Ehlers-Danlos syndromes: importance of defining the type

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ABSTRACT

Ehlers-Danlos syndromes (EDS) is an umbrella term describing 14 types, of which 13 are rare and monogenic, with overlapping features of joint hypermobility, skin, and vascular fragility, and generalised connective tissue friability. Hypermobile EDS currently has no identified genetic cause. Most of the rare monogenic EDS types can have neurological features, which are often part of major or minor diagnostic criteria for each type. This review aims to highlight the neurological features and other key characteristics of these EDS types. This should improve recognition of these features, enabling more timely consideration and confirmation or exclusion through genetic testing. In practice, many healthcare professionals still refer to patients as having 'EDS'. However, the different EDS types have distinct clinical features as well as different underlying genetic causes and pathogenic mechanisms, and each requires bespoke management and surveillance. Defining the EDS type is therefore crucial, as EDS is not in itself a diagnosis.

INTRODUCTION

'Ehlers-Danlos syndromes' (EDS) is an umbrella term, currently with 14 different types. Thirteen of the 14 types are monogenic and considered rare. These EDS types have overlapping features of joint hypermobility, skin, and vascular fragility, and generalised connective tissue friability.[1] Hypermobile EDS is the most commonly described type of EDS, but thus far it has no reported underlying genetic cause(s). Most monogenic EDS types are caused by deleterious gene variants encoding (1) proteins collagen I, III, V or (2) enzymes involved in their biosynthesis or (3) enzymes involved in proteoglycan biosynthesis.[2]

Ehlers and Danlos were dermatologists from Denmark and France, respectively, who in 1901 and 1908 first reported on people with features of the condition in the scientific literature.[3] From the 1960s, Professor Peter Beighton, consultant rheumatologist, reported consistently on EDS and was one of the first to describe EDS as an 'uncommon genetically determined disorder of connective tissue".[4] However, he soon recognised that: 'The syndrome is probably composed of five separate entities which are clinically recognisable'.[5] It was not until 1997 that the first genetic cause of an EDS type was published: recessive *PLOD1* pathogenic variants leading to kyphoscoliotic EDS (kEDS).[6]

In 1998, during a conference in Villefranche, it was agreed to classify EDS into five types (EDS types I–V: the Villefranche criteria).[7] At this point, a molecular cause was identified for each type of EDS except for type III, now known as hypermobile EDS. In 2017, a revised classification of the different EDS types was published through collaborations between many international experts, differentiating 13 types of EDS.[8] The genetic cause of the fourteenth type of EDS was reported later[9 10] (see table 1). The monogenic types of EDS are generally referred to as the rare EDS types, while hypermobile EDS remains without a genetic cause and is more commonly diagnosed. The clinical features are also now considered to overlap considerably with hypermobility spectrum disorders.

Most of the rare monogenic EDS types have neurological features, which are often part of their major or minor diagnostic criteria. This may lead to involvement of a (paediatric) neurologist in their assessment. This review aims to highlight the neurological features and other key characteristics of these different EDS types for (paediatric) neurologists (table 1, figure 1). This should increase recognition of features of rare EDS types, enabling more timely consideration and confirmation or exclusion of diagnosis through gold standard genetic testing.

UK NHS specialists in secondary or tertiary care who strongly suspect or have diagnosed a rare, monogenic EDS type can refer to national EDS service located in London and Sheffield. This is one of the few services internationally that is specifically

Table 1 Neurological features reported as part of the major (+M) or minor criteria (+m) defined for the current EDS types (8)

	Rare			Ultra-rare							
EDS types	**cEDS**	**vEDS***	**kEDS**	**aEDS**	**BCS**	**clEDS 1**	**clEDS 2**	**mEDS**	**mcEDS**	**pEDS**	**spEDS**
Inheritance	AD	AD	AR	AD	AR	AR	AR	AD/AR	AR	AR	AR
Gene	*COL5A1 COL5A2 COL1A1*	*COL3A1*	*PLOD1 FKBP14*	*COL1A1 COL1A2*	*ZNF469 PRDM5*	*TNXB*	*AEBP1*	*COL12A1*	*CHST14 DSE*	*C1R/ C1S*	*B4GALT7† B3GALT6† SLC39A13†*
Prevalence	1:20 000	1:90 000	1:100 000	<1:10^6	<1:10^6	<1:10^6	<1:10^6	<1:10^6	<1:10^6	<1:10^6	<1:10^6
(Congenital) hypotonia			+M	+m	+m (hypotonia in infancy (usually mild)			+M			+M
(Congenital) contractures		Talipes+m						+M proximal	+M		
Delayed motor development			+[1]	+[1]				+m	+[1]		+m
Delayed cognitive development						–					+m
White matter abnormalities						–				+[2]	
Mild proximal and distal weakness						+m					
Other		1)Stroke due to dissection of cervical arteries 2) Spontaneous CCSF				Axonal Polyneuropathy (+m) & muscle atrophy hands and feet (+m)		Myopathy on muscle biopsy (+m)			

