Ehlers-Danlos Syndromes Overview for primary care providers

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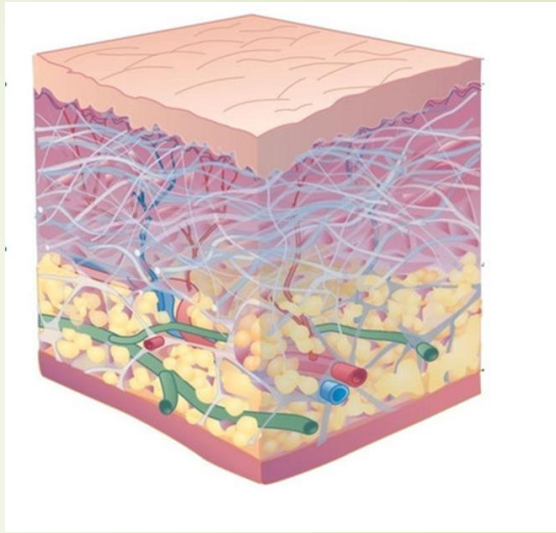
Outline

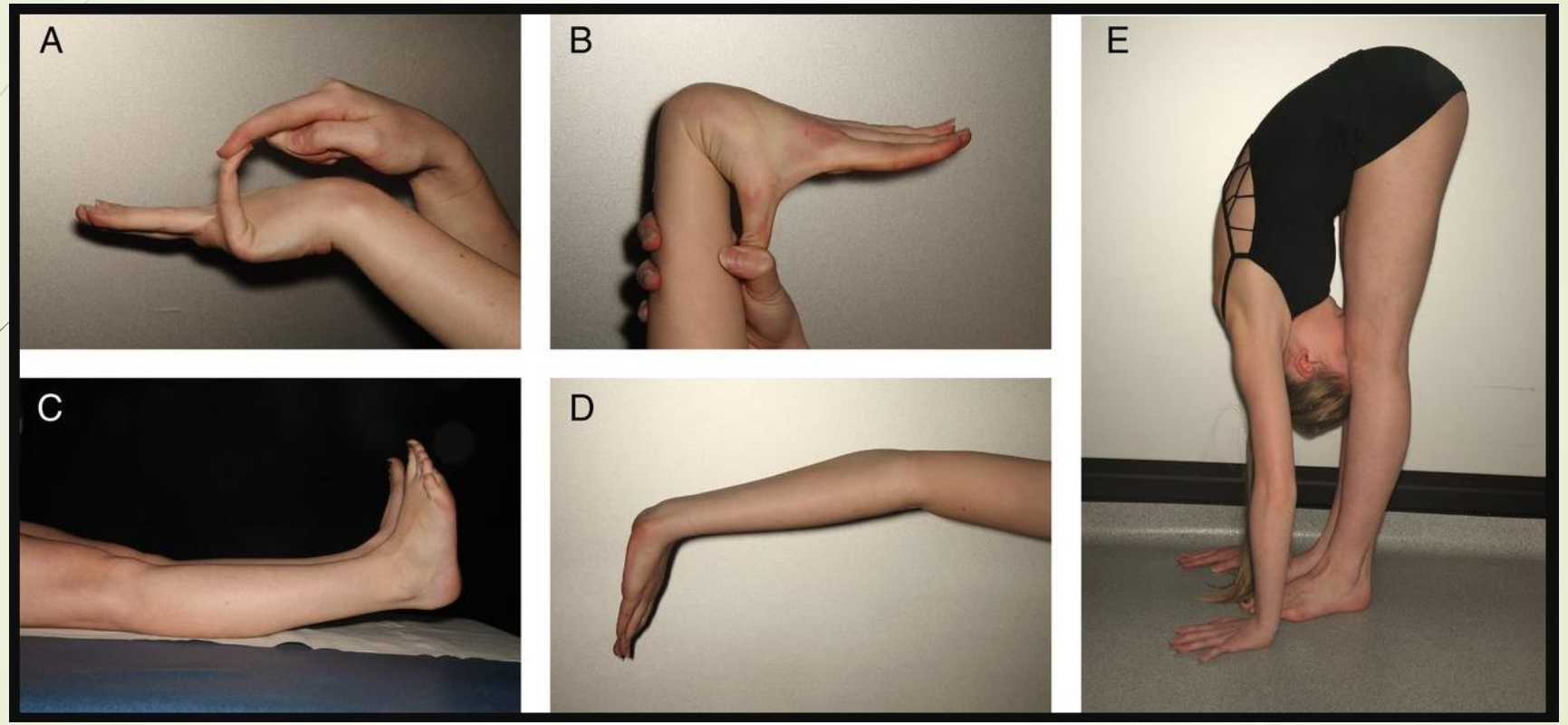
- Introduction to connective tissue disorders
- Disorders associated to hypermobility
- Hypermobile type EDS (hEDS)
  - Prevalence
  - Diagnostic criteria
  - Other associated symptoms and complications
  - Management goals
- The EDS clinic at HSC/ UHN
- Question and answer period

