EHLERS-DANLOS SYNDROME:
THE CHALLENGES IN DIAGNOSIS AND MANAGEMENT OF AN INCREASINGLY DIAGNOSED BUT POORLY UNDERSTOOD GENETIC DISORDER

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January 16, 2014

Objectives

- Name the components of connective tissue and clinical features of connective tissue disorders in general
- List the subtypes and characteristic features of Ehlers-Danlos Syndrome (EDS)
- Learn about what is currently known about the systemic manifestations and management of EDS
- Learn about the implications of genetic diagnosis on the treatment, management, and family planning for patients with EDS

Connective Tissue Disorders

- >100 different disorders described
- Result in abnormalities in the extracellular matrix

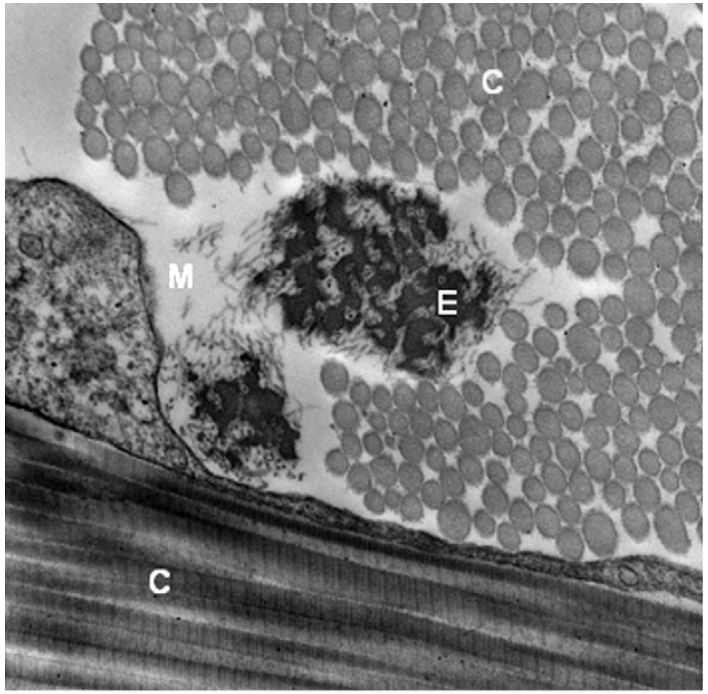
Shared features include

- Increased flexibility of the skin and joints
- Variable degrees of tissue fragility: Easy bruising and poor wound healing
- Depending on the function of protein involved in disorder: heart and blood vessel involvement, eye manifestations, other

Extracellular matrix composition

An interlocking "mesh" of fibrous proteins and glycosaminoglycans

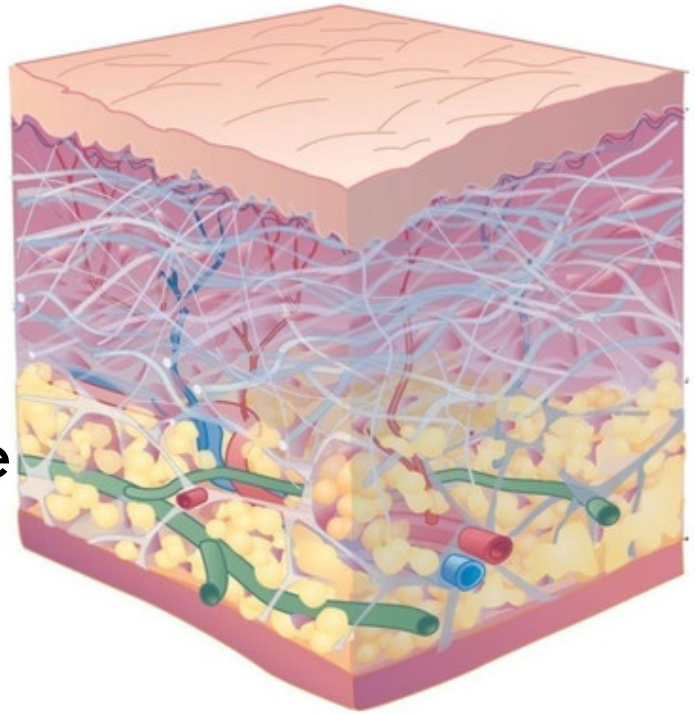
- Collagen Fibers: Ehlers-Danlos syndrome, Osteogenesis imperfecta
- Elastic Fibers and Microfibrils: Cutis Laxa, Marfan, Loetz-Dietz syndromes



Journal of Pediatric Surgery (2009) 44, 1423–1431

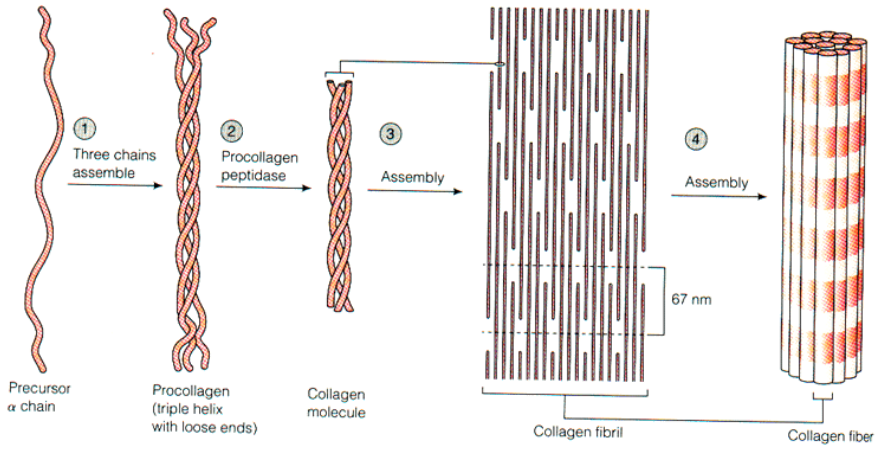
The Extracellular Matrix (ECM)

- Provides structural and biochemical support to cells
- Proteins in ECM are involved in directing the formation of elastic fibers, and linkage of elastic fibers to other components of the ECM (and to cells)
- Proteins are involved in the anchoring of a variety of cells



Collagens in the ECM

- Conserved family of proteins that form trimeric molecules



- Collagen type I: Expressed in bone, skin and sclerae
- Collagen type III: Expressed in vascular and hollow organ walls.
- Collagen type V: Expressed in ECM and cornea

The Ehlers-Danlos Syndromes

- Heterogeneous group of disorders of connective tissue
- Common features include:
  - Articular hypermobility
  - Skin hyperextensibility
  - Tissue fragility
- Nosology developed in 1988, revised in 1998. Aims:
  - Allow diagnostic uniformity
  - Describe the natural history
  - Facilitate Management and Genetic Counselling
  - Identify areas of research

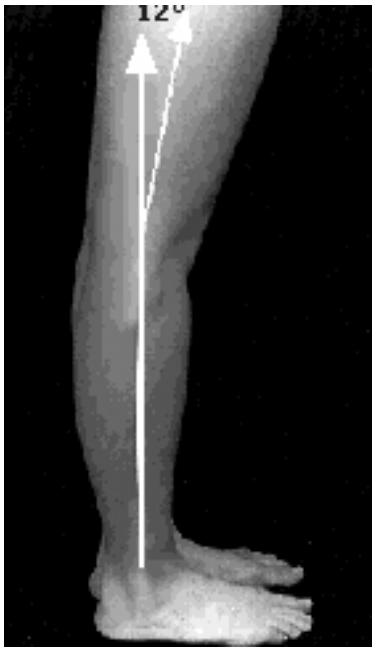
EDS Classification

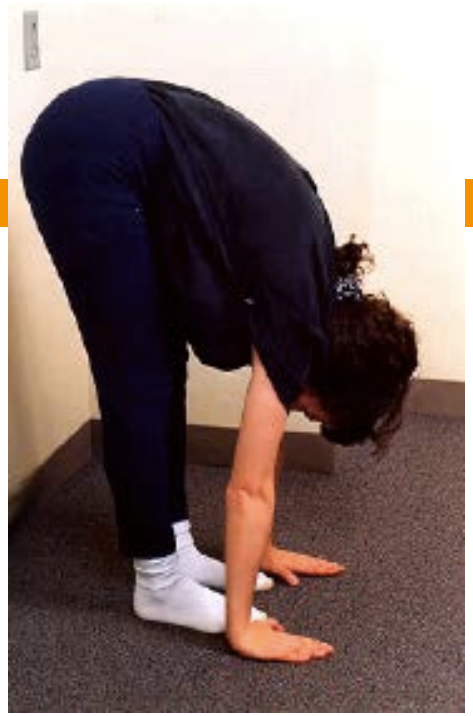
- Six major types
  - Types 1 and 2: Classical
  - Type III: Hypermobility
  - Type IV: Vascular: severe vascular events, poor prognosis
  - Type VI: Kyphoscoliotic type: severe hypotonia at birth, scoliosis at birth, scleral fragility- globe rupture
  - Type VII: Arthrochalasia: congenital hip dislocation, severe hypermobility
  - Type VIIC: Dermatopspraraxis type: severe skin fragility

