Skeletal effects of hypermobility, Ehlers-Danlos Syndrome and Marfan Syndrome

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Summary

- Connective tissue and heritable disorders of connective tissue
Connective Tissue

Heritable connective tissue disorders
HCTD: clinically overlapping conditions

- Marfan Syndrome
  - Fibrillin 1
- Ehlers-Danlos Syndrome
  - Collagen I, III V
- Chondrodysplasias
  - Collagen II, X, ...
- Osteogenesis imperfecta
  - Collagen I
HCTD, overlapping, multisystemic disorders

- Marfan
- Osteogenesis imperfecta
- Achondroplasia
- Ehlers-Danlos syndromes

multi-systemic involvement
phenotypic variability
monogenic inheritance
Overzicht

- Connective tissue and heritable disorders of connective tissue
- Marfan syndrome, a fibrillinopathy
History

• In 1896, Marfan described a hereditary disorder of connective tissue in a 5 yr old girl with disproportionately long limbs that later became to be known as ‘Marfan syndrome’.

Antoine Bernard-Jean Marfan (1858 1942), a French pediatrician
Marfan Syndrome

- One of the most common HCTD
- Autosomal dominant inheritance
- Incidence: 1:3000 - 1:5000 individuals, regardless of sex or ethnicity
- Characterised by loss of elastic tissue, affecting numerous body systems, including the musculoskeletal, cardiovascular, respiratory systems, the skin and the eyes.

Ectopia lentis

Aortic root dilation

Skeletal manifestations
Genetic basis

- Caused by a variety of mutations in the \textit{FBN1} gene
- \textit{FBN1} mutations have been identified in >90 percent patients
  - In 75\% of patients - autosomal dominant, although the appearance of family members and degree of pathological features may vary.
  - In 25\% of patients - mutation occurs spontaneously and may be associated with older paternal age.
- The first \textit{FBN1} mutation was identified in 1990. Subsequently, >1000 different mutations have been identified.
Marfan Syndrome

• Diagnosis: based on the identification of
  – a combination of clinical manifestations
  – in different organ systems
  – as defined in the (revised) Ghent nosology

Diagnostic criteria (revised Ghent Criteria)

Criteria for Marfan syndrome diagnosis in patients with no family history

- Ao (Z ≥ 2) AND ectopia lentis
- Ao (Z ≥ 2) AND FBN1 mutation
- Ao (Z ≥ 2) AND systemic features (≥ 7 points)
- Ectopia lentis AND FBN1 associated with known aortic involvement

Ao = aortic diameter above indicated Z-score or aortic root dissection
Diagnostic criteria (revised Ghent Criteria)

Criteria for Marfan syndrome diagnosis in patients with a positive family history

- Ectopia lentis AND family history of MFS
- Systemic features (≥ 7 points) AND family history of MFS
- Ao family history of MFS
  (Z ≥ 2 above 20 years, ≥ 3 below 20 years)
2. Scoring of systemic features for the diagnosis of Marfan syndrome

<table>
<thead>
<tr>
<th>Feature</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wrist OR thumb sign†</td>
<td>1</td>
</tr>
<tr>
<td>Wrist AND thumb signs‡</td>
<td>3</td>
</tr>
<tr>
<td>Pectus carinatum deformity</td>
<td>2</td>
</tr>
<tr>
<td>Hindfoot deformity</td>
<td>2</td>
</tr>
<tr>
<td>Plain pes planus</td>
<td>1</td>
</tr>
<tr>
<td>Pectus excavatum or chest asymmetry</td>
<td>1</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>2</td>
</tr>
<tr>
<td>Dural ectasia</td>
<td>2</td>
</tr>
<tr>
<td>Protrusio acetabulae</td>
<td>2</td>
</tr>
<tr>
<td>Reduced upper segment to lower segment ratio, AND increased ratio of arm span to height AND no severe scoliosis</td>
<td>1</td>
</tr>
<tr>
<td>Scoliosis or thoracolumbar kyphosis</td>
<td>1</td>
</tr>
<tr>
<td>Reduced elbow extension</td>
<td>1</td>
</tr>
<tr>
<td>Three of the five typical facial features (dolichocephaly, enophthalmos, downward slanting palpebral fissures, malar hypoplasia, retrognathia)</td>
<td>1</td>
</tr>
<tr>
<td>Skin striae</td>
<td>1</td>
</tr>
<tr>
<td>Myopia of &gt; 3 dioptres</td>
<td>1</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>1</td>
</tr>
</tbody>
</table>

- Maximum Total = 20
- Systemic Involvement if Total ≥ 7
Diagnostic criteria (revised Ghent Criteria)

- Special considerations for children (<20 yrs):
  - If insufficient systemic features (<7) and/or borderline aortic root measurements (Z < 3) are present (without FBN1 mutation) – “non-specific connective tissue disorder” until follow-up echo evaluation shows aortic root dilation (Z ≥ 3).
  