Connective Tissue Disorders



- >100 different disorders described
- Result in abnormalities of the extracellular matrix (ECM)
- Shared features include:
  - Increased flexibility of the skin and joints
  - Variable degrees of tissue fragility
  - Easy bruising and poor wound healing
  - Depending on the function and site of expression of protein involved
    - Heart and vessel involvement (valvular and aortic dilatation)
  - Eye manifestations (Keratoconus, lens dislocation)
  - Other systems

Assessing hypermobility
The Beighton Score



Maneuver	Left	Right
Bending elbow backward over 10°	1 point	1 point
Bending knee backward	1 point	1 point
Bending thumb back on to the front of forearm	1 point	1 point
Bending fifth finger up to 90° to the back of hand	1 point	1 point
Getting hands flat on the floor with straight knees	1 point	
Maximum score	9 points	

Disorders associated to hypermobility

- Marfan Syndrome
- Loeys-Dietz Syndrome
- Ehlers Danlos syndromes
  - 3 more common types
    - Classical
    - Hypermobile
    - Vascular
  - Rare types
- Neurological disorders associated with hypotonia

Hypermobile type EDS (hEDS)

- Heritable connective tissue disorder
- Characterized by
  - Generalized joint hypermobility
  - Related musculoskeletal manifestations
  - Milder involvement of the skin that that seen in the classical and vascular types of EDS
- Part of a spectrum with Joint Hypermobility Syndrome (JHS)
  - More strict diagnostic criteria
  - More debilitating complications
- Prevalence (depends on the definition)
  - 20/1,000 (0.75–2%) for "symptomatic" GJH [Hakim and Sahota, 2006]
  - 3.4% patients have joint hypermobility and widespread pain [Mulvey et al., 2013]

hEDS Diagnostic Criteria

- Major Criteria (REQUIRED)
  - Generalized joint hypermobility (Beighton ≥ 5)
- Minor Criteria (2 or more REQUIRED)
  - Feature A (see next slide)
  - Feature B: Family history of 1st degree relative meeting criteria
  - Feature C: (1 or more present)
    - MSK pain, 2 or more limbs, daily for ≥ 3 months
    - Chronic widespread pain for ≥ 3 months
    - Recurrent atraumatic joint dislocations or frank joint instability
- Exclusion Criteria (all REQUIRED)
  - Absence of unusual skin fragility
  - Exclusion of other connective tissue disorders
  - Exclusion of alternative diagnoses with joint hypermobility

hEDS Diagnostic Criteria Feature A

- Unusually soft or velvet skin
- Mild skin hyperextensibility
- Unexplained striae
- Bilateral piezogenic heel papules
- Recurrent abdominal hernia
- Atrophic scarring
- Pelvic floor, rectal or uterine prolapse
- Dental crowding and high or narrow palate
- Arachnodactyly (bilateral positive wrist or thumb sign)
- Arm span: height ≥ 1.05
- Mitral valve prolapse
- Aortic root dilatation (Z-score > +2)