No neurological features reported as part of the major or minor diagnostic criteria in cvEDS, dEDS and hEDS.
+[1]: resulting from (congenital) hypotonia. +[2]: present in large majority of patients who head imaging of the head.
*Rarely, specific Arg>Cys variants in the *COL1A1* gene have been reported to cause vEDS.
†Gene specific criteria are in place for this condition.
aEDS, arthrochalasia EDS; BCS, brittle cornea syndrome; CCSF, carotid-cavernous sinus fistula; cEDS, classical EDS; clEDS 1 and 2, classical-like EDS type 1 and 2; cvEDS, cardiac-valvular EDS; dEDS, dermatosparaxis EDS; hEDS, hypermobile EDS; kEDS, kyphoscoliotic EDS; mcEDS, musculocontractural EDS; mEDS, myopathic EDS; pEDS, periodontal EDS; spEDS, spondylodysplastic EDS; vEDS, vascular EDS.

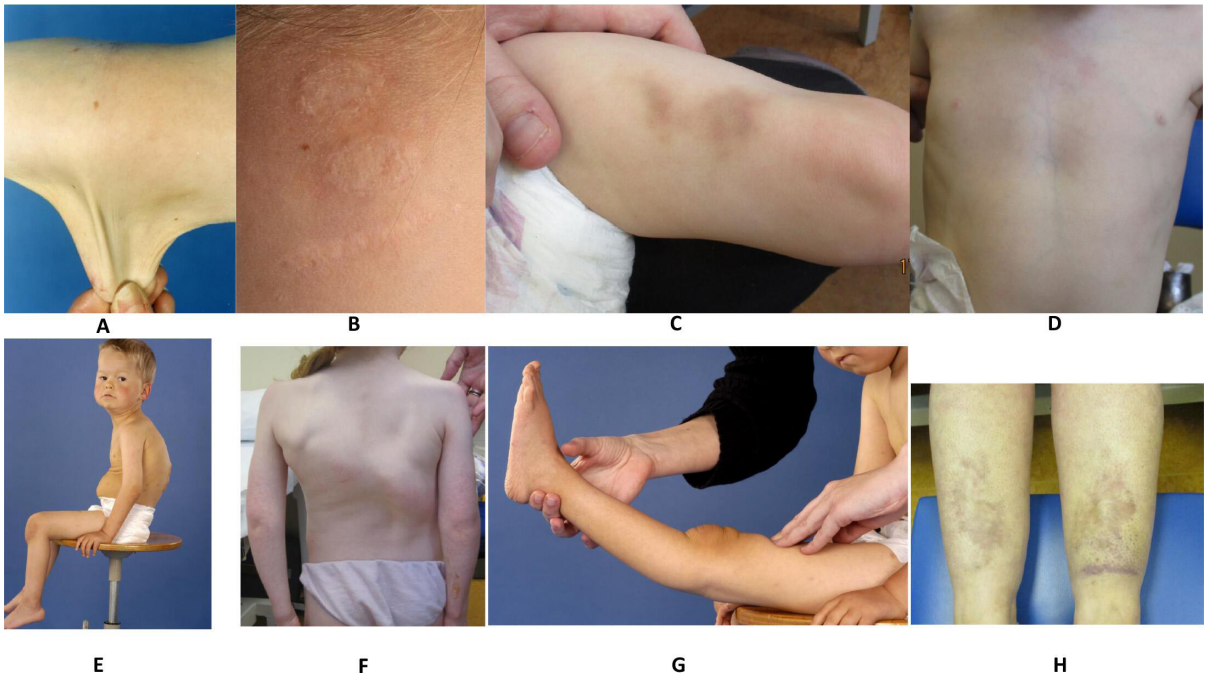

Figure 1 (A) Skin hyperextensibility at the elbow.[19] For the neck, elbow and knees, the stretched measurement should be at least 3 cm to be considered hyperextensible. (B) Widened, atrophic scarring on forehead.[17] (C) Easy bruising in a young girl with vascular Ehlers-Danlos syndromes (EDS).[27] (D) Translucent skin with visible veins in a young girl with vascular EDS.[27] (E) Young boy with kyphoscoliotic EDS due to recessive deleterious *PLOD1* variants. Epicanthic folds and positional kyphosis can be noted. No kyphoscoliosis was present on radiographs.[28] (F) Early-onset kyphoscoliosis in a girl with *FKBP14* related kyphoscoliotic EDS.[29] (G) Knee extension beyond 10◦ in a boy with kyphoscoliotic EDS.[17] (H) Pretibial plaques in an adult woman with periodontal EDS.[24]

for patients with a suspicion or diagnosis of a rare, monogenic type of EDS. If a rare monogenic EDS is confirmed, these patients and families are seen and often followed up. There are strong links in place for example with cardiovascular experts and rheumatology experts to facilitate ongoing surveillance and management.

THE DIFFERENT EDS TYPES

Classical EDS (Villefranche classification EDS type I and II)

Classical EDS is mainly caused by dominant deleterious variants that result in *COL5A1* haploinsuffiency and subsequent decreased production of collagen type V; they are rarely caused by dominant *COL1A1* variants. The major clinical criteria for a diagnosis of classical EDS are (1) skin hyperextensibility figure 1A, (2) widened atrophic scarring (figure 1B) and (3) generalised joint hypermobility figure 1G). Classical EDS is a diagnosis that is relatively easy to make in childhood as the skin hyperextensibility and fragility leading to atrophic scarring as well as generalised joint hypermobility, often present from early childhood and clearly recognisable during physical examination.

Children with classical EDS can have a low muscle tone due to increased ligamentous laxity and present in the neonatal period as a floppy infant with subsequently delayed developmental motor milestones. This can lead to suspicion of a neuromuscular condition and involvement of a consultant paediatric neurologist. Other rarely reported features in classical EDS are talipes and scoliosis.[11] Vascular fragility resulting in cervical artery dissection may occur in classical EDS but as a very rare phenomenon.[12]

