Manifestations of Ehlers-Danlos Syndrome (EDS) Hypermobility Type

Literature Review by Lillian Han

Background

- EDS is a broad term for a number of inheritable connective tissue disorders, mainly characterized by joint hypermobility and instability, skin texture anomalies, and vascular and internal organ fragility.[1]
- The overall incidence is 1:10,000 to 1:25,000 without any ethnic predisposition.
- There are six major subtypes: classic (EDS type I and II), hypermobile (EDS type III), vascular (EDS type IV), kyphoscoliotic (type VIA), arthrochalasia (type VIIA and VIIB) and dermatosparaxis (type VIIC). See Table 1 for more details.
- Most of them are linked to mutations in one of the genes encoding for fibrillar collagen proteins or enzymes involved in post-translational modification of these proteins.
- EDS hypermobility type (EDS-HT, also known as EDS type III) is the most common subtype and the least severe one.

General characteristics[2]

- EDS- HT is considered to be indistinguishable if not identical to the joint hypermobility syndrome.
- Clinical condition with symptoms of joint instability, arthralgia, myalgia, soft tissue injuries and arthritis.
- The predominant presenting complaint is widespread and longstanding pain. Chronic pain may start in adolescence and severity of pain correlates with the degree of joint instability.
- Affected individuals are often misdiagnosed with chronic fatigue syndrome, fibromyalgia, depression, hypochondriasis prior to recognition of joint laxity and establishment of underlying diagnosis.

Manifestations[2,3]

Cardiovascular and Autonomic Nervous System Manifestations

- A mild degree of aortic root dilatation in up to 1/3 of EDS-HT patients necessitating echocardiographic evaluation and surveillance.
- Raynaud phenomenon in 38% of EDS-HT patients.
- Mitral valve prolapse (MVP) causing palpitations, chest pain, dizziness, pre-syncope, and syncope in 28-67% of EDS-HT patients.

Gastroinstestinal Manifestations

- Gastroesophageal reflux found in 57% of EDS-HT patients.
- Chronic gastrointestinal discomfort in 86% of patients.
- Irritable bowel syndrome in 62% of patients.
- Early satiety and delayed gastric emptying are reported and exacerbated by opioids.

Hematologic Manifestations

- Easy bruising and bleeding tendency are common in all EDS types due to mechanically impaired collagen too weak to afford adequate protection to the capillaries.
- Small and large arterial dissections have not been reported in EDS-HT.

Musculoskeletal Manifestations

- Musculoskeletal complaints manifest with joint pain of non-inflammatory origin, joint instability leading to dislocation or subluxation, and involving peripheral joints as well as central joints, including the temporomandibular joints.
- Although inflammatory component is rare, EDS-HT carries a high potential for disability due to recurrent dislocations and subluxations and chronic pain.

Neurologic Manifestations

- A total of 40-50% of children and adults with EDS-HT suffer from headaches, characterized as chronic recurrent headaches in the absence of structural, congenital, or acquired central nervous system lesions that correlate with their symptoms.
- Many complain of headaches related to neck and face which may be related to temporomandibular joint problems.
- Headaches may also be part of dysautonomia, found in 78% of EDS-HT patients, characterized by dizziness, lightheadedness, and pre-syncopal episodes.
- Partial or complete failure of local anesthesia has been described during biopsies, dental and obstetric procedures.
    - Arendt-Nielsen et al.[3] have studied the insufficient effect of local analgesics in EDS-HT patients and they found that these patients could obtain total analgesia from intradermally injected lidocaine but the effect of analgesia lasted only a very short time, even with a use of vasoconstrictor.
    - The patients also have reported that they all had previously experienced difficulties in obtaining sufficient analgesia at the dentist although substantial doses of local anesthetic were used as inifiltration or nerve blocks.
    - It could be speculated that the permeability of the analgesic substance through the walls of vessels is increased in these patients. If the vascular uptake is increased either due to increased permeability through the vessels or due to the loose tissue surrounding the vessels, the analgesic substance could be removed rapidly from the area around the nociceptors, reducing the dose of analgesics exposed to the nerve endings.