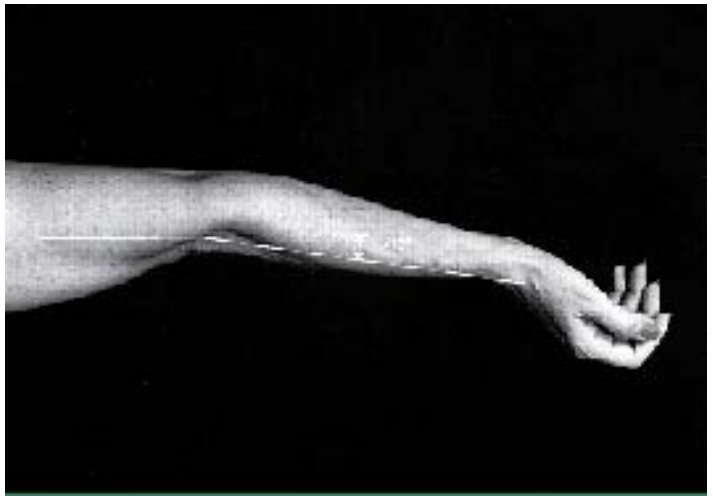
Beighton score for hypermobility (1983)

- Passive dorsiflexion of 5th digit (2)
- Passive apposition of thumbs to flexor aspect of forearm (2)
- Hyperextension of elbows (>10 degrees) (2)
- Hyperextension of the knees (>10 degrees) (2)
- Forward flexion of the trunk-knees extended-palm on floor (1)
- Hypermobility = 5/9 or greater

Hypermobility of joints

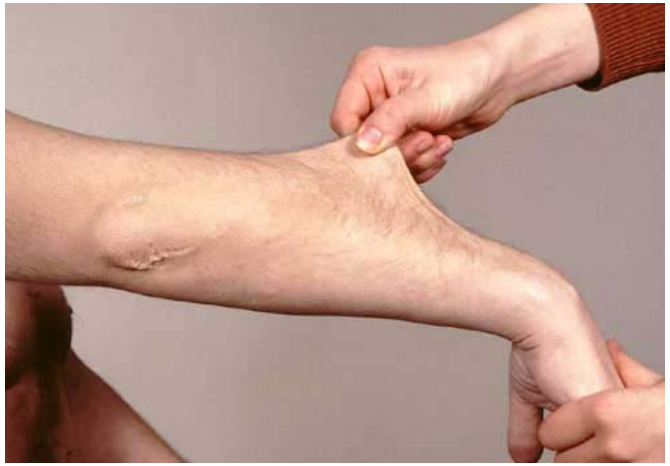




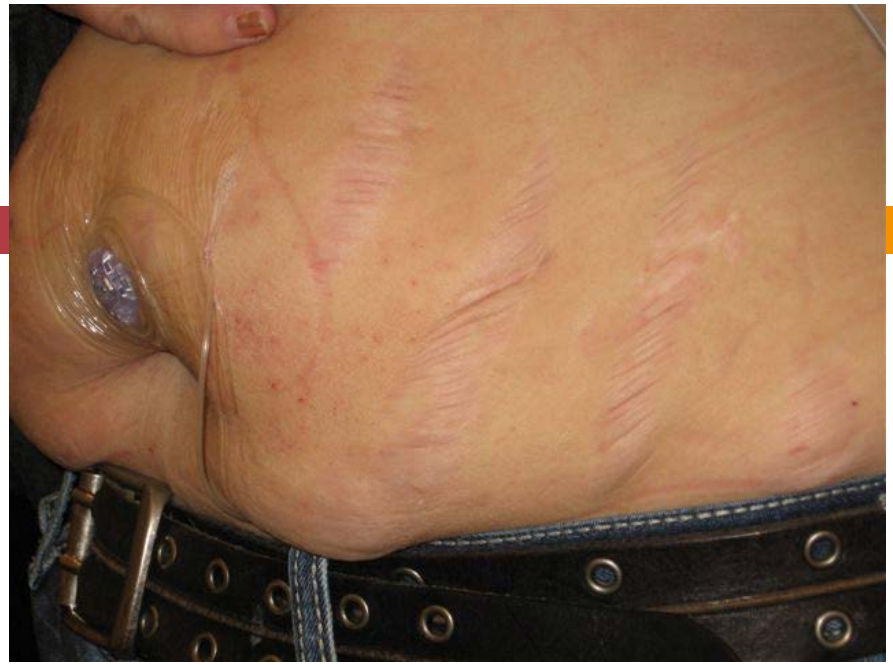


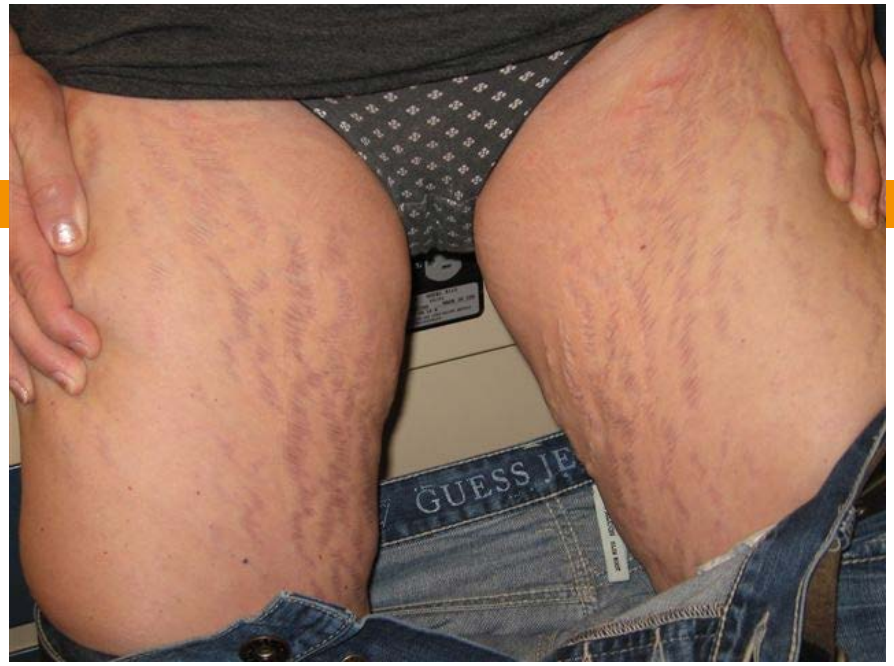
Classical Type (EDS I and II)

- Major Criteria
  - Skin hyperextensibility
  - Widened atrophic scars (tissue fragility)
  - Joint hypermobility



- Autosomal Dominant inheritance
  - Molecular genetics: Heterogeneous
    - Mutations in COL5A1 and COL5A2 (50-90%)
    - Null mutations in COL1A2
    - Homozygous mutations of Tenascin X (TNXB)
    - Skin biopsy: Cauliflower deformity of collagen fibers .