hEDS Diagnostic Criteria

HYPERMOBILE-TYPE EDS

1. Major Criteria (REQUIRED) ☐ Generalized joint hypermobility (Beighton ≥ 5)	Y N
2. Minor Criteria (2 or more REQUIRED) Feature A: (5 or more present) ☐ Unusually soft or velvet skin ☐ Mild skin hyperextensibility ☐ Unexplained striae ☐ Bilateral piezogenic heel papules ☐ Recurrent abdominal hernia ☐ Atrophic scarring ☐ Pelvic floor, rectal or uterine prolapse ☐ Dental crowding and high or narrow palate ☐ Arachnodactyly (bilateral +ve wrist or thumb sign) ☐ Arm span: height ≥ 1.05 ☐ Mitral valve prolapse ☐ Aortic root dilatation (Z-score > +2)	Y N
Feature B: ☐ Family history: 1st degree relative meeting criteria _____	Y N
Feature C: (1 or more present) ☐ MSK pain, 2 or more limbs, daily for ≥ 3 months ☐ Chronic widespread pain for ≥ 3 months ☐ Recurrent atraumatic joint dislocations or frank joint instability	Y N
3. Exclusion Criteria (all REQUIRED) ☐ Absence of unusual skin fragility ☐ Exclusion of other connective tissue disorders ☐ Exclusion of alternative diagnoses with joint hypermobility	Y N

Evolving presentation

- The formal diagnosis may be influenced by age
  - Children usually meeting the criteria
  - Adults develop symptoms with age and may change presentation
- An Italian study on disease progression with 21 hEDS patients described three "discrete" disease phases
  - Hypermobility
  - Pain
  - Stiffness
- Not every patient experiences all three phases
- The rate of transition between phases can be highly variable

Hypermobility phase

- Dominates the first several years
- Increased joint mobility (contortionism)and propensity for sprains and dislocations.
- Pain is often limited to lower limbs or with fine motor or repetitive tasks such as handwriting
- Easy fatigability may be a feature,
- Voiding dysfunction
- Some hypermobile children experience developmental dyspraxia
  - Mild hypotonia
  - Non-specific developmental delay in gross and fine motor skills attainment

Pain Phase

Characterized by:

- Generalization and progressive chronicity of musculoskeletal pain
- Often diagnosed as fibromyalgia
- Development of other forms of chronic pain, such as pelvic pain (in women) and headache
- Exacerbation of fatigue
- Typically starts in the second to the fourth decade of life
- Additional complaints include paresthesias, mixed and treatment-resistant functional gastrointestinal disorders, orthostatic intolerance, and pelvic dysfunction.