Conclusions

- EDS is a broad term for a number of inheritable connective tissue disorders, which are linked to mutations in one of the genes encoding for fibrillar collagen proteins or enzymes involved in post-translational modification of these proteins.

- EDS hypermobility type (EDS-HT, also known as EDS type III) is the most common subtype and the least severe one.
- Patients with EDS-HT suffer from joint hypermobility, chronic pain, chronic gastrointestinal discomfort/IBS, and chronic recurrent headaches.
- The patients' reporting of an insufficient effect of local anesthetic have been verified. These patients should therefore be very carefully and continuously monitored before and during surgical procedures to test if adequate analgesia is present. The reason for the short duration of anesthetic is suggested to be abnormal loose connective tissue in around the vessels leading to a more rapid washout of the anesthetic.

Table 1

Table 1 Overview on EDS variants, relevant criteria and genetic background

Common variant	Major criteria	Minor criteria	Inheritance	Causative gene(s)
Classic	Skin hyperextensibility	Smooth, velvety skin	AD	*COL5A1, COL5A2*
	Widened atrophic scars	Molluscoid pseudotumors		
	Joint hypermobility	Subcutaneous spheroids		
		Complications of joint hypermobility		
		Muscle hypotonia, motor delay		
		Easy bruising		
		Manifestations of tissue extensibility and fragility		
		Surgical complications		
		Positive family history		
Hypermobility	Hyperextensible and/or	Recurring joint dislocations	AD (?)	Unknown
	smooth, velvety skin	Chronic joint/limb pain		(single reports with mutations in *TNXB* and *COL3A1*)
	Generalized joint hypermobility	Positive family history		
Vascular	Thin, translucent skin	Acrogeria	AD	*COL3A1*
	Arterial/intestinal/uterine fragility or rupture	Hypermobility of small joints		
	Extensive bruising	Tendon and muscle rupture		
	Characteristic facial appearance	Talipes equinovarus		
		Early-onset varicose veins		
		Arteriovenous, carotid-cavernous sinus fistula		
		Pneumothorax/pneumohemothorax		
		Gingival recessions		
		Positive family history, sudden death in a close relative		
Kyphoscoliotic	Generalized joint hypermobility	Tissue fragility, including atrophic scars	AR	*PLOD1*
	Congenital hypotonia	Easy bruising		
	Congenital and progressive scoliosis	Arterial rupture		
	Scleral fragility and rupture of the ocular globe	Marfanoid habitus		
		Microcornea		
		Osteopenia/porosis		
		Positive family history		
Arthrochalasis	Generalized joint hypermobility with recurrent subluxations	Skin hyperextensibility	AD	*COL1A1, COL1A2* (recurrent mutations)
	Congenital bilateral hip dislocation	Tissue fragility, including atrophic scars		
		Easy bruising		
		Hypotonia		
		Kyphoscoliosis		
		Osteopenia/porosis		
Dermatosparaxis	Severe skin fragility	Soft, doughy skin texture	AR	*ADAMTS2*
	Sagging, redundant skin	Easy bruising		
		Premature rupture of fetal membranes		
		Large hernias (umbilical, inguinal)		

Abbreviations: EDS Ehlers Danlos Syndrome, *AD* autosomal dominat, *AR* autosomal recessive.

References

1. Wiesmann *et al*. Recommendations for anesthesia and perioperative management in patients with Ehlers-Danlos syndrome(s). *Orphanet Journal of Rare Diseases* 2014, 9:109.
2. Gazit et al. Ehlers-Danlos Syndrome- Hypermobility Type: A Much Neglected Multisystemic Disorder. *Rambam Maimonides Medical Journal* 2016 Oct; 7(4):e0034.
3. Arendt-Nielsen et al. Insufficient effect of local analgesics in Ehlers Danlos type III patients (connective tissue disorder). *Acta Anaesthesiol Scand* 1990: 34: 358-361.