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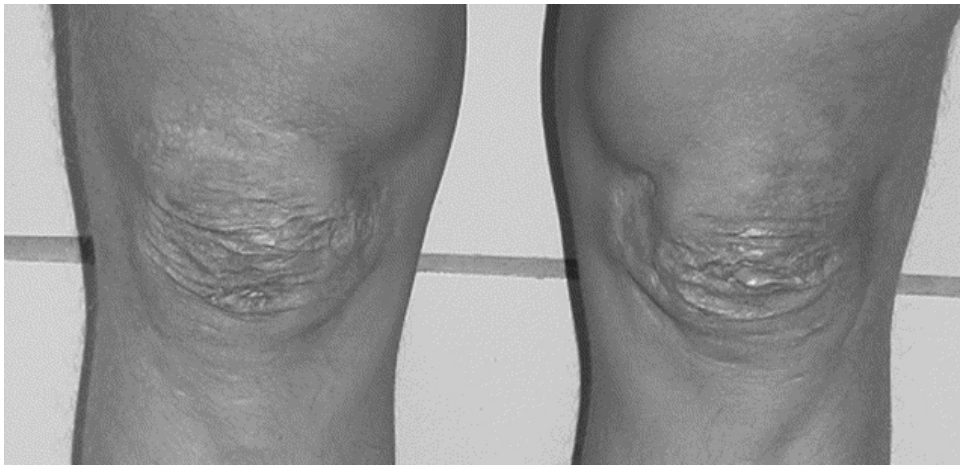
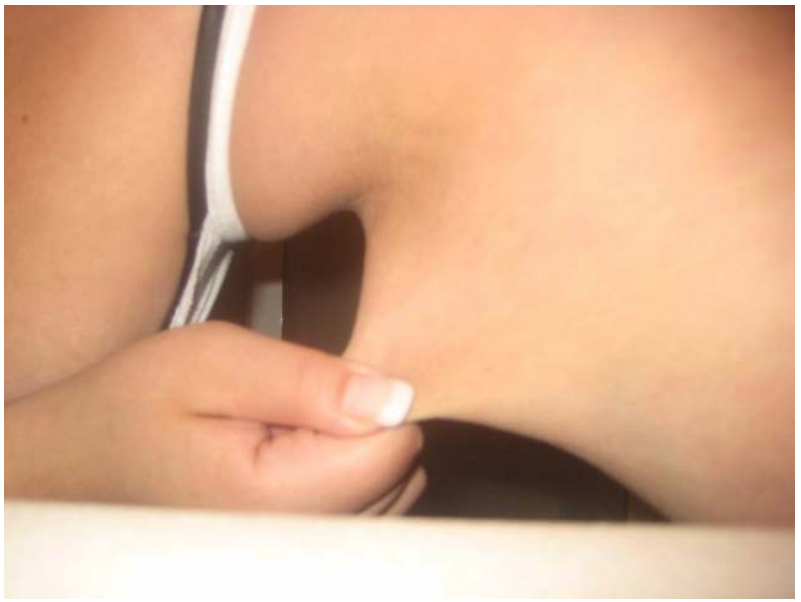




Hypermobility Type (EDS III)

- Major Criteria
  - Generalized joint hypermobility
  - Significant pain syndrome
  - Less skin involvement (lax but not as overtly fragile)
- Autosomal Dominant inheritance
- Molecular Basis: Mostly unknown
  - Heterozygosity for TNXB null mutations
  - Rarely COL3A1 G637S mutation

Villefranche Criteria (1998)

2 major or 1 major 2 minor (no consensus on minimum criteria)

- Major criteria
  -Beighton Score 5 or greater
  -Skin involvement (hyperextensibilty and/or smooth velvety skin)
- Minor criteria
  -Recurrent Joint Dislocations
  -Chronic joint/limb pain
  -Positive Family history

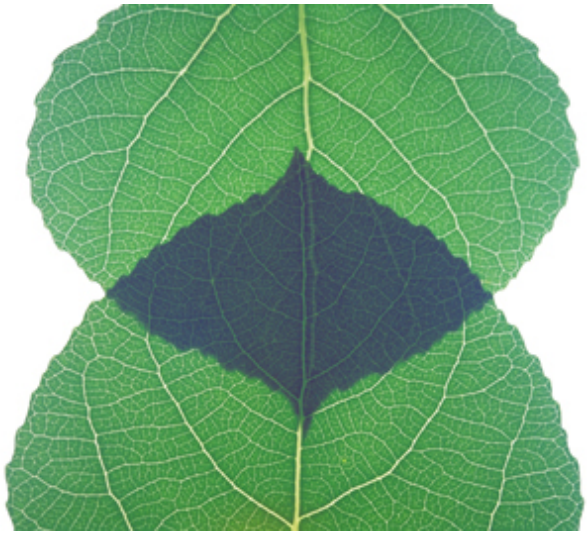
Brighton Criteria (1998): 2 major, 1 major/2 minor, or 4 minor

- MAJOR:
  - A Beighton score of 4/9 or greater (either currently or historically)
  - Arthralgia for longer than 3 months in 4 or more joints
- MINOR:
  - A Beighton score of 1,2, or 3 (if 50+ years old)
  - Arthralgia (>3 months) in one to three joints or back pain (>3 months), spondylosis/listhesis
  - Dislocation/subluxation in more than one joint on more than one occasion
  - Soft tissue rheumatism >3 lesions (epicondylitis, bursitis, tenosynovitis)
  - Marfanoid habitus
  - Abnormal skin: striae, hyperextensibility, thin skin, abn scars
  - Eye signs: drooping eyelids or myopia
  - Varicose veins or hernia or uterine/rectal prolapse

Pitfalls of the Beighton score

- Young children (<5 years of age) tend to be very flexible and therefore difficult to interpret whether flexibility is pathological
- Woman are, on average, more flexible than men
- Older individuals tend to lose flexibily
- Post-surgical or arthritic joints often have reduced range of motion
- Beighton score only looks at laxity at particular joints but misses joints such as the shoulder and hip
- Therefore, a HISTORY of former joint laxity or clinical demonstration of substantial laxity in multiple joints is sometimes accepted in lieu of a positive Beigton score in cases where family history and minor criteria are strongly suggestive

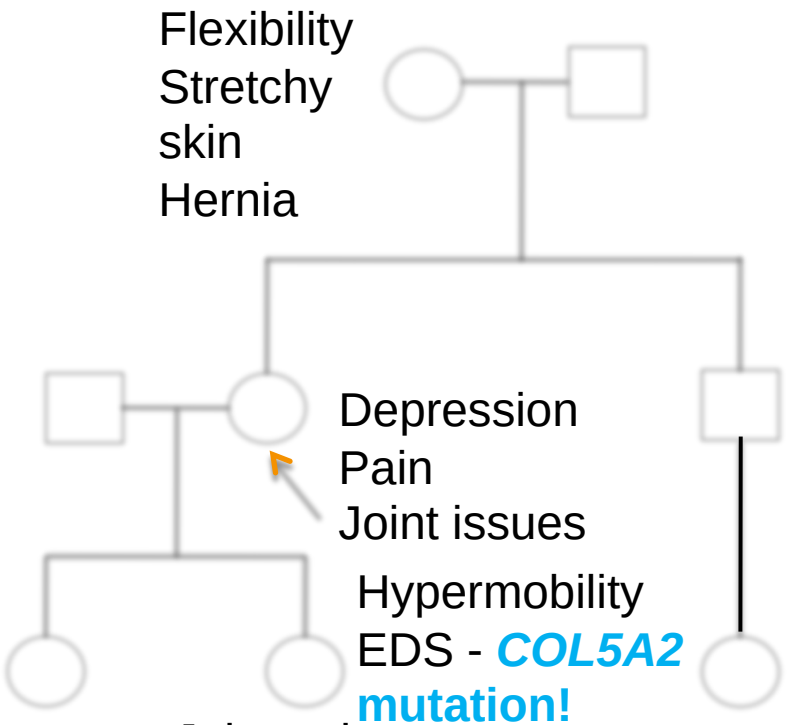
Clinical overlap between classical and hypermobility EDS subtypes