Vascular EDS (Villefranche classification EDS type IV)

Vascular EDS (vEDS) is characterised by predisposition to arterial and hollow organ rupture from a young age resulting in life-threatening events.[1] Frank *et al* reported 17% of their vEDS cohort having a first complications by the age of 20 years and 71% had at least one major complication by aged 40 years.[13]

vEDS is caused by dominant deleterious variants in the *COL3A1* gene, leading to an 87.5% decrease in collagen type III production. Major diagnostic criteria are (1) family history of vEDS with documented causative variant in *COL3A1*, (2) arterial rupture at a young age, (3) spontaneous sigmoid colon perforation in the absence of known diverticular disease or other bowel pathology, (4) uterine rupture during the third trimester in the absence of previous caesarean section and/or severe peripartum perineum tears and (5) carotid-cavernous sinus fistula formation in the absence of trauma.[8]

Minor features include bruising unrelated to identified trauma and/or in unusual sites such as cheeks and back, thin, translucent skin with increased venous visibility, characteristic facial features hypermobility of small joints as well as talipes equinovarus (table 1). Therefore, the paediatric neurologist may see these patients soon after birth. Additionally, patients can come to the attention of

adult neurologists because of stroke. It is important to note that medium-sized vessels are most prone to dissection in vEDS, which includes supra-aortic trunk dissections. In a recent series, >55% of individuals with vEDS were identified to have supra-aortic trunk lesions with internal carotid arteries and vertebral arteries being most common locations. Furthermore, 19.5% of this group had ischaemic complications secondary to cervical artery dissection.[14]

As supra-aortic trunk dissections are quite common in the general population and vEDS is rare (estimated prevalence 1:90,000), it is important to refer such patients for assessment for vEDS if there are other major vEDS criteria (see above) and/or a combination of the minor criteria (see online supplemental table 1). These minor criteria include bruising unrelated to identified trauma and/or in unusual sites (such as cheeks and back) and thin, translucent skin with increased venous visibility (figure 1C,D).[14] Recurrence of supra-aortic trunk dissections especially if at young age (eg, before aged 50 years) and without classical cardiovascular risk factors, also warrants assessment for vEDS. In contrast to hypermobility of the small joints, which is part of the minor criteria for vEDS, generalised joint hypermobility is not a major or minor criterion for vEDS. It may be present in individuals with vEDS but it is also quite common in the general population and it is therefore not considered sufficiently specific to raise suspicion of vEDS.

