Classical Ehlers-Danlos Syndrome

Clair A. Francomano, MD
EDS Center for Clinical Care and Research
Harvey Institute for Human Genetics
Greater Baltimore Medical Center
Committee Members

• Jessica M. Bowen
• Glenda J. Sobey
• Nigel P. Burrows
• Marina Columbi

• Mark Lavallee
• Fransiska Malfait
• Christina Schwarting
• Clair A. Francomano
Classical EDS: History

• Beighton, 1968: EDS Gravis and Mitis
• Beighton, 1988: EDS Types I and II
• Villefranche nosology, 1997: Classical EDS

• 1996: Identification of mutations in COL5A1 (Nicholls et al., 1996; Wenstrup et al., 1996; De Paepe et al., 1997)
Recommended Naming

- Retain the name “Classical Ehlers-Danlos Syndrome”
- Abbreviation: cEDS
Proposed Diagnostic Criteria

Major criteria

1. Skin hyperextensibility and atrophic scarring
2. Joint hypermobility
Minor Diagnostic Criteria

1. Easy bruising
2. Soft, doughy skin
3. Skin fragility (or traumatic splitting)
4. Molluscoid pseudotumours
5. Subcutaneous spheroids
6. Hernia (or history thereof)
7. Epicanthal folds
8. Family history of a first degree relative who meets clinical criteria
To Establish a Clinical Diagnosis

Major Criterion (1): Skin hyperextensibility and atrophic scarring

Plus

• Either: Major criteria (2) – joint hypermobility

• Or: three of the eight minor criteria
Clinical considerations

Skin is considered hyperextensible if it can be stretched over a standardized cut off in three of the following areas

- 1.5 cm for the distal part of the forearms and the dorsum of the hands
- 3 cm for neck, elbow and knees
Skin Hyperextensibility
Scarring

• Abnormal scarring can range in severity.
• Most patients have extensive atrophic scars at a number of sites.
• These can sometimes be haemosiderotic.
• A minority of patients are more mildly affected.
Scarring
Joint Hypermobility

• Joint hypermobility is assessed through the Beighton score. A score of 5 or more is considered positive for the presence of joint laxity.
Beighton Scale
Clinical Considerations (2)

• Easy bruising can occur anywhere on the body, including unusual sites.
• The pretibial area often remains stained with hemosiderin from previous bruises
Bruising
• Subjective abnormality of the skin texture is appreciable on exam

• Molluscoid pseudotumors are fleshy lesions associated with scars, found over pressure points (e.g. elbow, fingers)
Molluscoid Pseudotumors
Clinical Considerations (3)

• Subcutaneous spheroids are small spherical hard bodies, frequently mobile and palpable on the forearms and shins. Spheroids may be calcified and detectable radiologically.

• Epicanthal folds are often seen in childhood but may also be seen in adults.
Verification of Clinical Diagnosis

• Confirmatory analysis is recommended for any patient meeting the recommended clinical criteria.

• Molecular analysis of **COL5A1** and **COL5A2** genes identifies a causal mutation in more than 90% of the patients and should be used as the standard confirmatory test.

• In case of unavailability of genetic testing, electron microscopy findings of collagen flowers on skin biopsy can support the clinical diagnosis.

• Absence of these confirmatory findings does not exclude the diagnosis, however alternative diagnoses should be considered in the absence of a type V collagen gene mutation or electron microscopy findings.
Comprehensive Molecular Analysis Demonstrates Type V Collagen Mutations in over 90% of Patients with Classic EDS and Allows to Refine Diagnostic Criteria

Sofie Symoens,† Delfien Syx,† Fransiska Malfait, Bert Callewaert, Julie De Backer, Olivier Vanacker, Paul Coucke, and Anne De Paepe*  

Center for Medical Genetics, Ghent University Hospital, Ghent, Belgium
Organ System Review

- Musculoskeletal
- Skin
- Cardiovascular
- Gastrointestinal
- Neurologic
Musculoskeletal

• Joint hypermobility
• Complications of joint hypermobility
• Mild muscle hypotonia
• Skeletal morphology alterations
• Increased bone fragility (osteopenia or osteoporosis)
Skin

- Stretchy
- Soft
- Severe atrophic scarring
- Hemosideric scars over the shins and extensor surfaces of the forearm
- Easy bruising
Cardiovascular

• Aortic root dilation; rarely progresses
• Mitral valve prolapse
• Venous insufficiency
Gastrointestinal

- Dysphagia
- Dyspepsia
- Gastro-esophageal reflux
- Hiatal hernia
- Irritable bowel syndrome
- Unspecified abdominal pain
- Constipation
- Diarrhea
- Rectocele
Neurologic

- Pain
- Dysautonomia
- Headache
- Frequency of Chiari I, craniocervical instability, tethered cord as yet undefined.
Others

- Prolonged bleeding time
- Chronic fatigue syndrome
- Mast cell activation
- Giant bladder diverticuli
Management - Skin

• Avoidance of trauma
• Closure of wounds – plastic surgeon if possible
• Ascorbic acid (2 gm/day for adults)
• DDAVP may help to normalize bleeding time
• Avoid excessive sun exposure
Management - Musculoskeletal

- Physiotherapy
- Avoid high-impact activities
- Avoid excessive demonstrations of hypermobility
- A multi-disciplinary team is very helpful for management
- Ring splints, carefully considered bracing and orthotics may be helpful
- DEXA analysis
Management – Pain

• Neurological assessment in patients with symptoms suggestive of neuropathic pain/compression neuropathy
• Regular, light, non-weight-bearing exercise.
• Physical therapy for muscle relaxation and myofascial trigger point release
• Relaxation techniques including mindfulness-based stress reduction and biofeedback
• Counselling support including cognitive behavioural therapy
• Anti-inflammatory drugs and pain medications
Management - Cardiac

- Echocardiography to look for aortic root dilation and mitral valve prolapse.
- Aortic root size and mitral valve prolapse are increased in patients with classical EDS, but they tend to be of little clinical significance.
- Echo frequency in symptom-free adults frequency can be reduced (Atzinger et al., 2011).
- If echo is normal in adulthood no follow up is required (Malfait et al., 2010).
- Consider vascular imaging /aggressive blood pressure control if the patient has a glycine substitution identified near the C-terminal end of the triple helix, or on the basis of their family history (Monroe et al., 2015)
Management - Gastrointestinal

- Upper gastrointestinal endoscopy or 24 h pH-metry to evaluate reflux disease in symptomatic patients. Treatment with proton-pump inhibitor if needed.

- Colonoscopy should be performed with care due to a possibly increased risk of mucosal bleeding.

- Treatment of functional gastrointestinal complaints in EDS patients is problematic due to the absence of tailored strategies and an apparent resistance to pharmacologic treatments at standard dosages/regimens.

- Patient education, also comprising diet and nutritional advice, seems at the moment the most effective management tool.
Management - Pregnancy

- Follow up throughout pregnancy is warranted.
- Prematurity happens more often when the fetus is affected and is mainly due to premature rupture of the membranes.
- Breech presentation is more common if the baby is affected, due to hypotonia.
Differential Diagnosis

- Cardiac-valvular type EDS
- Tenascin X deficient EDS
- Spondylocheiroidysplastic type EDS
- Loeys Dietz syndrome
- OI/EDS overlap syndrome
Thanks

• The Classical EDS committee
• Our patients and their families
• The Ehlers-Danlos Society and EDS-UK
• Lara Bloom and Shane Robinson