a diagnosis.

Joints	Skin	Blood vessels and hollow organs
Hypermobility	Bruising	Rupture
+/- Dislocations	Hyperextensibility	Sudden death
+/- Pain	Atrophic scars	

Also consider additional features:

Kyphoscoliosis
Chiari malformation
Postural orthostatic tachycardia syndrome
Undiagnosed bleeding diathesis
Family history

Table 2. Examples of Ehlers–Danlos syndrome presentation to different specialties.

Specialty	Potential presentation
Paediatrics	Can be early in life with late walking (because of joint hypermobility), child protection concerns (easy and severe bruising)
Haematology	Abnormal bruising and bleeding diathesis (common presentation in classical, vascular and tenascin-X EDS)
Dermatology and/or plastic surgery	Suggestive skin lesions, large wounds from minor trauma, wound dehiscence
Rheumatology and/or orthopaedic surgery	Joint pain and recurrent dislocations
Neurosurgery	Hypermobility patients can present rarely with symptomatic Chiari malformations
Gastroenterology and/or gastrointestinal surgery	Gastrointestinal motility problems are commonly associated with joint hypermobility; bowel rupture in vascular EDS
Urology	Urinary tract dysfunction
Cardiology	Risk of vessel rupture, dissection and aneurysms in vascular EDS, mitral valve prolapse and POTS
Obstetrics	Life-threatening scenarios in undiagnosed EDS with risk of eversion of uterus at vaginal delivery in classical EDS. Risk of uterine rupture, arterial rupture or severe haemorrhage in vascular EDS
Emergency	Might see all of the above presentations and also the acute presentations of bowel rupture, pneumothorax and blood vessel rupture of vascular EDS

EDS = Ehlers–Danlos syndrome; POTS = Postural orthostatic tachycardia syndrome.



Fig 1. Hallmarks of classical Ehlers–Danlos syndrome. (a) Skin hyperextensibility and (b) atrophic scars.

Patients with vascular EDS should wear a medical warning bracelet with information on their emergency care supplied to the organisation providing the bracelet.

Patients with vascular EDS also need to be seen regularly by a cardiologist. The role of vascular imaging is controversial because there is no safe method for treating aneurysms in vascular EDS. The absence of aneurysms

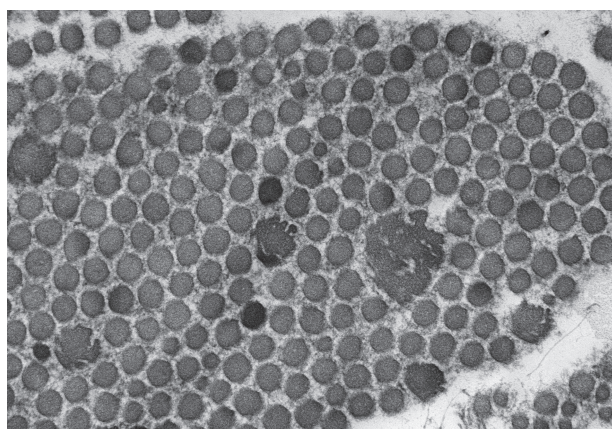


Fig 2. Collagen flowers on electron microscopy of skin in classical Ehlers–Danlos syndrome.

is no definite reassurance because these patients might rupture blood vessels at nonaneurysmal sites. Vessel fragility means that any invasive procedure is best avoided because of the risk of inducing vascular rupture by catheterisation.

In 2010 a multicentre randomised trial suggested that celiprolol decreased the incidence of arterial rupture or dissection in patients with a clinical diagnosis of vascular EDS. Further trials are expected.⁵

Clinicians should be aware that patients with vascular EDS might need psychological support following this diagnosis. The needs of children and adolescents merit specific attention in this area, including transitional care.

Hypermobile Ehlers–Danlos syndrome and/or joint hypermobility syndrome

Much controversy surrounds the naming and diagnosis of hypermobile EDS. There is no diagnostic test for this condition and the genetic basis remains unknown. Moreover, joint hypermobility is a common finding in the general population (approximately 10%) and, within the same family, members might be variably affected. It is no surprise that accurate diagnosis remains a challenge. It is uncertain whether the group of conditions named hypermobile EDS and joint hypermobility syndrome have a similar genetic cause. Inheritance appears to be autosomal dominant.

The Beighton score is used to assess the presence of a generalised joint hypermobility,⁶ with a score of 5 or more being regarded as indicative of hypermobility.

Although this group of patients is not prone to the life-threatening complications of some other types of EDS, the effects can be debilitating. Severe chronic joint pain coupled with symptoms of autonomic dysfunction can severely impair quality of life and limit opportunities for education and employment. It is more common for women to present with this condition than men, which is still unexplained.⁷

Assessment in rheumatology is recommended for patients in this group, both to exclude other rheumatological conditions and to advise on management through specialised physiotherapy and occupational therapy. This multidisciplinary approach, together with the assistance of a specialised pain clinic, is helpful.

Postural orthostatic tachycardia syndrome (POTS) is well recognised in this group of patients. POTS is a syndrome of dysautonomia, characterised by multiple symptoms, many of which occur on postural change or standing. These include transient loss of consciousness, presyncope, dizziness, palpitations, chest pain and shortness of breath.

In patients with the autosomal recessive condition of tenascin X-deficient EDS, the clinical features include marked skin laxity, pronounced joint hypermobility and severe bruising. These patients do not show the abnormal scarring of classical EDS. The carrier parents of affected patients, with a single tenascin-X mutation, can have features of joint hypermobility (particularly their mothers).⁸ There is no evidence to suggest that this is a widespread cause for hypermobile EDS and/or joint hypermobility syndrome.