Antiplatelet and anticoagulant therapies are generally not recommended for people with vEDS due to their generalised tissue fragility. However, antiplatelets are often prescribed for 3–12 months in people with a supra-aortic trunk dissection, and for longer in those with recurrent dissection and/or when the vessel has not completely healed. People with vEDS have generalised tissue fragility and so it is generally recommended to (1) discuss antiplatelet prescription on an individual basis, (2) limit the prescription to the minimum duration possible and (3) limit the prescription of non-steroidal anti-inflammatory drugs and if necessary, use only infrequently (https://vascern.eu/app/uploads/2023/03/Fiches_Vascular-Ehlers-Danlos-Syndrome_FINAL-web-2.pdf).

People with vEDS can develop the specific complication of carotid-cavernous sinus fistula where there is an abnormal communication between the high-pressure carotid arterial system and the low-pressure cavernous venous system. This can occur spontaneously by rupture/dissection of the internal carotid artery or secondary to the rupture of an internal carotid artery aneurysm or by dissection. The most common symptoms are swelling of the eye, chemosis, pain, ophthalmoplegia and bruit. A spontaneous carotid-cavernous sinus fistula is rare in the general population and strongly suggests vEDS, and hence is a major criterion for this condition.

The European Reference Network for Rare Multisystemic Vascular Diseases (VASCERN) has published international guidance regarding do's and don'ts in vEDS https://vascern.eu/app/uploads/2023/03/Fiches_Vascular-Ehlers-Danlos-Syndrome_FINAL-web-2.pdf). In summary, everyone with vEDS is recommended to have cardiovascular surveillance and blood pressure lowering medication. Conservative management is preferred above invasive or endovascular procedures unless these are unavoidable. Activities such as contact sports and heavy lifting are discouraged. Instead, individuals are recommended to do aerobic exercise to the extent that they can still hold a conversation. Obstetric management of women with vEDS should take place in tertiary centres with regular cardiovascular surveillance due to increased pregnancy-related death of 5.3%.[15] Everyone with vEDS is advised to carry an emergency card with details of their condition and instructions for their care.[3]

Case vignette 1

A 25-year-old woman presented at the Emergency Department with sudden onset of headaches and vertigo, with difficulties speaking, neck pain, unsteadiness and vertigo. She was initially suspected to have rhomboid or brainstem encephalitis and received intravenous antibiotics. However, her symptoms persisted, and head and neck imaging showed bilateral vertebral artery dissections, which had caused cerebellar strokes. She was managed conservatively and recovered well. She was prescribed short-term antiplatelets.

She was subsequently referred to the Ehlers-Danlos syndromes (EDS) service by the stroke consultant due to bilateral cervical arterial dissections at a young age. In clinic, she mentioned that she had been born at 28 weeks gestation due to premature rupture of membranes. She was bendy and had hypermobile small joints. Due to easily bruisable skin and spontaneous occurrence of ecchymoses, she had consulted a consultant haematologist several years before, but extensive haematological investigations had been normal. Her father had a stroke in his thirties and was doing well in his late forties.

On examination, she had prominent eyes due to thinning of infraorbital skin. The skin was translucent with thin veins visible on the chest. She had generalised joint hypermobility and marked distal joint hypermobility and several large bruises on her legs.

She gave informed consent for the aortopathy gene panel testing, which identified a likely pathogenic *COL3A1* variant, confirming the diagnosis of vascular EDS. Her parents have been contacted to discuss predictive genetic testing.

When the GP contacted the regional Clinical Genomics service for advice, the Consultant Clinical Geneticist realised that she had advised a Forensic Pathologist on the same patient only days before.