50-year-old woman with history of major depression

- Hospitalization for 2 weeks in past year
- Shoulder dislocation
- Chronic joint and jaw pain
- Scoliosis
- Rectal prolapse
- Irritable bowel
- Examination revealed significant hypermobility in nearly all joints
- COMPLETELY normal skin

Family history



Flexibility
Stretchy skin
Hernia

Depression
Pain
Joint issues

Hypermobility EDS - ***COL5A2*** **mutation!**

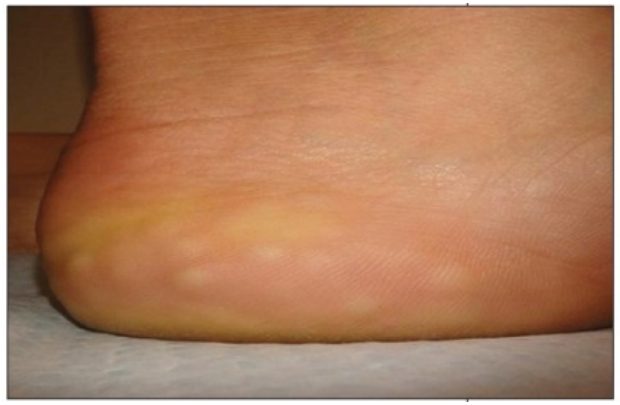
Joint pain

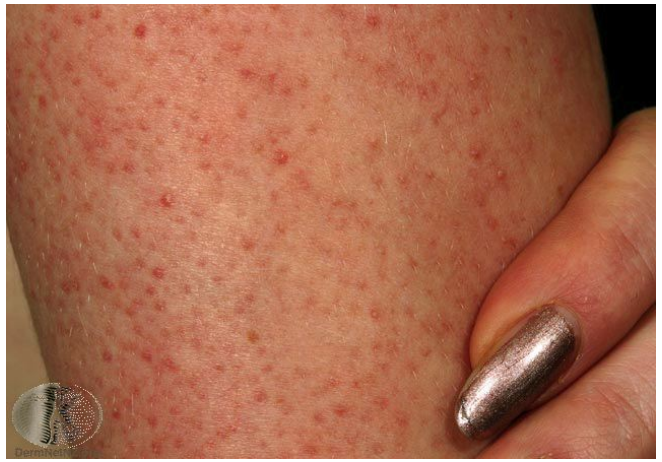
Pain
Joint dislocations
Excessive bruising

Hyperextensible joints and skin
Congenital hip dislocation
Chronic pain
Classic EDS - ***COL5A2*** **mutation**

Skin Findings

- Classical EDS- noted previously
- In both Classical and hypermobile: skin can be velvety or hyperextensible
- Piezogenic papules can be seen on heels- rarely painful
- Keratosis pilaris may be more common than in general population





Musculoskeletal: Joint instability

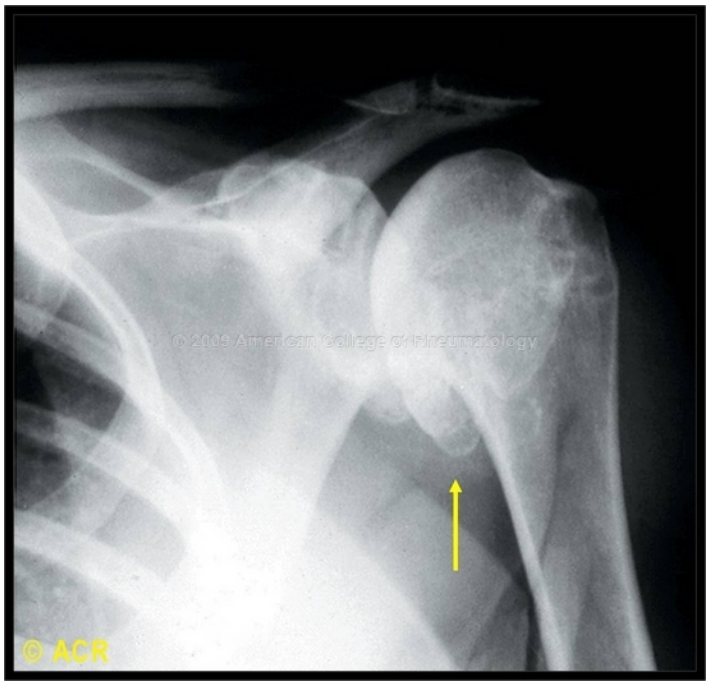
- Subluxations and dislocations with minimal trauma
- All sites: including extremities, vertebral column, costo-vertebral and costo-sternal joints, clavicular articulations, TMJ
- Sprains or twisting of ankles/knees “giving out”
- Iliotibial band syndrome or “snapping hip” perceived as hip instability
- Females worse laxity than males, younger more than older
- Tendinitis and bursitis

Limitation in success of orthopedic surgery in stabilizing EDS joints

- In a cross-sectional study (Arch Phys Med Rehabil p. 1106, Vol 92: 2011) involving 150 patients with EDS with questionnaires, 52% of patients underwent orthopedic surgery to the upper limb, 62% to the lower limb, and 11% to the spine
- Less than a third of patients who underwent surgery were reported to have a favourable outcome
- Possible reasons: tissues may be less robust in EDS thus limiting the success of surgery, problems with wound closure and homeostasis and delayed wound healing
- Other studies have shown similar lower success rates for orthopedic surgery

Musculoskeletal: Osteoarthritis

- Degenerative joint disease occurs at a younger age than in the general population, possibly because of chronic joint instability resulting in increased mechanical stress



Generalized joint laxity including elbow in a 35 year old male
Arrow points to a large osteophyte

Musculoskeletal: Osteoporosis

- Bone mineral density in individuals with EDS may be reduced by up to 0.9 SD compared to healthy controls, even in young adulthood ?Due to reduced mobility vs. innate feature of the disease
- However there are inconclusive follow-up reports: correlation requires more robust studies

Ann Rheum Dis 1998;57:630–633

Osteoporos Int (2000) 11:388–392

Chronic Pain is found in majority of patients with EDS

- The chronic pain is distinct from that associated with acute dislocations and may not relate to specific hyperlax joints
- Variable age of onset (childhood-60s), number of sites, duration, quality, severity and response to therapy
- Severity is often greater than expected based on physical/radiological examinations
- Some correlation with joint instability and sleep impairment (Voermans et al 2010)

Pain in Ehlers-Danlos Syndrome

- Muscular or Myofascial: sometimes palpable spasm, especially in paravertebral musculature
- Neuropathic: NCV often non-diagnostic
- Headache: cervical muscle tension, TMJ dysfunction, stress can contribute
- Abdominal pain
- Pelvic pain
- Complex regional pain syndrome

Forms of Pain in EDS

TABLE II. Forms of Pain in the Joint Hypermobility Syndrome

Pain subtype	Manifestations	Key reference(s)
Nociceptive pain	Soft-tissue injuries	Hudson et al. [1998]
	Dislocations	Voermans et al. [2010a]
	Arthralgias	Sacheti et al. [1997]
	Back pain	Simmonds and Keer [2008], Castori et al. [2011a]
	Myalgias/myofascial pain	De Coster et al. [2005], Castori et al. [2011a]
Neuropathic limb pain	Compression neuropathy	Voermans et al. [2011a]
	Peripheral neuropathy	Voermans et al. [2011a]
Dysfunctional pain	Complex regional pain syndrome type I and II	Stoler and Oaklander [2006]
	Fibromyalgia	Ofluoglu et al. [2006], Sendur et al. [2007]
	(Some) headache disorders	
	Functional abdominal pain	Hakim and Grahame [2004], Castori et al. [2011a]
	Dysmenorrhea	Castori et al. [2012a]
	Vulvodynia/dyspareunia	McIntosh et al. [1995]

Am J Med Genet Part A 161A:2989–3004.