Stiffness Phase

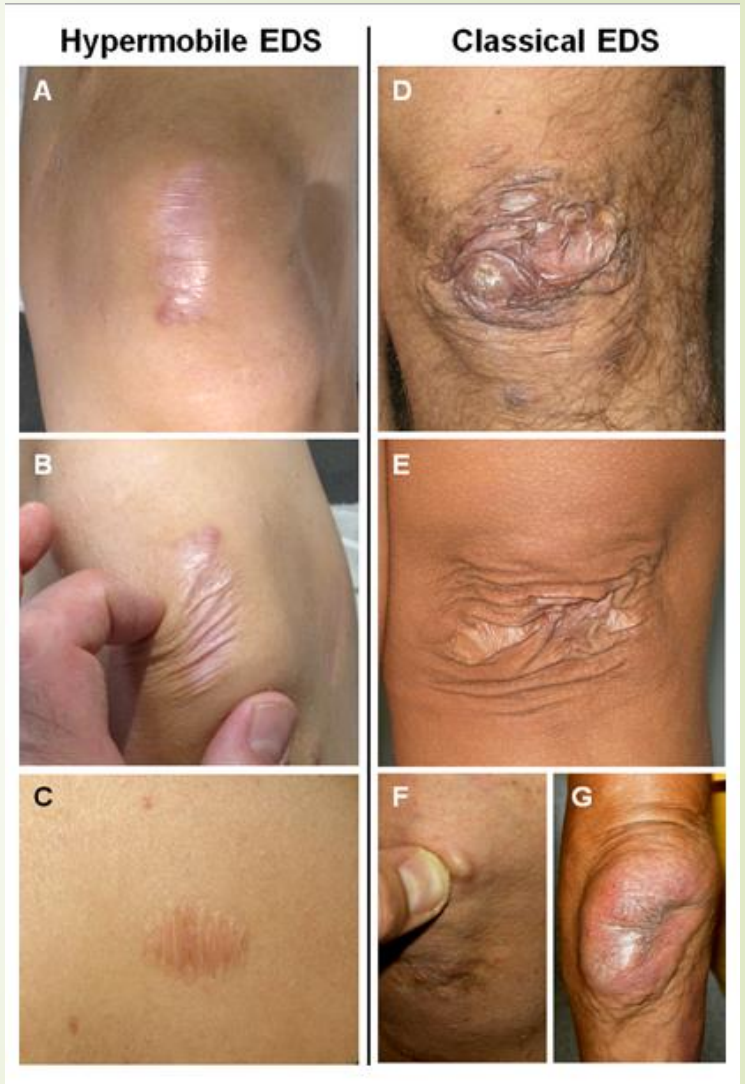
- Generalized reduction of joint mobility
- Significant reduction in functionality due to the combination of:
  - Disabling symptoms (e.g., pain and fatigue)
  - Motor limitations
    - Reduced muscle mass and weakness
    - Defective proprioception
    - Prior injuries
    - Arthritis

hEDS and Pain

- Specific underlying cause (s) and mechanism(s) of pain in hEDS, are not well understood
- Acute and chronic pain are common
- Nociceptive pain directly related to affected muscles, joints, and connective tissue
- Neuropathic pain, characterized by allodynia and/or typical quality descriptors, such as electrical, burning, numb, or tingling.
- Anatomic imaging and functional electrodiagnostic studies are often negative
- Skin biopsy may reveal reduction of intradermal nerve fiber density, suggestive of small fiber neuropathy
- Central sensitization, generalized hyperalgesia, chronic regional pain syndrome, and similar systemic or regional pathogenic mechanisms contribute in later stages [

Skin and Fascia

- Skin in hEDS skin is more fragile than normal, but much less so than in the other types of EDS.
- Easy bruising is common but poorly defined.
- Wound healing may be impaired with the production of mildly atrophic scars
- Striae atrophicae often appear during adolescence
- Striae gravidarum may be minimal or non-existent



Other connective tissue weakness

- Cerebrospinal fluid (CSF) leaks are a possible cause of orthostatic headaches.
- Failure of musculotendinous support
  - The diaphragm
    - hiatal hernia
  - The pelvic floor
    - Uterine/rectal prolapse, rectocele, cystocele, and/or enterocele
- Fascial weakness can lead to hernias in the inguinal, femoral, or umbilical areas or at sites of previous surgical incisions

Fatigue in hEDS

- Chronic, debilitating fatigue is common in hEDS
- Multifactorial
  - Pain
  - Sleep disturbance
  - Dysautonomia
  - Medications
  - Allergies.
- Decreases muscle control and coordination
- Inhibits physical activity
- May increase risk for injury
- Mental fatigue leads to impaired cognition and memory

Cardiovascular Involvement

- Mild dilation of the aortic root may develop
  - Unlikely to progress
  - Baseline echocardiography is not recommended
- Postural Orthostatic Tachycardia (POTS) and orthostatic intolerance are common
  - Head-up tilt test may or may not establish a specific etiology
  - Often does not affect therapeutic decision-making
- Mitral valve prolapse (MVP)
  - Frequency of 28–67% among hEDS patients
  - Increased prevalence of mitral and tricuspid insufficiency has also been reported