  - If an FBN1 mutation is identified in sporadic or familial cases but aortic root measurements are still Z < 3 - “potential MFS” until the aorta reaches threshold.
Aortic Disease

- Aortic root disease, leading to aneurysmal dilatation, aortic regurgitation, and dissection - main cause of morbidity and mortality
- Poor correlation between the severity of the cardiovascular and the ocular or skeletal manifestations
- Although dilated, the aorta in MFS tends to be stiffer and less distensible
- Dilatation of the aorta, often (about 25%) accompanied by aortic regurgitation, progresses with time
- Dilation may also involve other segments of the thoracic aorta, the abdominal aorta, the root of the pulmonary artery or even the carotid and intracranial arteries.
Aortic Disease

MFS; Ao root dilatation

In this coronal CT view, the aortic root is dilated at the level of the sinuses of Valsalva.
Ocular abnormalities

- **Ectopia lentis** - 50 to 80 percent. Detected on slit-lamp examination after maximal dilatation of the pupil and the lens is usually displaced upward and temporally. It is caused by failure of the supporting ciliary zonules.

- **Myopia >3 diopters** - secondary myopia due to increased axis globe length.

- **Flat cornea, hypoplastic iris, hypoplastic ciliary muscle causing decreased miosis, retinal detachment, glaucoma, and early cataract formation.**
  Retinal tears and detachment are commonly bilateral.
Ocular abnormalities

Ectopia Lentis - Marfan's Syndrome

Edge of Dislocated Natural Lens with Cataract (Ectopia Lentis)

Slit-lamp photomicrography shows ectopia lentis with microspherophakia; the lens is completely luxated into the anterior chamber, predisposing to pupillary block glaucoma.
Musculoskeletal manifestations

N. Paganini

A. Lincoln

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Skeletal disease

- Excess linear growth of the long bones – Individuals taller than predicted by their genetic background
- Long slender arms, fingers, legs and feet
- Arachnodactyly
  - Thumb sign - entire distal phalanx protrudes beyond the ulnar border of a clenched fist with or without the assistance of the patient or examiner to achieve maximum adduction
  - Wrist sign - the top of the thumb covers the entire fingernail of the fifth finger when wrapped around the contralateral wrist
Bone overgrowth

- Abnormal US/LS and arm span/height
  - disproportionately long extremities in comparison to the length of the trunk (dolichostenomelia)
  - upper segment to lower segment (US/LS) ratio is decreased and the arm span to height ratio is increased.
Pectus deformities

Pectus carinatum (more specific for MFS than pectus excavatum or chest asymmetry)
- Cosmetic problems

- Pectus excavatum
  - Cosmetic problems
  - Breathing problems in more severe cases
Spinal deformities

present in ± 60 % of patients with MFS
caused by abnormally loose ligaments of spine and rapid growth

• Scoliosis
  Cobbs’ angle of at least 20°

• Kyphosis

→ Curves progress at a faster rate than in idiopathic scoliosis
→ Back pain (three times as frequent in MFS as in general population)
(Hind)foot deformities

- Claw toes
- Hammer toes
- Flat feet
Protrusion acetabulae

Can be diagnosed by plain radiograph, CT or MRI

On an AP pelvic film, medial protrusion of the acetabulum $\geq$ 3 mm beyond the ilio-ischial (Kohler) line is diagnostic.