Visceral pain in EDS

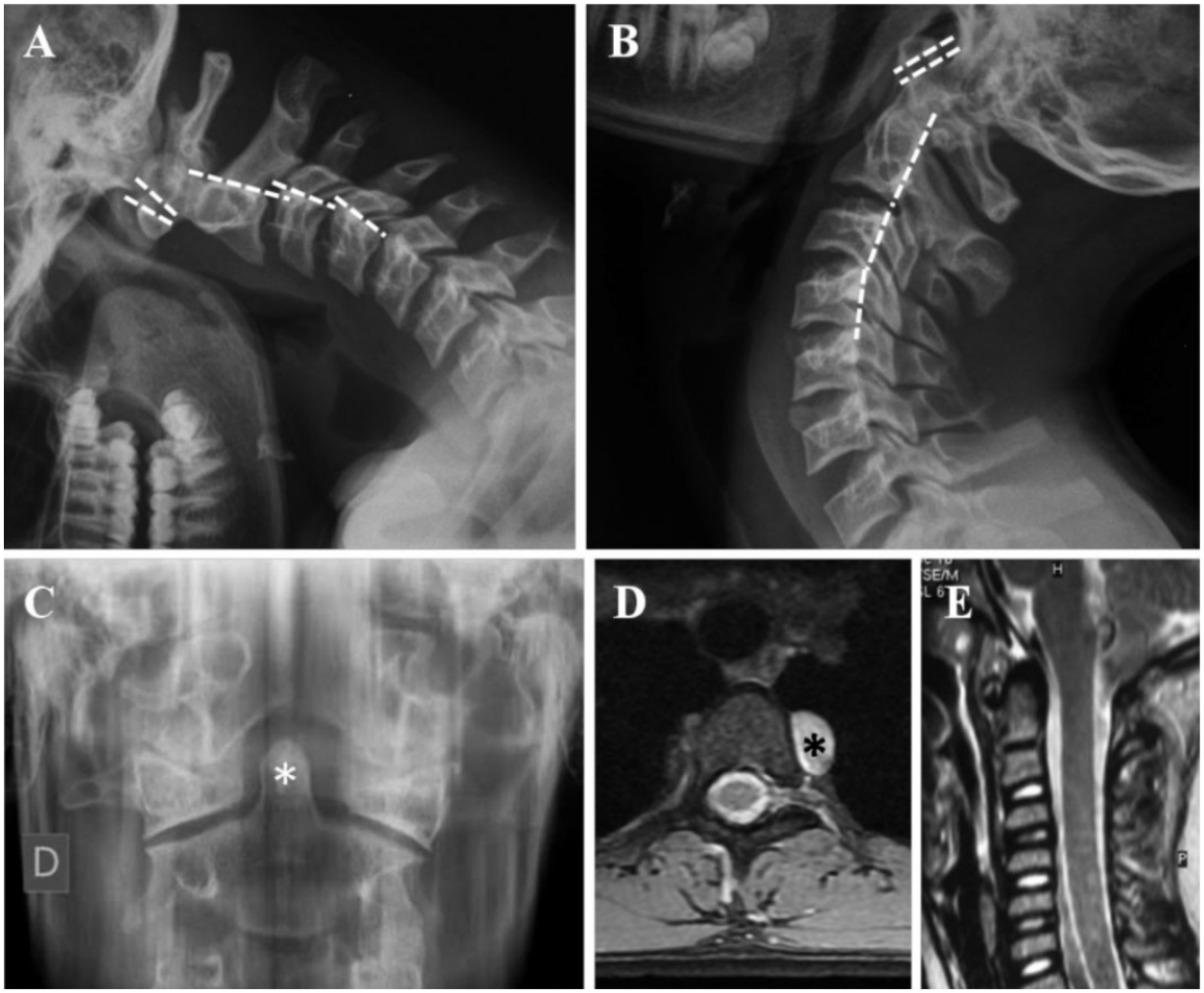
- Visceral pain in EDS is less understood
- Recurrent abdo pain is common in EDS
- Upper abdo pain can be related to heartburn, symptoms of GERD, and bloating gas well as abdominal distension
- Colonic compliance may be responsible for variation in gas and pain sensation in healthy subjects (Iturrino et al, 2012) so it is possible that increased laxity of the colonic wall is a trigger for GI hypersensitivity
- "Irritable bowel syndrome"

Headache

All types of headache have been described in EDS (Sacheti et al., 1997)

- Migraine (most common)
- Muscle
- TMJ dysfunction
- Myofascial pain
- Spontaneous CSF leakage (Schievink et al 2004)
- Chiari malformation (Castori et al 2010a)
- Cervical spine hypermobility/dysfunction predisposing to cervicogenic headache (Hall et al 2008)

Possible radiologic findings in EDS patients with headache



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A/B: Flexed and extension lateral neck spine x rays: instability of cervical vertebrae- Odontoid process of C2 more distant from anterior arch of C1. ? Brainstem intermittent compression

C: Xray of occipitoaxial junction shows right deviation of the odontoid process at rest (white star)

D: Large meningeal cyst (black star) on spine

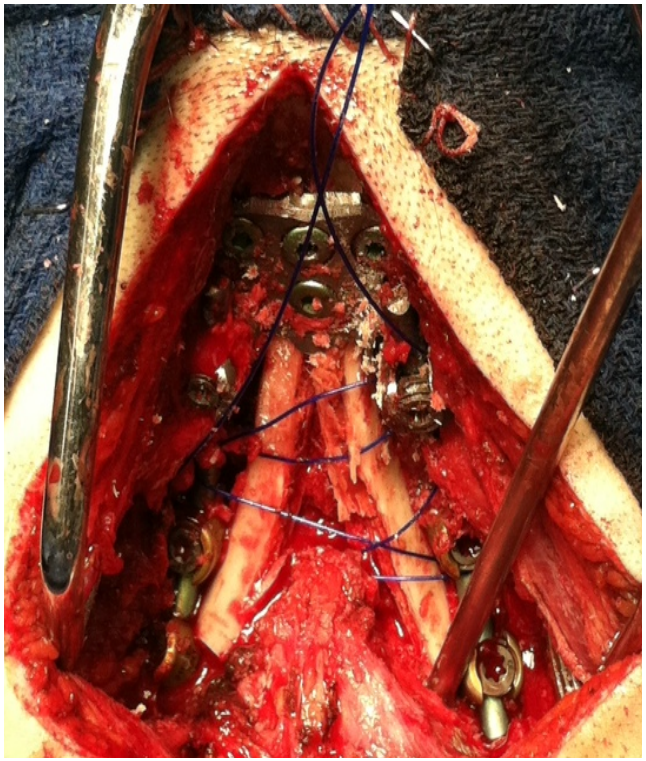
E: Arnold-Chiari malformation

?Cervico-medullary syndrome

- Headache, neck and face pain
- Double vision
- Memory loss
- Speech difficulties
- Dizziness, vertigo
- Hearing loss, tinnitus
- Difficulty swallowing, choking
- Clumsiness, tripping, unsteady gait
- Orthostatic intolerance
- sleep apnea
- Numbness, paresthesias
- Weakness, tremors
- Urinary and GI issues