Gastrointestinal Disorders

- Wide range of functional complaints in adults
- Link between a congenital laxity of the soft connective tissue and gut diseases is still unclear
- Functional Features may be observed in 1/3 to 3/4 of the patients
  - Gastroesophageal reflux/Heartburn
  - Recurrent abdominal pain and bloating
  - Irritable bowel syndrome
  - Constipation or Diarrhea
  - Dysphagia

Dysautonomia

- Orthostatic hypotension
- POTS
- Uncategorized orthostatic intolerance
- Increase of the physiological heart rate variability
- Greater blood pressure fall during Valsalva maneuver
- Lower initial systolic blood pressure
- Cardiovascular dysautonomia contributes to
  - Atypical chest pain
  - Neurological secondary manifestations

Spine Hypermobility

- Joint hyperlaxity may affect cranio-cervical junction
  - Cranio-vertebral instability
  - Chiaru type I
    - gait disturbance
    - Numbness and tingling of the hands and feet
    - Dizziness
    - Dysphagia
    - Speech difficulties
- Postural kyphosis
- Scoliosis acquired and flexible

Gynecologic Issues

- Mucosal problems in genital area
- Heavy menstrual bleeding (menorrhagia)
- Painful intercourse
- Pelvic Dysfunction
  - Urinary incontinence
  - Pelvic organ prolapse
  - Sensory and emptying abnormalities.

Mast Cell Activation Disorder

- Characterized by:
  - Increased number of mast cells
  - Increased mast cell mediators (e.g., histamine, tryptase)
- Clinical symptoms of MCAS include
  - Flushing
  - Pruritis
  - Hypotension
  - Asthma
  - Diarrhea
  - Abdominal bloating
  - Cramping

Psychiatric co-morbidities

- Psychological dysfunction and emotional problems are comon
  - Depression
  - Anxiety
  - Affective disorder
  - Low self-confidence
  - Negative thinking
  - Hopelessness
- May exacerbate the other symptoms

Management of hEDS

- Assessment is based on symptoms
- Musculoskeletal symptoms should be approached conservatively
  - Physical therapy, education, and pacing are paramount
  - Frank joint instability should be evaluated by orthopedics
- Symptoms of orthostatic intolerance, tachycardia with palpitations, and/or near-syncope
  - Treated conservatively by fluid and salt intake
  - Education and the appropriate exercise.
  - Syncope should be evaluated further by specialists such as neurology or cardiology for concerns of arrhythmia, seizure disorder, cardiomyopathy

Management of hEDS

Includes :

- Treatment of acute/emergency manifestations
- Attenuation of chronic symptoms
- Primary and secondary prevention of acute and chronic complications
- As many patients with hEDS have multiple symptoms, a coordinated effort is required as other specialists are incorporated into the medical team.
- The approach should be holistic focusing on the complications, the desire(s) of the patient, QoL and functionality, as well as the psychological aspects.

The EDS clinic

Vision:

- Improving the lives of patients with EDS through collaborative clinical care and driving best practices, knowledge translation, innovation and research.

Mission:

- To support patients and families living with EDS by providing timely diagnosis, coordination of medical care, and expertise in the treatment and management of EDS both internally at SickKids and UHN, and through external partnerships and collaboration.

Referral system:

- Paediatric patients can be referred through the Ambulatory Referral Management System (ARMS) at https://www.sickkids.ca/referralsystem/
- Adult patients can be referred by faxing (416) 340-3792, the following form:
  - http://www.uhn.ca/MCC/Health_Professionals/Referrals/Documents/Ehlers_Danlos_Syndrome_Clinic_Referral_Form.pdf#search=eds%20program

Questions and comments?