$\rightarrow$ most patients have adequate hip function, but rare patients develop severe joint degeneration at young age
Dural ectasia

enlargement of the outer layer of the meningeal sac

- Very common in MFS (60-90% of pts)
- MRI most sensitive technique
- Most pronounced distally where the hydrostatic pressure of the cerebrospinal fluid is greatest (L5, S1, S2)
- Risk for dural tears and fixation failure during corrective surgery for spine deformity

- Associated with back pain in many cases
- Dural volume correlates with the degree of pain
- Other symptoms:
  - Headache
  - Leg pain, numbness
  - Abdominal pain
  - Pain in the perineum
Spondylolisthesis

a slip forward of one vertebra upon the one below it

→ Low back pain and/or stiffness, unable to bend forward to touch toes
→ Usually no neurologic damage, except in very severe cases
Other musculoskeletal problems (1)

Joint hypermobility

Joint dislocations
Elbow contractures

Reduced elbow extension
Other musculoskeletal problems (2)

Underdevelopment of muscles, lack of strength
(muscle hypotonia)

→ Combination of underdeveloped muscles and joint
  hypermobility can contribute to a poor coordination and
delay in acquiring gross and fine motor skills
Pain

- In children and adults with MFS, prevalence of pain in at least one location of the body ranges between 70% and 96%

- 40% of MFS patients have pain in multiple locations

- 50% have daily symptoms, often causing missed school or work

- The pathophysiology of these prevalent pain symptoms is yet to be explored
Other manifestations

• **Pulmonary disease** — Some patients develop emphysematous changes with lung bullae predominantly in the upper lobes, can predispose to spontaneous pneumothorax.

• **Skin striae** — The presence of striae atrophicae contributes one point to the systemic score if not associated with pronounced weight changes or pregnancy and if in uncommon location such as the mid back, lumbar region, upper arm, axillary region, or thigh.
Step-by-step diagnostic approach

- History and physical examination (including slit-lamp ophthalmic examination with pupil dilation) in conjunction with imaging of the aortic root and the ascending, descending, and abdominal aorta (echo, CT, MRI) are usually sufficient for diagnosis.

- Identification of risk factors
  - Family history of Marfan's syndrome, or of aortic dissection or aneurysm.

- Other historical considerations
  - Family history of ocular problems (myopia, astigmatism, strabismus, amblyopia, premature cataract or other lens abnormalities, glaucoma, retinal detachment), dental extraction or braces for dental crowding, hernias, or spontaneous pneumothorax. Patients may have a history of joint pain or low back ache.
Step-by-step diagnostic approach

- Physical examination
  - Tall stature, wide arm span, high level of pubic bone, high arched palate, arachnodactyly, positive wrist and thumb sign, pectusdeformity, scoliosis, striae, flat feet, myopia, hernias, aortic or mitral valve murmur may be present.
  - Spontaneous pneumothorax or emphysematous bullae may present as dyspnoea.
  - There may be signs of heart failure due to valve disease or cardiomyopathy.
  - Complete ophthalmic examination, including fundus examination with pupil dilation - signs of lens subluxation or dislocation, cataract, glaucoma, or retinal detachment.
  - May present with acute aortic dissection or rupture.
Step-by-step diagnostic approach

- **Subsequent investigations**
  - Echocardiography, thorax CT, and thorax MRI are used initially for aortic root imaging.
  - Abdominal ultrasound, CT, and MRI are used for visualisation of the descending aorta.
  - CXR is performed to exclude the presence of a pneumothorax, and may reveal emphysematous bullae.
  - Lower spine CT scan or MRI can be performed to exclude dural ectasia.
  - Plasma homocysteine levels help in unclear cases to differentiate homocystinuria.
  - Genetic test for mutations in the fibrillin-1 (FBN1) gene confirms the diagnosis if in doubt. Once detected, the mutation can be used to screen other relatives, and used for antenatal diagnosis and pre-implantation genetic diagnosis.
Multidisciplinary clinical evaluation:
- Cardiologist
- Ophthalmologist
- Genetic counselling
- Physiatrist
- Cardiac, lumbosacral MRI

Clinical diagnosis
- STOP
- Genetic analysis

Uncertain diagnosis
- Genetic analysis
Overzicht

- Connective tissue and heritable disorders of connective tissue
- Marfan syndrome, a fibrillinopathy
- Ehlers-Danlos syndrome, a collagenopathy
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“The Ehlers-Danlos Syndrome”

Dr. Edvard Ehlers, of Copenhagen
1863-1937

Dr. Henri-Alexandre Danlos
1844-1912
The Ehlers-Danlos syndrome

Skin:
- Hyperextensibility
- Slow wound healing
- Atrophic scarring

Joints, ligaments, tendons:
- Hyperlaxity
- Dislocations
- Pain

Connective Tissue fragility
- Hernia umbilicalis
- Hemorrhage, vascular ruptures
- Gastro-intestinal rupture