Craniovertebral fusion surgery

- For Treatment of symptomatic craniocervical instability in EDS



Picture from Dr. Fraser Henderson

Tethered cord syndrome

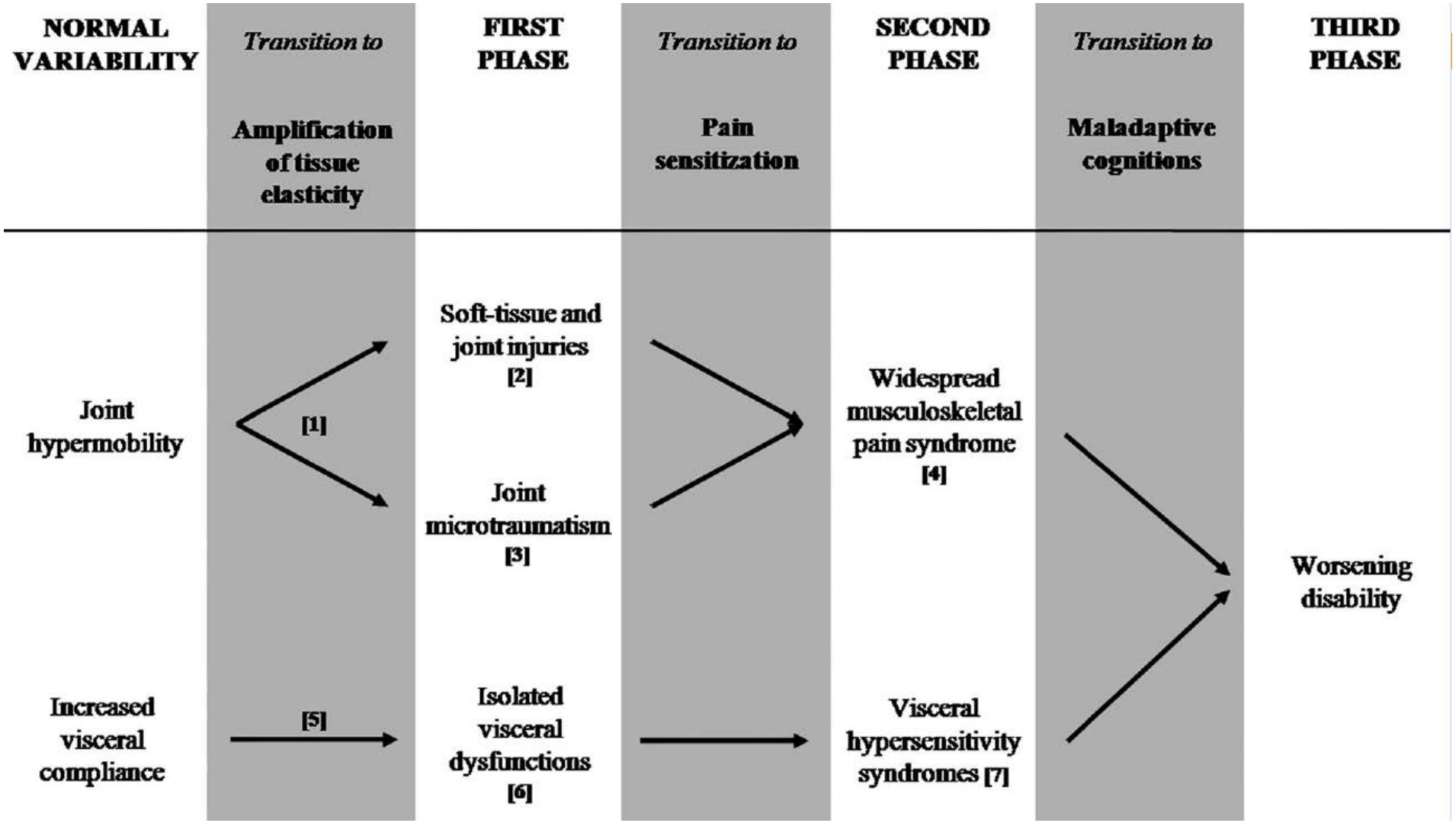
- Stretching of the spinal cord by the filum terminale
- Clinical diagnosis in majority of cases in EDS- radiological diagnosis less often made

Symptoms:

- Weakness of the legs
- Low backpain
- Sensory loss, neurogenic bladder
- Paresthesias, headaches

- Surgery: Filum terminale is clipped "Tethered cord release"

Theory for pathogenesis of pain in EDS



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Maladaptive behaviours in EDS

- **Pain catastrophizing**
- **Fear of Pain**
- **Kinesophobia:** some evidence that it does not correlate with actual intensity of pain or quality of life scores (Biomed Res Int. 2013; Jul 2014) and it has been proposed that it is a major prognostic determinant in EDS (Curr Pain Headache Rep 2009, 13:593-600)

Pain often misdiagnosed

- Fibromyalgia
- Depression
- Hypochondriasis
- Malingering

Chronic fatigue in EDS

- Impact of fatigue can be equal or more severe than pain for patients
- Over 80% of patients with EDS-III are affected by pain
- <u>Possible contributors:</u>
  Muscle weakness/exercise intolerance
  Poor sleep- OSA, Restless legs, pain
  Postural changes- dysautonomia
  Anxiety/Depression
  Excessive use of analgesics

Voermans et al., 2010b

Baseline labs for patients with chronic fatigue and EDS

Investigation

Urinalysis for blood, protein, and glucose
Complete blood count
Erytrocyte sedimentation rate
C reactive protein
Serum urea, creatinine, electrolytes, calcium
Random blood glucose
Creatine kinase
Liver function (PT/INR, aPTT, albumin, direct/indirect billirubin, and transaminases)
Thyroid stimulating hormone, FT3, FT4
Celiac antibody screening (IgG and IgA for AGA, EMA, and anti-tTG)
Serum ferritin (children and young adults only)

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Management of Pain and Fatigue

Management of Pain and Fatigue in The Joint Hypermobility Syndrome (a.k.a. Ehlers–Danlos Syndrome, Hypermobility Type): Principles and Proposal for a Multidisciplinary Approach

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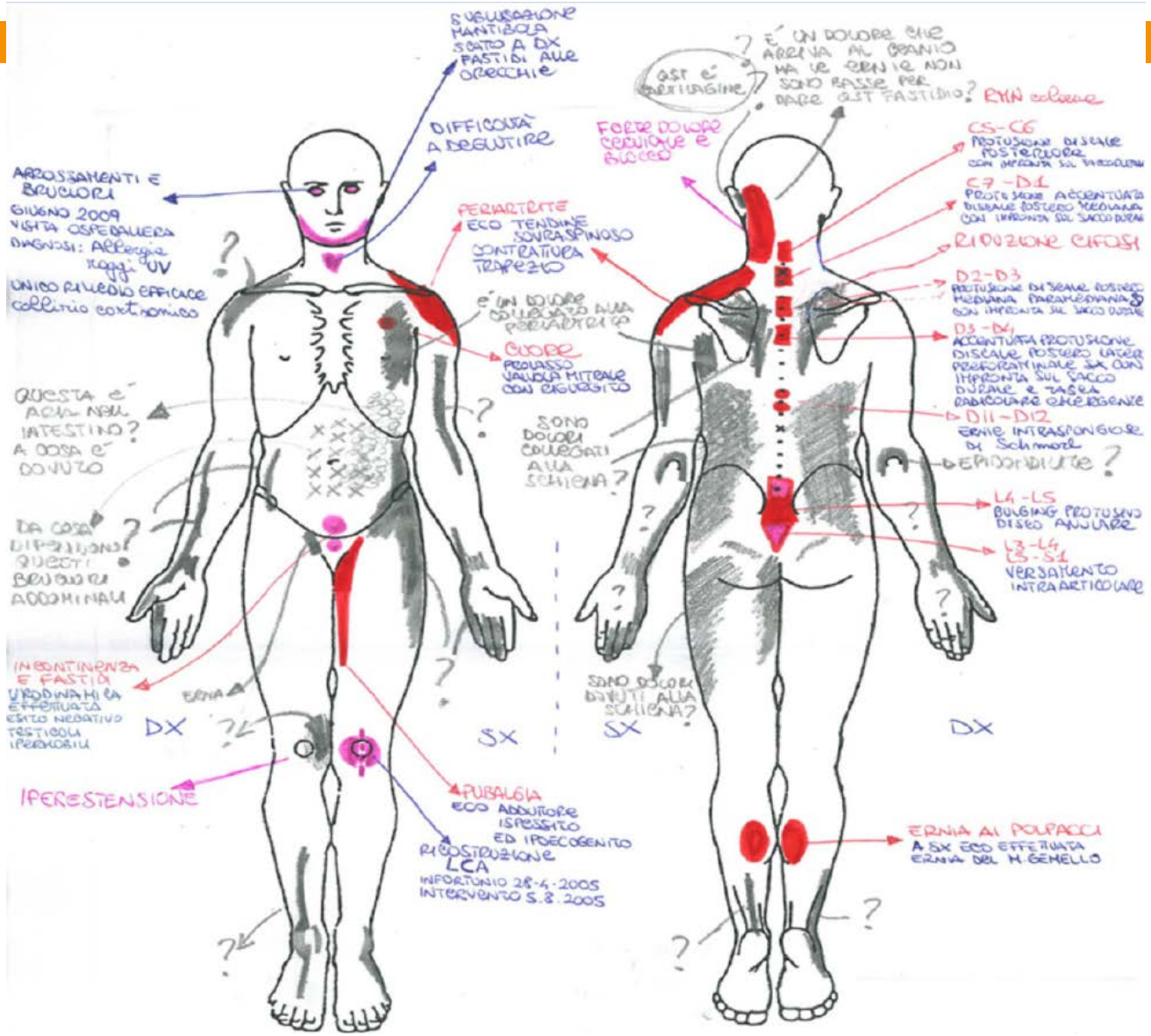
Manuscript Received: 1 December 2011; Manuscript Accepted: 15 April 2012

Am J Med Genet Part A 158A:2055–2070.

