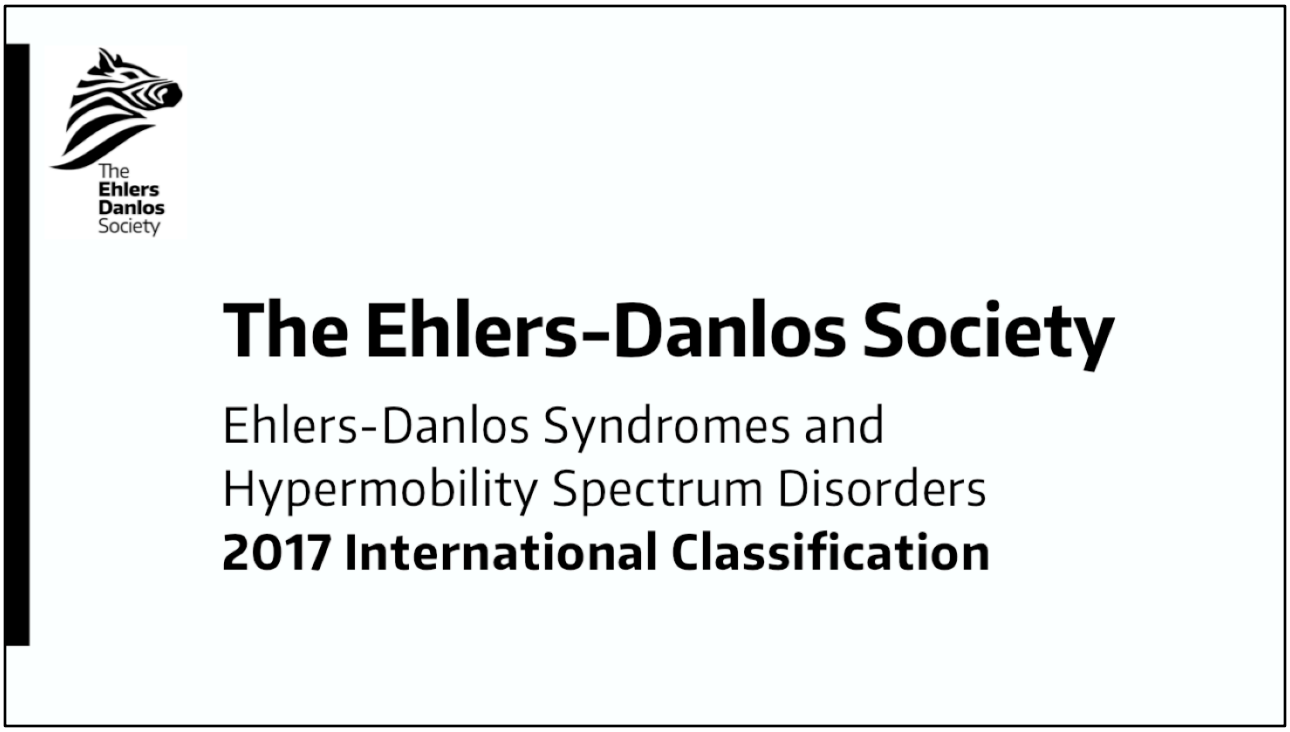
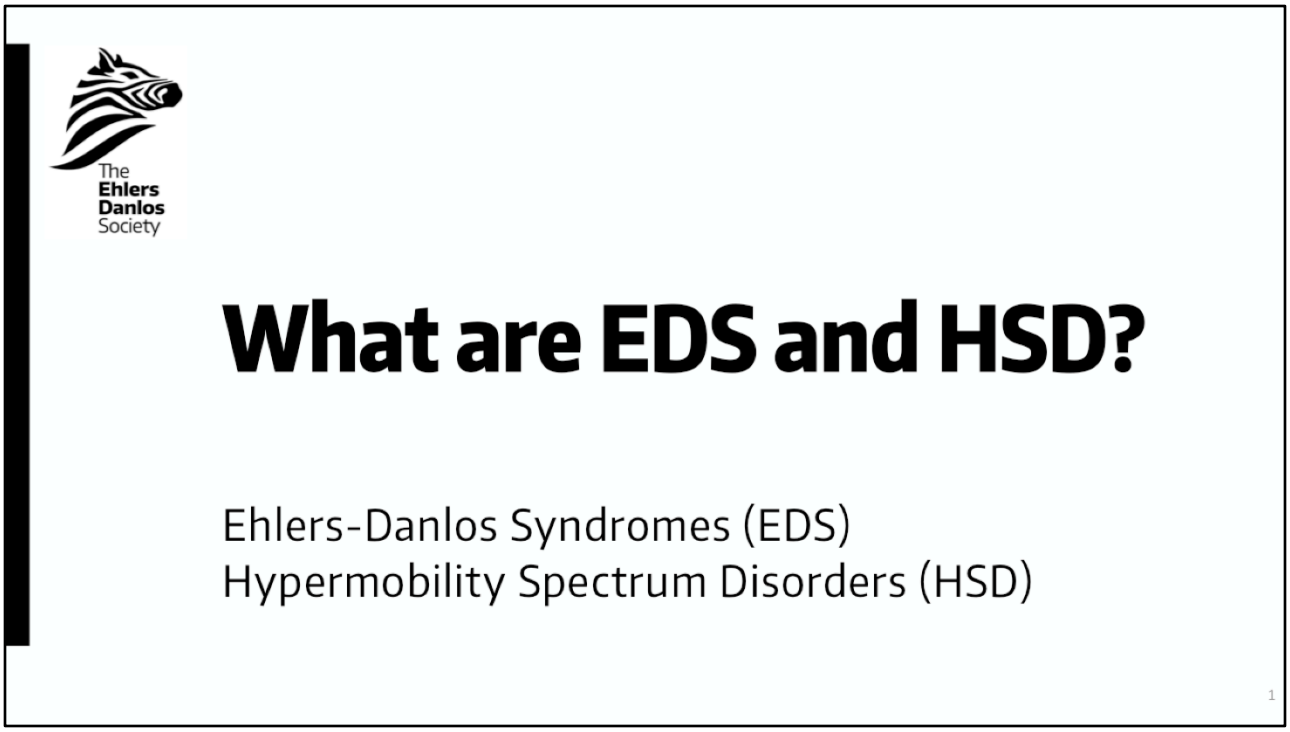


The 2017 Interntional Classification papers were published after peer review on March 17, 2017 in the *American Journal of Human Genetics*. They were written by the International Consortium on Ehlers-Danlos Syndromes