Kyphoscoliotic EDS (previously EDS type VI)

kEDS is a recessive condition (figure 1E) characterised by major criteria: (1) congenital muscle hypotonia, (2) congenital or early-onset kyphoscoliosis (progressive

or nonprogressive) (figure 1F) and (3) generalised joint hypermobility (figure 1G) with dislocations/subluxations.[8] It is often the marked congenital muscle hypotonia that leads to paediatric neurologist referral through suspicion of a severe underlying neuromuscular disorder. kEDS is caused by recessive variants in *PLOD1* or *FKBP14*. People with *PLOD1*-related kEDS often have skin fragility and/or scleral and ocular fragility and/or microcornea. Those with *FKBP14*-related kEDS often have congenital hearing impairment, follicular hyperkeratosis, muscle atrophy and bladder diverticulae.[16] Importantly, even though congenital or early-onset kyphoscoliosis is part of the major criteria, not everyone with kEDS has this[17] (figure 1E). Also, people with kEDS may develop rupture of medium-sized arteries and this is part of the minor clinical criteria. A diagnosis of kEDS warrants regular cardiovascular screening starting from the moment of diagnosis, which is usually in childhood. Brady *et al*[16] reported six cases of antenatal/neonatal haemorrhages in 84 people with kEDS, highlighting that neurovascular complications can occur in the very young.

Arthrochalasia EDS (previously EDS type VIIa and VIIB)

Arthrochalasia EDS is an autosomal dominant condition caused by deleterious alterations in the *COL1A1* or *COL1A2* gene. The major clinical features are (1) congenital bilateral hip dislocation, (2) severe generalised joint hypermobility with multiple dislocations/subluxations and (3) skin hyperextensibility. Muscle hypotonia and kyphoscoliosis are part of the minor criteria and may be reason for a paediatric neurologist to become involved.[8 16–18]

Brittle cornea syndrome

Brittle cornea syndrome is a recessive condition caused by deleterious variants in either *ZNF469* or *PRDM5*. As the name suggests, it is characterised by (1) a thin cornea, with or without rupture, (2) early-onset progressive keratoconus or (3) keratoglobus and (4) blue sclerae. The diagnosis is often made following corneal rupture after minor trauma. Hypotonia in infancy, scoliosis, mild contractures of fingers (especially digits) may be a reason for a paediatric neurologist to become involved.[8 16]

Classical-like EDS type 1

Classical-like EDS (ClEDS) type 1 or *TNXB*-related ClEDS is an autosomal recessive condition. Its major clinical features are (1) hyperextensible skin with velvety skin texture and absence of atrophic scarring, (2) generalised joint hypermobility and (3) easy bruisable skin/spontaneous ecchymoses. Mild proximal and distal muscle weakness as well as axonal polyneuropathy have been reported in individuals with this condition.[8 16 19 20]

Classical-like EDS type 2

ClEDS type 2 or *AEBP1*-related ClEDS is an autosomal recessive condition due to deleterious *AEBP1* variants. Being the most recent EDS type added (first reported

Case vignette 2

A 22-month-old girl was seen in the Ehlers-Danlos syndromes (EDS) service because of delayed motor developmental milestones likely related to ligamentous laxity. She had been born by elective caesarean section to consanguineous parents after an uncomplicated pregnancy because of breech presentation and had unilateral hip dislocation requiring a brace. At the age of 6 months, she had been noted to have poor head control, weak grasp and reduced central tone and she was subsequently assessed by the neuromuscular service. She had screening bloods including full blood count and renal, liver and bone profiles, thyroid, amino organic acids, CMV and toxoplasmosis serology. Urinary glycosaminoglycans and serum creatine kinase measurements were normal. Nerve conduction studies were normal and microarray, DNA analysis for Prader-Willi syndrome and spinal muscular atrophy was normal. At this time, the low muscle tone appeared likely to be due to ligamentous laxity.

When aged 22 months, she could not stand without support. There were no concerns about speech and language development. On examination, she had bilateral epicanthal folds, no scoliosis/kyphosis, tapering fingers and flat, pronated feet with piezogenic papules. The skin was soft and mildly hyperextensible. There was no visible atrophic scarring or excessive bruising. Beighton score was 6/8, confirming generalised joint hypermobility.

Due to congenital muscle hypotonia and generalised joint hypermobility as well as the soft, mildly hyperextensible skin, we arranged DNA analysis of the EDS gene panel including for kyphocoliotic EDS. This identified a homozygous variant of unknown significance in the *PLOD1* gene. Her parents were tested and shown each to be carriers of the identified variant of uncertain significance. Urinary collagen cross-linking assay was arranged in the girl, which was abnormal, strongly supporting a diagnosis of *PLOD1*-related kyphoscoliotic EDS. As such, the homozygous *PLOD1* variant was reclassified as likely pathogenic.

At follow-up, her parents mentioned that she had started walking at the age of 2.5 years and would often walk with knock knees and knee hyperextension. She had been noted to bruise very easily, which had also been flagged up by the nursery.