Self reported assessment of pain



Lifestyle recommendations for pain/ fatigue in EDS

Promote regular, aerobic fitness
Promote fitness support with strengthening, gentle stretching and proprioception exercises
Promote postural and ergonomic hygiene especially during sleep, at school and workplace
Promote weight control (BMI <25)
Promote daily relaxation activities
Promote lubrication during sexual intercourse (women)
Promote assumption of generous isotonic liquid intake (2–2.5 L/day)
Promote assumption of high salt intake (avoided in case of arterial hypertension)
Promote early treatment of malocclusion
Avoid high impact sports/activities
Avoid low environmental temperatures
Avoid prolonged sitting positions and prolonged recumbency
Avoid sudden head-up postural change
Avoid excessive weight lifting/carrying
Avoid large meals (especially of refined carbohydrates)
Avoid hard foods intake and excessive jaw movements (ice, gums, etc.)
Avoid bladder irritant foods (e.g., coffee and citrus products) intake
Avoid nicotine and alcohol intake

Physical therapy

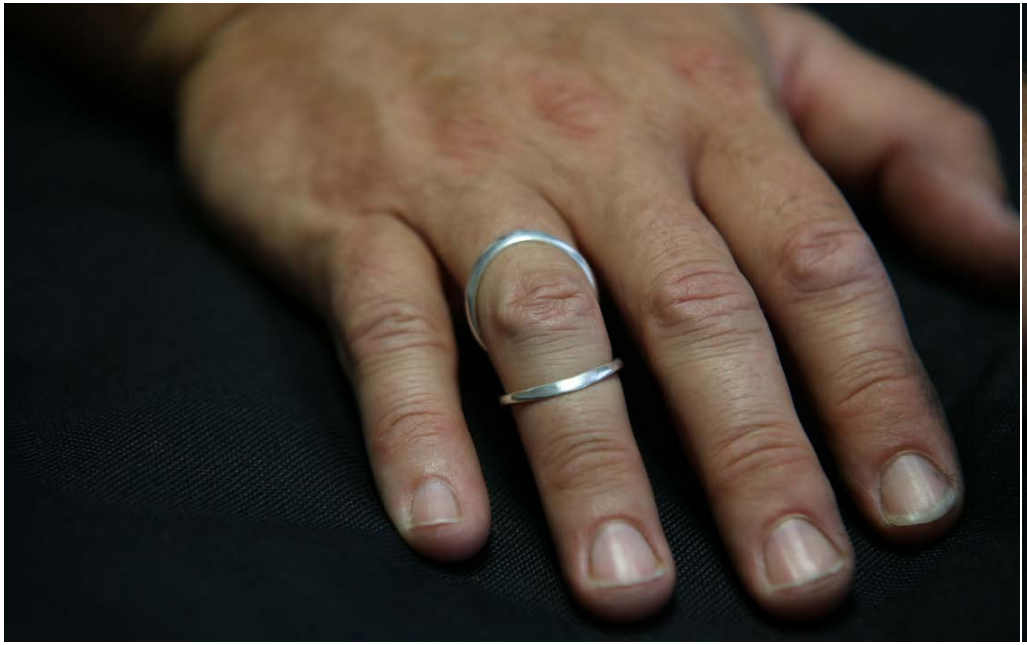
- Myofascial release may be short-term relief, but can be critical in facilitating participation in toning exercises for stabilization of joints
- Massage therapy
- Acupuncture
- Biofeedback/conscious relaxation
- Low-resistance muscle toning exercise program

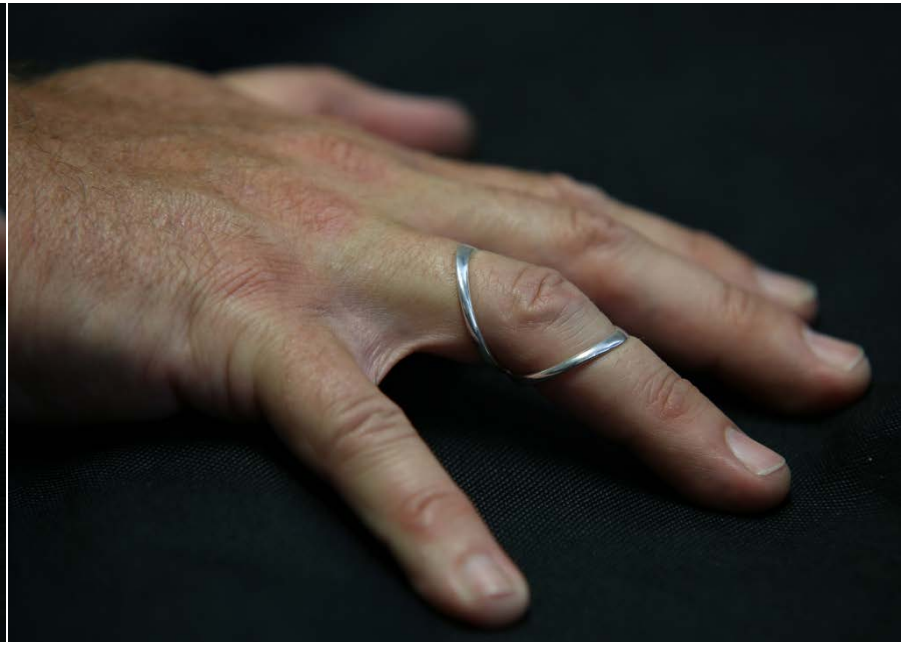
* Ideally to be administered by someone with expertise and who is mindful of hypermobility and injury risk

Assistive devices

- A physiatrist is often helpful in determining which assistive devices are most useful in patients with EDS
- Braces are often used to improve joint stability, best used in ankles and knees, shoulders and hip more problematic
- Ring splints are used to stabilize interphalangeal joints
- A soft neck collar can be helpful for neck pain and headaches
- Wheelchairs, scooters as needed
- Foam mattresses and/or pillows for increased support and improved sleep quality

Digisplint.ca





Pharmacologic interventions- no systematic studies

- Acetominophen 4000 mg in three or four divided doses but can be well tolerated and used as an adjunct
- NSAIDs can be titrated to maximal doses as tolerated by GI symptoms, consider gastroprotection
- COX-2 in cases where bruising is present
- Tramadol may be added to acetominophen plus an NSAID/Cox-2 inhibitor before opoid is considered
- Topical lidocaine as a cream or patch for localized pain
- Skeletal muscle relaxants
- Tricyclic antidpressents for neuropathic pain (with additional benefits of mild sedation if there is a sleep disturbance and mood elevation
- SSRI/SNRI for depression and neuropathic pain
- Anti-epileptic meds for neuropathic pain in addition to TCA or SSRI/SNRI Gabapentin/ Pregabalin (Lyrica)
- Opioids for myofascial and neuropathic pain, should be used in addition to above to minimize opioid requirements- long acting preferred given chronic requirements, short acting for breakthrough
- Supplemental magnesium and potasssium anectodally may be useful