and Related Disorders, who conferred by telephone, email, and web meetings over more than two years. The papers were presented in preliminary form at the EDS International Symposium in May, 2016


The
Ehlers
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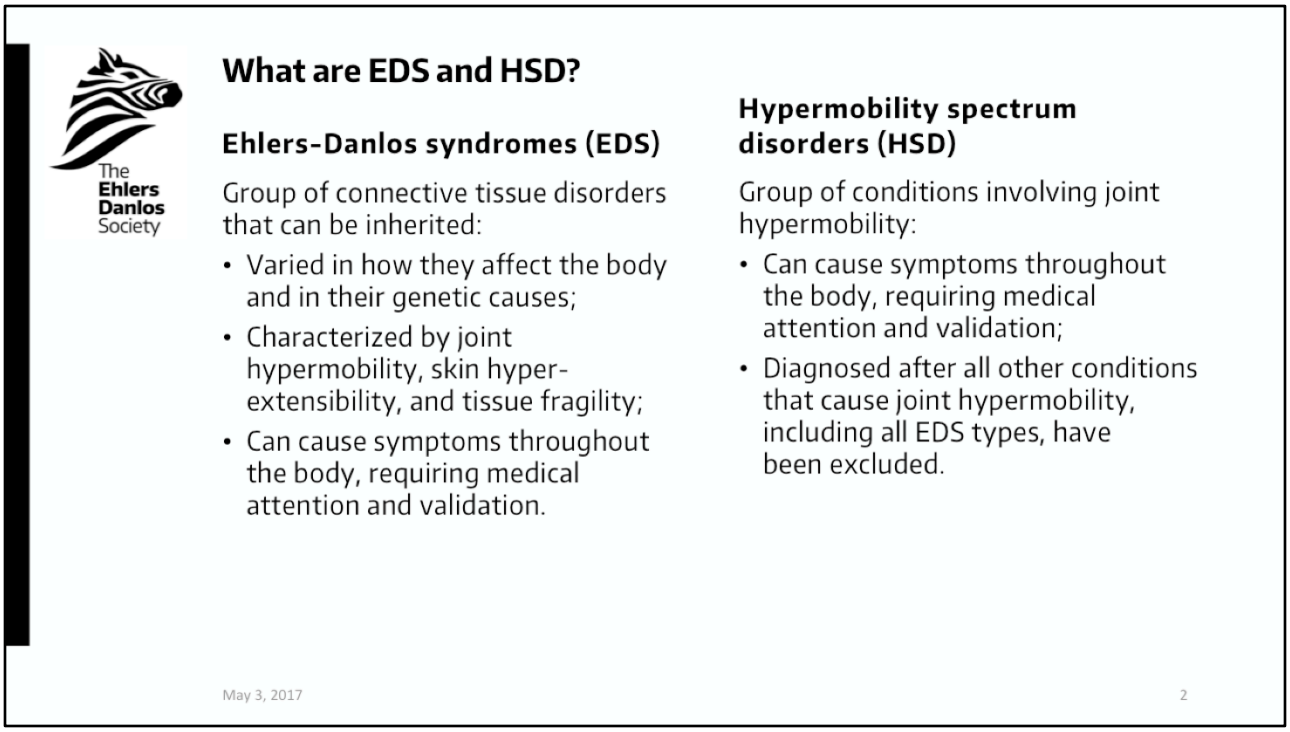