Rare types of Ehlers–Danlos syndrome

Details on the rare types of EDS mentioned in Table 2 are beyond the scope of this brief review. If these diagnoses are considered, it is recommended that specialist assistance with diagnosis is requested.

The UK EDS National Diagnostic Service

The UK EDS National Diagnostic Service accepts referrals at all ages for clinical assessment and diagnostic testing. The referral criteria are detailed in Box 3.

Summary

All clinicians need to be aware of EDS and its variable presentations that, in some types, can be life threatening. Recognition of EDS can allow accurate diagnosis by genetic testing, genetic counselling and specific, appropriate management and follow-up. ■

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Fig 3. Lobeless ears in vascular Ehlers–Danlos syndrome.

Box 2. Clinical cameo – vascular Ehlers–Danlos syndrome.

John, aged 40, has vascular EDS. He is admitted to hospital with right upper quadrant pain and a diagnosis of acute cholecystitis is made. Emergency imaging confirms that there is no evidence of vessel or organ perforation. His surgeon is aware of the vascular EDS diagnosis and so John does not undergo the current standard treatment of laparoscopic cholecystectomy. He is instead managed conservatively and recovers. Laparoscopic surgical procedures are discouraged in vascular EDS because there is thought to be an increased risk of vessel and organ perforation. The fact that John has a confirmed genetic diagnosis of vascular EDS also means that he and his partner are able to have prenatal diagnosis or pre-implantation genetic diagnosis for this dominantly inherited condition, should they wish to start a family.

Table 3. Current classifications of Ehlers–Danlos syndrome. Reproduced with permission from Sobey (2014).⁹

Villefranche classification	Inheritance pattern	Molecular classification
Classical	Autosomal dominant	COL5A1, COL5A2
Hypermobile	Autosomal dominant	Unknown
Vascular	Autosomal dominant	COL3A1
Kyphoscoliotic	Autosomal recessive	Lysyl hydroxylase 1 (PLOD1)
Arthrochalasic	Autosomal dominant	Targeted COL1A1, COL1A2
Dermatosparactic	Autosomal recessive	Procollagen N-proteinase (ADAMTS2)
Subtype identified after Villefranche		
Tenascin-X deficient	Autosomal recessive	TNXB
EDS with scoliosis, myopathy, hearing impairment	Autosomal recessive	FKBP14
Musculocontractural EDS	Autosomal recessive	CHST14

EDS = Ehlers–Danlos syndrome.

Box 3. Referral criteria to Ehlers–Danlos syndrome National Diagnostic Service.

Referrals are invited from consultants in secondary and/or tertiary care for patients in whom the diagnosis of EDS is suspected but not confirmed for one of the following reasons:

- > Diagnostic criteria according to Villefranche classification are not met
- > Diagnostic testing does not confirm the diagnosis suspected
- > Diagnostic criteria of more than one type of EDS are identified
- > There are significant additional findings aside from the diagnostic criteria

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Address for correspondence: Dr G Sobey, EDS National Diagnostic Service, Department of Clinical Genetics, Sheffield Children's NHS Foundation Trust, Sheffield. Email: eds@sch.nhs.uk

Mainstreaming genetic testing of cancer predisposition genes

Author: Nazneen Rahman^A

Cancer predisposition genes (CPGs) describe genes in which germline mutations result in increased risk of cancer. Over 100 CPGs have already been discovered and transformative advances in DNA analysis are leading to many new CPG discoveries. These fast, affordable methods for analysing the DNA sequence can also be utilised in diagnostics to substantially increase clinical testing of CPGs. In turn, this has potential to provide substantial cost-effective health benefits with respect to cancer treatment in people with the disease and cancer prevention in healthy individuals. In this review, I outline the clinical benefits of testing for CPGs and how increased testing can be achieved.

Cancer predisposition genes

There are two ways in which gene mutations contribute to cancer. Oncogenic mutations that occur after birth, within a specific cell, are a hallmark of cancer and are called 'somatic cancer mutations'.¹ Mutations that are present in every cell, either because they have been inherited or occur at conception,

are called 'germline mutations'. Genes in which germline mutations lead to increased risks of cancer are called CPGs.² It is currently estimated that, overall, approximately 3% of cancers are the result of germline mutations in CPGs. However, the contribution to individual cancers is variable. A high proportion of childhood embryonal cancers, such as retinoblastoma and pleuropulmonary blastoma, are caused by germline mutations in *RBI* and *DICER1*, respectively.^{3,4} By contrast, CPG mutations make a small contribution to some adult cancers, such as prostate and lung cancer. However, germline CPG mutations in multiple genes predispose to other adult cancers, such as breast, colorectal and ovarian cancer (Table 1). For some cancers, the overall contribution of CPGs is sizeable, with approximately 15% of ovarian cancer, approximately 20% of medullary thyroid cancer and >30% of pheochromocytoma resulting from CPG mutations.^{5–7}

Clinical utility of cancer predisposition genes

Identifying whether a cancer is the result of an underlying CPG mutation has significant impact for the cancer patient and, potentially, their relatives. As such, CPG testing has become standard for many genes, although typically only in highly selected cases. From the patient perspective, simply having a better understanding of why their cancer occurred is usually highly valued.

Author: ^Ahead, Division of Genetics and Epidemiology, The Institute of Cancer Research, Sutton, Surrey, UK and head, Cancer Genetics Clinical Unit, The Royal Marsden NHS Foundation Trust, Sutton, Surrey, UK