Pyschological dysfunction and emotional issues are common in EDS

- Specific manifestations may include depression, anxiety, affective disorder, low self-confidence, negative thinking, hopelessness, and desperation (Rombaut et al, 2011, Castori et al 2010)
- Affected individuals can feel misunderstood, disbelieved, marginalized, and alone (Baeza Valesco et al): this may be also worsened by distrust of a medical system after a diagnostic odyssey has taken place
- Fatigue and pain can exacerbate psychological dysfunction, and psychological distress can exacerbate pain

Cardiovascular features: Autonomic dysfunction

- Many individuals with EDS report atypical chest pain, palpitations at rest or at exertion, and/or orthostatic intolerance with syncope or near syncope (Mathias et al. 2012)
- Postural orthostatic tachycardia syndrome (POTS) in a proportion of individuals with EDS
- POTS is diagnosed by specialist who specializes in Autonomic disorders- Tilt table testing can reveal POTS

POTS AND EDS TYPE III

- Association could have several possible explanations:
  - Peripheral neuropathy that leads to abnormal sympathetic control and venous blood pooling in the lower limbs
  - Impaired central sympathetic control (Brainstem)
  - Connective tissue laxity allows for a greater than normal degree of vascular distensibility leading to an exaggerated amount of blood pooling

Grubb, Indian Pacing Electrophysiol J. 2010;10:173-8

POTS CLINICAL CRITERIA

- Orthostatic tachycardia during the first 10 min of standing
  - > 30 bpm increase of HR from supine baseline
  - > 40 bpm in 12 to 19 years old
  - Standing HR with average of > 120 bpm
- Symptoms of orthostatic intolerance
- No other acute cause of orthostatic tachycardia

Clin Auto Res 2011; 21:69-72

POTS management

- Salt supplementation considered
- Water supplementation
- Exercise training
- Pharmacologic management

PHARMACOLOGICAL MANAGEMENT

Medication	LE	Medication	LE
• Fludrocortisone	III	• Octreotide	III
• Midodrine	IIb	• Erythropoeitin	III
• Beta-blockers	III	• ddAVP/desmopressin	IV
• Central sympatholytic	III	• SSRIs	IV
• Pyridostigmine	IIb	• Methylphenidate	IV
• Ivabradine	III		

Level of evidence: Ia, systematic review or meta-analysis of RCTs; Ib, at least one RCT; IIa, at least one well-designed controlled study without randomization; IIb, at least one well-designed quasi-experimental study; III, well-designed non-experimental descriptive studies, such as case–control or cohort studies; IV, expert opinion

Europace 2009 11: 18-25

Other cardiovascular features

- Possible aortic dilatation: in up to 1/3 of patients but do not appear to be at risk for dissection
- Mitral valve prolapse: Not typically clinically significant
- Raynaud syndrome and acrocyanosis: may be a manifestation of immune dysfunction

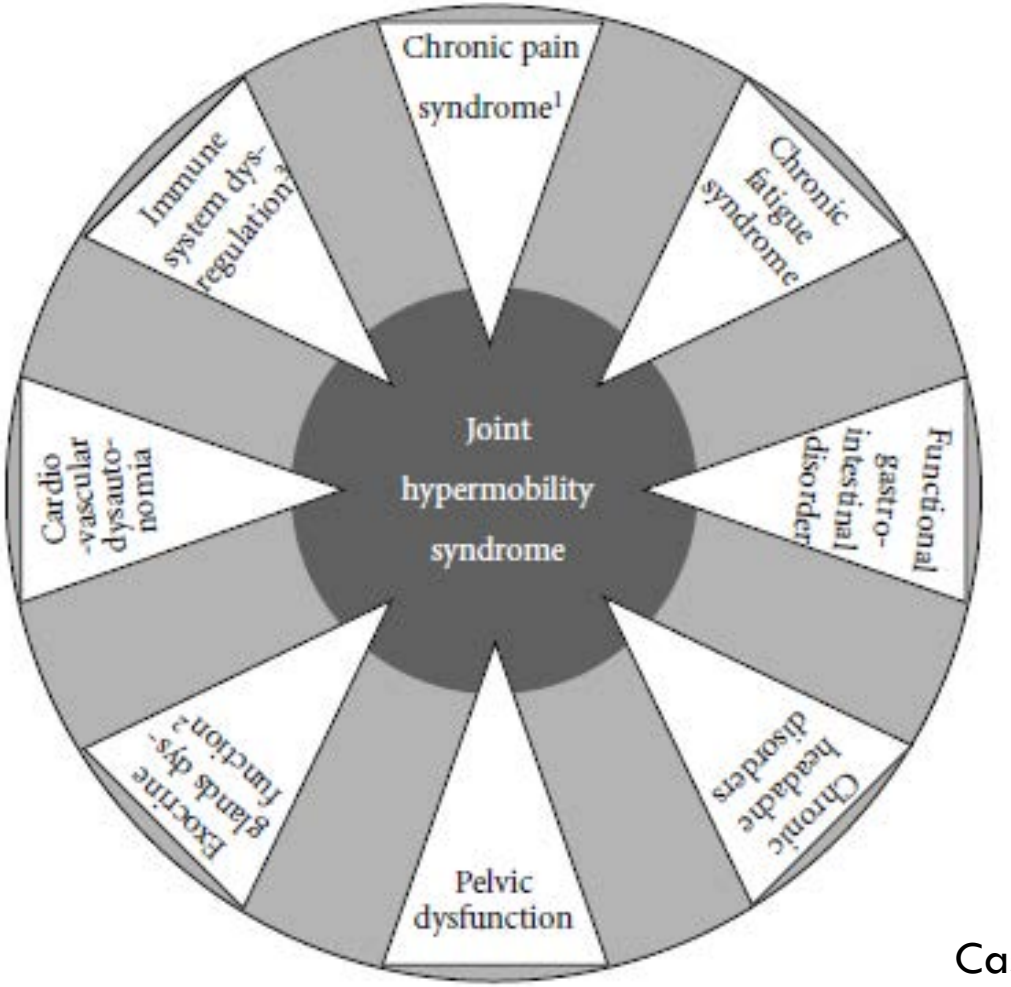
Genetic testing and counselling aspects

- Low yield for genetic testing in Hypermobility type EDS, often genetic testing not completed
- If there are significant skin findings, consider COL5A1 and COL5A2 testing
- Recurrence risk of condition 50%
- Children of our patients are assessed by Sickkids Genetics clinic, first degree relatives can be assessed in appropriate genetics clinics

Possible obstetric complications

- Looser joints and extra weight can exacerbate pain, worsening sleep/GI changes, worsening of features in 40% of women in a recent study (Am J Med Genet Part A 158A:2176-2182)
- Preterm delivery due to premature rupture of membranes has been repeatedly reported in EDS-III and in a recent review, found in approx 10% of pregnancies (ref above)
- Precipitous labour has been seen in 1/3 of cases
- Possible increased chance for postpartum hemorrhage but most not life-threatening
- Pelvic prolapse can be a complication, particularly in patients with episiotomy
- No evidence for C-section over Vaginal delivery- case by case decision making

Need for multidisciplinary care



Castori, ISRN Dermatology, 2012

Support groups

- ILC foundation
  theilcfoundation.org/
- Ehlers-Danlos syndrome
  ehlers-danlossyndromecanada.org/
- Ehlers Danlos National Foundation
  ednf.org
- Others: EDS of Ontario, other EDS support groups, etc.

Questions and challenges

- What should the precise and universally used clinical definition of hypermobility type EDS be?
- What is the molecular basis of hypermobility type EDS? Need proper phenotyping
- Large scale studies are lacking to determine the efficacy of treatments in EDS
- Prospective studies are required to delineate the natural history of the condition for directing evidence based management guidelines
- Education of caregivers about EDS, and rare diseases in general

Possible future plans?

- Retrospective chart review of patients with EDS in Wasser pain clinic
- Patient registry for EDS patients in Ontario
- A tailored rehabilitation program for EDS in Toronto and elsewhere
- Research project looking at molecular pathophysiology of EDS
- Possible research project ?FMRI to look at any cognitive changes in EDS correlating with psychological features
- More studies necessaries to investigate neurosurgical options for patients with EDS

Thank you