...
## A Disorder of Collagen type I, III or V

<table>
<thead>
<tr>
<th>Type</th>
<th>Gene</th>
<th>Protein</th>
<th>IP</th>
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<tbody>
<tr>
<td>Classical</td>
<td>COL5A1, COL5A2</td>
<td>Type V procollagen</td>
<td>AD</td>
</tr>
<tr>
<td>Hypermobility</td>
<td>?</td>
<td>?</td>
<td>AD</td>
</tr>
<tr>
<td>Vascular</td>
<td>COL3A1</td>
<td>Type III procollagen</td>
<td>AD</td>
</tr>
<tr>
<td>Kyphoscoliosis</td>
<td>PLOD1</td>
<td>Lysyl hydroxylase 1</td>
<td>AR</td>
</tr>
<tr>
<td>Arthrochalasis</td>
<td>COL1A1, COL1A2</td>
<td>Type I procollagen (processing defect)</td>
<td>AD</td>
</tr>
<tr>
<td>Dermatosparaxis</td>
<td>ADAMTS2</td>
<td>Procollagen I N-proteinase</td>
<td>AR</td>
</tr>
</tbody>
</table>

*Beighton et al AJMG 1998*
The 2017 International Classification of the EDS

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Abbr</th>
<th>IP</th>
<th>Genetic basis</th>
<th>Protein</th>
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</thead>
<tbody>
<tr>
<td>1 Classical</td>
<td>cEDS</td>
<td>AD</td>
<td>COL5A1, COL5A2</td>
<td>Collagen V</td>
</tr>
<tr>
<td>2 Classical-like</td>
<td>cLED</td>
<td>AR</td>
<td>COL1A1 (p.R312C)</td>
<td>Collagen I</td>
</tr>
<tr>
<td>Cardiac-Valvular</td>
<td>cvEDS</td>
<td>AR</td>
<td>COL1A2</td>
<td>Tenascin X</td>
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<tr>
<td>3 Vascular</td>
<td>vEDS</td>
<td>AD</td>
<td>COL3A1</td>
<td>Type I collagen (total absence alpha2 chain)</td>
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<tr>
<td>4 Hypermobile</td>
<td>hEDS</td>
<td>AD</td>
<td>unknown</td>
<td>unknown</td>
</tr>
<tr>
<td>5 Arthrochalasia</td>
<td>aEDS</td>
<td>AD</td>
<td>COL1A1, COL1A2</td>
<td>Collagen I</td>
</tr>
<tr>
<td>7 Dermatosparaxis</td>
<td>dEDS</td>
<td>AR</td>
<td>ADMTS2</td>
<td>ADAMTS-2</td>
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</table>
# The 2017 International Classification of the EDS

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Abbr</th>
<th>IP</th>
<th>Genetic basis</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>8  Kyphoscoliotic</td>
<td>kEDS</td>
<td>AR</td>
<td>PLOD1</td>
<td>LH1</td>
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<tr>
<td>9  Brittle cornea syndrome</td>
<td>BCS</td>
<td>AR</td>
<td>ZNF469, PRDM5</td>
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<td>10 Spondylodysplastic</td>
<td>spEDS</td>
<td>AR</td>
<td>B4GALT7</td>
<td>β4GalT7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B3GALT6</td>
<td>β3GalT6</td>
</tr>
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<td></td>
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<td>SLC39A13</td>
<td>ZIP13</td>
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<td>11 Musculocontractural</td>
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<td>AR</td>
<td>CHST14</td>
<td>D4ST1</td>
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<td>DSE</td>
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<tr>
<td>12 Myopathic</td>
<td>mEDS</td>
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<td>COL12A1</td>
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<tr>
<td>13 Periodontal</td>
<td>pEDS</td>
<td>AD</td>
<td>C1R, C1S</td>
<td>C1r, C1s</td>
</tr>
</tbody>
</table>
EDS: Musculoskeletal system

- Generalized joint hypermobility
- Recurrent joint dislocations
- Muscle hypotonia and delayed gross motor development
- Congenital or progressive (kypho)scoliosis
- Broad and flat feet
- Club feet
- Congenital hip dislocation
- Broad hands, severe hyperlaxity of fingers with swan-neck deformities
- Chronic widespread pain
- Predisposition to early-onset osteoarthritis?
Joint hypermobility: assessment with Beighton score