After her diagnosis, she was referred for monitoring for kyphosis/scoliosis by a paediatric orthopaedic surgeon. She was also referred to consultant cardiologist with expertise in EDS who organised an echocardiogram, which showed a bicuspid aortic valve, probably an incidental finding. Cardiovascular surveillance was organised due to reported risk of rupture of medium-sized arteries. She was referred for ophthalmology assessment for myopia, astigmatism and potential for retinal detachment. Scleral fragility can occur in *PLOD1*-related kyphoscoliotic EDS. She had already been referred by the paediatrician for physiotherapy and occupational therapy.

in 2016[9]), there have been only 11 cases so far reported in the literature. The major clinical features are largely similar to ClEDS type 1 although atrophic scarring is more common.[21]

Musculocontractural EDS

Musculocontractural EDS has several major criteria: (1) multiple contractures, characteristically adduction-flexion contractures and/or talipes equinovarus (club-foot), (2) characteristic craniofacial features, evident at birth or in early infancy, and (3) characteristic cutaneous features including skin hyperextensibility, easy bruisability, skin fragility with atrophic scars and increased palmar wrinkling. The characteristic craniofacial features allow its diagnosis in early childhood. There may be multisystemic problems involving multiple specialties,[8 16] including paediatric neurologists to assess for neurological causes of their contractures.

Myopathic EDS

Myopathic EDS (mEDS) can be autosomal dominantly or autosomal recessively (n=1 family) inherited due to deleterious variants in *COL12A1*, which encodes collagen type XII. Major criteria are (1) congenital muscle hypotonia and/or muscle atrophy that improves with age, (2) proximal joint contractures (knee, hip, elbow) and (3) distal joint hypermobility. Only five families had been reported at the time of the nosology publication in 2017.[8] Delbaere *et al* 2021[22] reported clinical and molecular data of 11 additional families and noted that variable muscle hypotonia or atrophy is a main feature. Also, contractures were not limited to the proximal joints, as patients may also have congenital talipes equinovarus and finger contractures. Additionally, there can be generalised joint hypermobility. The myopathic manifestations can improve during childhood but return in the fourth decade of life or later, predominantly in the distal muscles. Clinically, the features of mEDS can resemble Bethlem myopathy and Ullrich myopathy, caused by deleterious variants in *COL6A1/2/3* encoding collagen type VI.[22] An alternative name for dominant mEDS is Bethlem myopathy 2. There is no specific guidance for managing people with mEDS but often neuromuscular specialists, occupational and physical therapists are involved, depending on the patient's clinical symptoms.

Periodontal EDS

Periodontal EDS (pEDS) is characterised by (1) severe and intractable periodontitis of early onset (childhood or adolescence) often leading to early loss of teeth, (2) lack of attached gingiva, (3) pretibial plaques (figure 1H) and (4) family history of a first-degree relative who meets clinical criteria.[8] Intriguingly, the condition is caused by dominant pathogenic variants in the genes *C1R* and *C1S* encoding the protein esterases C1r and C1s, subunits of the complement 1 complex. Activation of C1r and C1s is the first step in the classical complement cascade, a major antimicrobial pathway of the innate immune system. The likely mechanism underlying the early-onset periodontitis and subsequent dental loss is gingival hyperinflammation in response to mild biofilm accumulation. People with mEDS may come to the attention of adult neurologists if brain imaging identifies white matter abnormalities. There is currently insufficient evidence to suggest that these abnormalities relate to any specific degenerative or mental health disorder, and therefore individuals with pEDS do not require cerebral surveillance imaging, unless they develop neurological symptoms requiring imaging.[23 24]

Case vignette 3

A 42-year-old woman attended the Ehlers-Danlos syndromes (EDS) service in 2011 because of bilateral congenital hip dislocations and complications of joint hypermobility. There was also a family history of congenital hip dislocation affecting two out of three of her daughters.

She had been born at term and was very floppy with bilateral hip dislocations, treated with splints and callipers. She had gross motor delay with multiple joint instabilities, strains and sprains, and subsequent significant problems with shoulder, knee and temporomandibular joint instability together with chronic polyarthralgia and fatigue. She had longstanding difficulties with walking long distances and would fall over easily when tired.

On examination, she had distal joint hypermobility and mild wrinkling of the skin at the hands, but no proximal joint contractures. When aged 50 years, with no gene panel testing then available, she participated in a genetic research study and was found to have a dominant pathogenic variant in the *COL12A1* gene, consistent with a diagnosis of myopathic EDS. Her two daughters with congenital hip dislocation were also affected, and were referred for neuromuscular assessment.