Beighton score ≥ 5/9 indicates generalized joint hyperlaxity

<table>
<thead>
<tr>
<th>SCORE</th>
<th>Left</th>
<th>Right</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Can you put your hands flat on the floor with your knees straight?</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2. Can you bend your elbow backwards?</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3. Can you bend your knee backwards?</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>4. Can you bend your thumb back on to the front of your forearm?</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>5. Can you bend your little finger up at 90° (right angles) to the back of your hand?</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Total: 9
Joint Hypermobility: symptoms and complaints

- Recurrent joints dislocations
- Recurrent soft tissue injuries, such as sprains and sports injuries
- Clicking joints
- Reduced joint proprioception
- Pain and stiffness in the joints and muscles
- Back pain, neck pain
- Fatigue
Joint Hypermobility/Instability in children

- May be apparent in infancy
  - “Floppy baby”
- JH greatest at this age but may be difficult to discern from age peers
- Recurrent elbow dislocations
- Normal to mild gross motor delay
EDS and Development

Mild to moderate motor delay

Developmental Coordination Disorder

• Clumsiness
• Problems with gross motor coordination (for example: jumping, hopping, or standing on one foot)
• Problems with visual or fine motor coordination (for example: writing, using scissors, tying shoelaces, or tapping one finger to another)
Congenital hip dyslocation/dysplasia

- (congenital) bilateral/unilateral hip dislocation

- Developmental dysplasia of the hip
  - As many as half of children with DDH have signs of hypermobility
Hands and Feet

- Hands/fingers
  - Arachnodactyly
  - Adducted thumbs
  - Hyperlaxity with swan neck deformities
  - Wrinkled palms

- Clubfoot
Handwriting

- Altered grip
- Poor endurance
- Pain
- Avoidance behavior
  - May be misinterpreted as:
    - ADHD
    - Defiant behavior
    - Laziness
Flat Feet

• May or may not have foot pain

• Will c/o leg pain or excessive tiredness when standing or walking for prolonged periods

• Plantar fasciitis or Achilles tendonitis

• May lead to bunions and osteoarthritis of the big toe

• May cause chronic low back pain
Spine

- Congenital scoliosis may not be present at birth but often develops in the first year
- Spondylolysis/listhesis
- Early degenerative changes
Pain

- Musculoskeletal
  - Joint hypermobility related to shoulder, elbows, hands/fingers, knee, and ankle/foot pain
- Chronic
- Headaches
- Abdominal pain
- Complex regional pain?
Gait

- Dynamic imbalance with decreased trunk and head stability
- Fall risk
- Unsteady/clumsy
General characteristics of EDS: Skin

- Soft, velvety, doughy texture
- Skin splitting upon minor trauma
- Skin hyperextensibility
- Slow wound healing, cigarette paper scars
- Easy bruising
- Hemosiderotic plaques on shins
- Molluscoid pseudotumors
- Subcutaneous spheroids
- Other: inguinal/umbilical hernia
General characteristics of EDS: Skin

- Hypermobile EDS
- Classical EDS

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General features
EDS: Other signs of connective tissue fragility

- Arterial dissection/rupture (esp when medium-sized vessels, and when no pre-existing aneurysm)
- Rupture of GI tract, gravid uterus, liver, spleen
- Repetitive pneumothorax
- Bladder diverticulae
- Carotid-cavernous fistula
- Early-onset, severe varicose veins
- Inguinal hernia, umbilical hernia etc
- Microcornea, scleral/corneal fragility, keratoconus, keratoglobus
- Pelvic organ prolapses
Associated non-skeletal manifestations

- Digestive System problems: gastroparesis, constipation, irritable bowel syndrome, ...
- Dysautonomia: palpitations, sweating, dizziness, postural orthostatic hypotension syndrome, POTS, ...
- Urogenital: Stress incontinence
- Chronic fatigue
- Mast Cell Activation Syndrome
- Arnold Chiari
Diagnostic strategies

- History taking
- Clinical investigation
- Family history

→ Clinical diagnosis or suspicion of EDS (+/- subtype)
Additional clinical investigations

- Cardiovascular imaging
  - Cardiac ultrasound (trans-thoracic or esophageal)
  - CT or MR Angiogram of cerebral, neck, thoracic, abdominal and pelvic arteries
- Skeletal X-ray survey
- Bone densitometry
- Ophthalmologic evaluation
- Audiologic evaluation
- Dental evaluation
Thank you for your attention!