Spondylodysplastic EDS

Spondylodysplastic EDS (spEDS) is an autosomal recessive condition characterised by (1) short stature, (2) muscle hypotonia (ranging from severe congenital, to mild later onset) and (3) bowing of limbs. It is caused by recessive deleterious variants in *B4GALT7*, *B4GALT6* or *SLC39A13*. There are additional gene-specific diagnostic criteria for each genetic cause. spEDS is the only type of EDS in which delayed cognitive development is a diagnostic criterion (minor). It also has characteristic clinical features that should lead to a diagnosis in early childhood and early involvement of a paediatric neurologist.[8 16]

Hypermobile EDS and hypermobility spectrum disorders

In the 1997 Villefranche criteria, hypermobile EDS (then defined as EDS type III) was considered an autosomal dominant condition.[7] The major criteria for hypermobile EDS were then skin hyperextensibility and/or smooth velvety skin and generalised joint hypermobility with minor criteria of chronic pain, recurrent joint dislocations, and positive family history. However, no monogenic cause of hypermobile EDS has been identified since, despite

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Case vignette 4

A 40-year-old woman attended the Ehlers-Danlos syndromes (EDS) service because of severe periodontitis with onset in childhood, lack of attached gingiva and pretibial plaques. She had first-degree relatives who met the clinical criteria for a diagnosis of periodontal EDS. She was diagnosed with periodontal EDS due to a dominant deleterious variant in the *C1R* gene. Genetic testing took place outside the UK.

When aged 41 years, she attended the emergency department because of severe headache. A CT scan of head and an MR scan of brain showed extensive white matter changes. Subsequently, testing for very long-chain fatty acids was normal and the consultant neurologist requested a white matter gene panel (R62.1 panel).

She subsequently contacted the EDS service, who confirmed that white matter abnormalities can develop in many people with periodontal EDS although the causal mechanism was unclear. The molecular report showed the deleterious variant was as expected, having again been identified through white matter gene panel testing.

She has episodic migraines, which are symptomatically treated. Currently, there is insufficient evidence to prove that the migraines relate to the white matter abnormalities.

Practical advice for (paediatric) neurologists

The most common presenting features in different rare types of Ehlers-Danlos syndromes (EDS) that might lead to involvement of a (paediatric) neurologist are low muscle tone, contractures such as clubfeet, or cervical artery aneurysms and dissections leading to stroke. The following practical advice applies for the (paediatric) neurologist to assess for a rare EDS type:

- Take a systematic family history.
- Assess for generalised joint hypermobility using the Beighton score.
- Assess for skin hyperextensibility, atrophic scarring, translucent skin and bruising unrelated to identified trauma and/or in unusual sites.

If these items lead to suspicion of a rare type of EDS, it might still be appropriate to exclude an underlying neurological and neuromuscular disorder. It is also recommended to refer such patients to a clinical genetics service or national EDS service.

multiple and ongoing attempts. In 2017, stringent new criteria for a diagnosis of hypermobile EDS were introduced, with the aim of creating a clinically homogeneous cohort to increase the chances of gene discovery in hypermobile EDS. The current criteria for hypermobile EDS are available through the following link: https://www.ehlers-danlos.com/wp-content/uploads/2017/05/hEDS-Dx-Criteria-checklist-1.pdf.

The prevalence of hypermobile EDS according to the 2017 criteria is unknown but clinical experience suggests that few people fulfil the current criteria for this condition. A new category called hypermobility spectrum disorder (HSD) was also introduced in 2017 for people with (generalised) joint hypermobility, not fulfilling the hypermobile EDS criteria while having a spectrum of other potentially associated health problems. It has been agreed that individuals diagnosed with hypermobile EDS pre-2017 criteria will keep this diagnosis.

Importantly, neurological features are not part of the clinical criteria for hypermobile EDS table 1 despite many reports in the literature commenting on its different neurological and spinal manifestations.[25] For hypermobile EDS as well as for hypermobility spectrum disorder, the general advice is that management of hypermobile EDS should address its specific clinical problems and an individual's medical history. While people with hypermobile EDS/hypermobility spectrum disorder may bruise more easily, patients with hypermobile EDS/hypermobility spectrum disorder who develop significant tissue fragility (with complications such as vessel and/or organ rupture) must always be investigated to exclude a rare EDS type or condition with overlapping features.

Differential diagnostic considerations

Conditions that overlap with different types of EDS include other inherited connective tissue conditions that predispose to arterial aneurysms and blood vessel fragility. These include Marfan syndrome, Loeys-Dietz syndrome, conditions with abnormal skin such as cutis laxa, neuromuscular conditions such as collagen VI-related conditions (Ullrich congenital muscular dystrophy, Bethlem myopathy),[3] and conditions with significant joint hypermobility such as osteogenesis imperfecta and Stickler syndrome. Importantly, there are many other rare genetic syndromes with clinical features including joint hypermobility and hypotonia, and often intellectual disability. Furthermore, clinicians should consider other conditions that can present with easy bruising, such as clotting disorders and non-accidental injury.[3]

Confirmation of the diagnosis

In the past, diagnostic tests for EDS included transmission electron microscopy (assessing the collagen fibrils) and collagen biochemical analysis (assessing production of different collagens by cultured skin fibroblasts). However, the only transmission electron microscopy findings specifically associated with an EDS type were those in people with the ultrarare condition dermatosparaxis EDS, where they are considered to be pathognomonic.[8] However, advances in genomic technology have meant DNA analysis has rapidly replaced these techniques and is currently the gold standard for confirming a clinical diagnosis of a rare EDS type. Transmission electron microscopy can still help in a few cases to support a diagnosis of a rare EDS type, for example, when

there are variants of uncertain significance[11 26]; this is the case for collagen biochemical analysis and urinary collagen crosslinking for *PLOD1*-related kEDS.

A specific EDS gene panel (R101) is available in the UK through the 'national genomic test directory', assessed through https://www.england.nhs.uk/publication/national-genomic-test-directories/. The document for '*Rare and Inherited Disease*' can be found here and is regularly updated. The R101 EDS gene panel incorporates 47 genes, including all known genetic causes of rare EDS types, but also those of inherited connective tissue conditions that have overlapping clinical features (see above). These include Marfan and Loeys-Dietz syndromes, cutis laxa syndromes and dominant osteogenesis Imperfecta caused by deleterious *COL1A1/2* variants, as well as Bethlem and Ullrich myopathies. Clinicians can request this exome-based panel following patient assessment by a clinical geneticist or other expert in a highly specialised Ehlers-Danlos service. There are also several genetic causes of EDS included in other gene panels. For example, the *COL3A1* gene in which deleterious alterations cause vEDS is also present in the aortopathy gene panel (R125); cardiologists can request aortopathy gene panel and haematologists can request the bleeding disorders panel (R90). Other countries have similar gene panels.

It is important to be aware that sometimes no genetic cause can be identified in a patient with clear features of an inherited connective tissue condition such as a rare EDS type. As the detection rate of monogenic causes is still improving with newer techniques, patients with a clinical diagnosis or a strong suspicion on a rare EDS type but no identified genetic cause need to be managed as per the guidelines regarding the suspected EDS type, and offered reassessment in the following years.

CONCLUSION

Although many healthcare professionals still in practice refer to patients as having EDS, it is important to appreciate first, that the different EDS types have overlapping features, and second that the distinct clinical features and different genetic causes that distinguish them from each other require different management and surveillance. Medical professionals including (paediatric) neurologists must therefore seek information and advice to clarify the type of EDS.

Individuals with a diagnosis of a rare type of EDS, and particularly vEDS, will usually have undergone genetic testing and often there will be correspondence available regarding their diagnosis to take into consideration. People suspected to have a rare EDS type must have further assessment and/or genetic testing.

Key points

- "EDS" is not in itself a diagnosis and so it is crucial to clarify the EDS type.
- There are 14 different EDS types of which 13 are monogenic and rare with a prevalence varying from 1:20 000 to less than 1:1 000 000; most monogenic EDS types have neurological features as part of their major and/or minor criteria.
- Supra-aortic trunk lesions, particularly of internal carotid arteries and vertebral arteries, often develop in vascular EDS (vEDS); clinicians should consider vEDS if there are other major vEDS criteria and/or combination of minor criteria and/or when there is recurrence at a young age (eg, <50 years), especially without classical cardiovascular risk factors.
- Genetic testing is gold standard to confirm a clinical diagnosis of rare, monogenic EDS.

Further reading

- Malfait F, Francomano C, Byers P, *et al*. The 2017 international classification of the Ehlers-Danlos syndromes. *Am J Med Genet C Semin Med Genet* 2017;175:8–26.
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