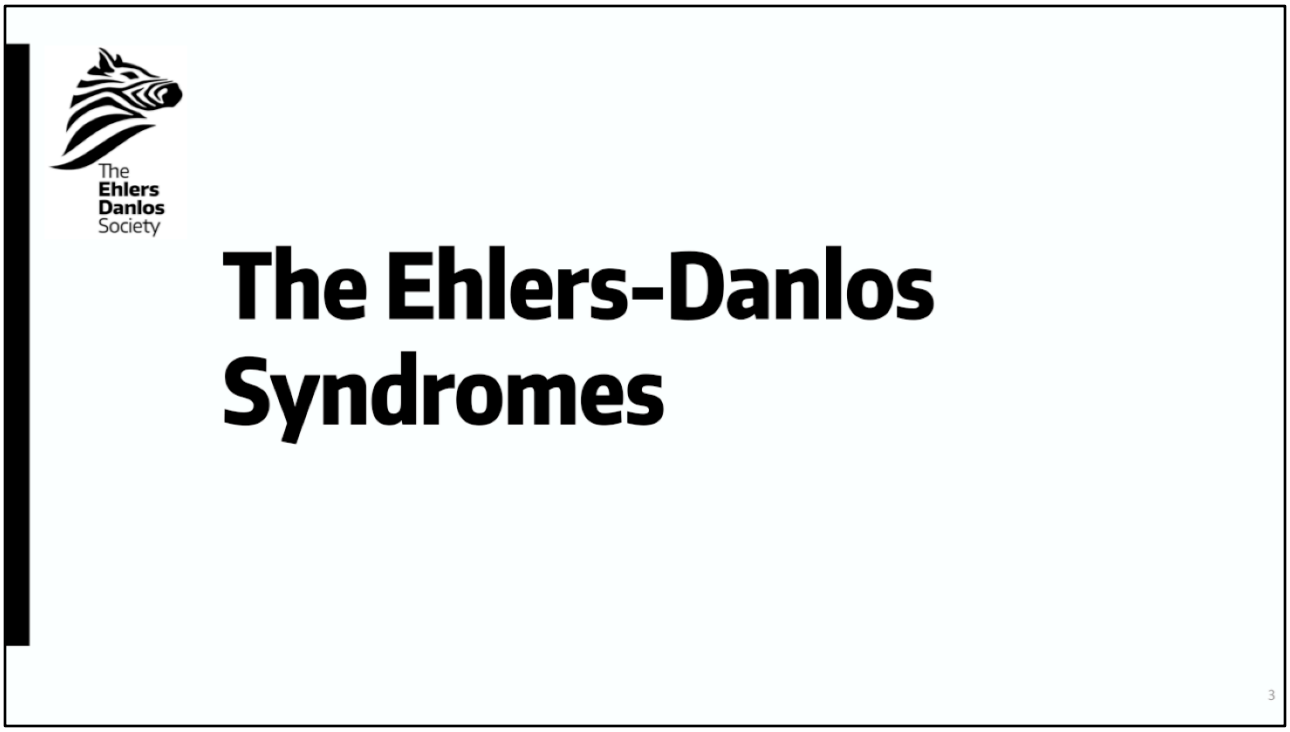
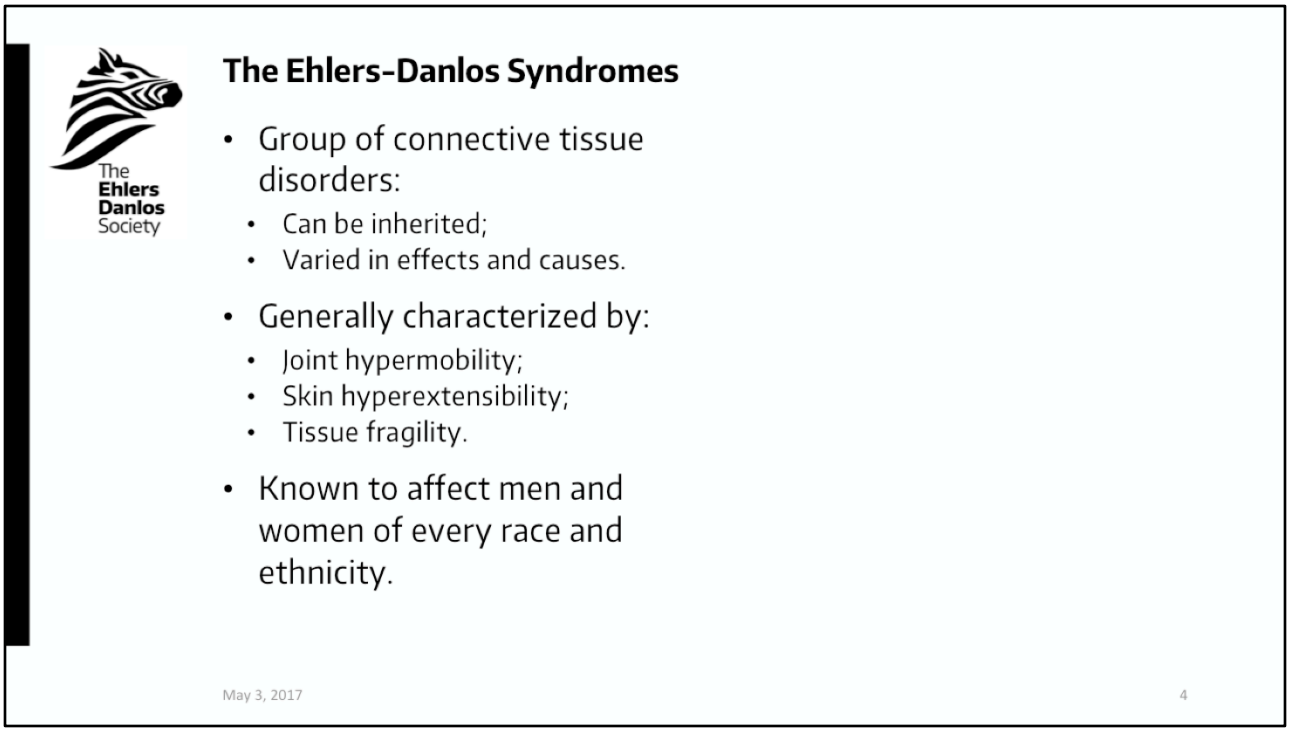
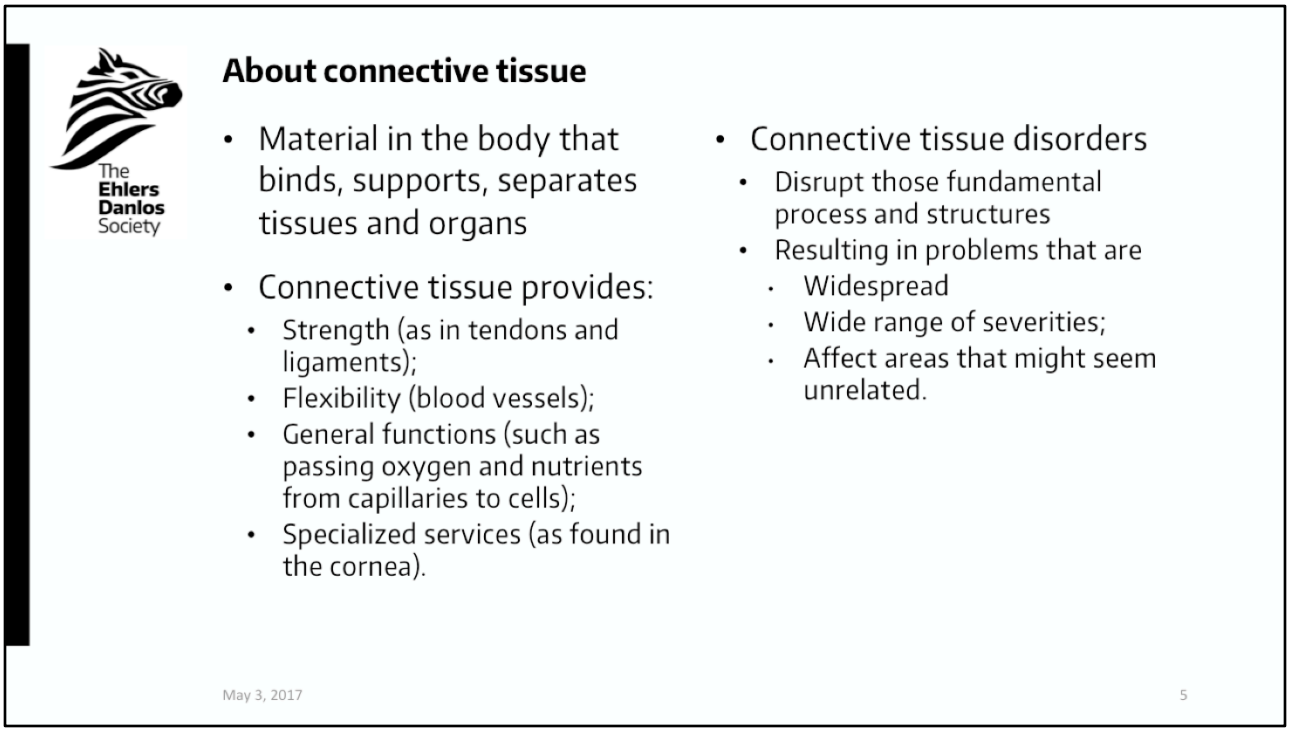
Society
What are EDS and HSD?
Ehlers-Danlos Syndromes (EDS)
Hypermobility Spectrum Disorders (HSD)
1


The Ehlers Danlos Society
What are EDS and HSD?
Ehlers-Danlos syndromes (EDS)
Group of connective tissue disorders that can be inherited:
• Varied in how they affect the body and in their genetic causes;
• Characterized by joint hypermobility, skin hyper-extensibility, and tissue fragility;
• Can cause symptoms throughout the body, requiring medical attention and validation.
Hypermobility spectrum disorders (HSD)
Group of conditions involving joint hypermobility:
• Can cause symptoms throughout the body, requiring medical attention and validation;
• Diagnosed after all other conditions that cause joint hypermobility, including all EDS types, have been excluded.
May 3, 2017
2

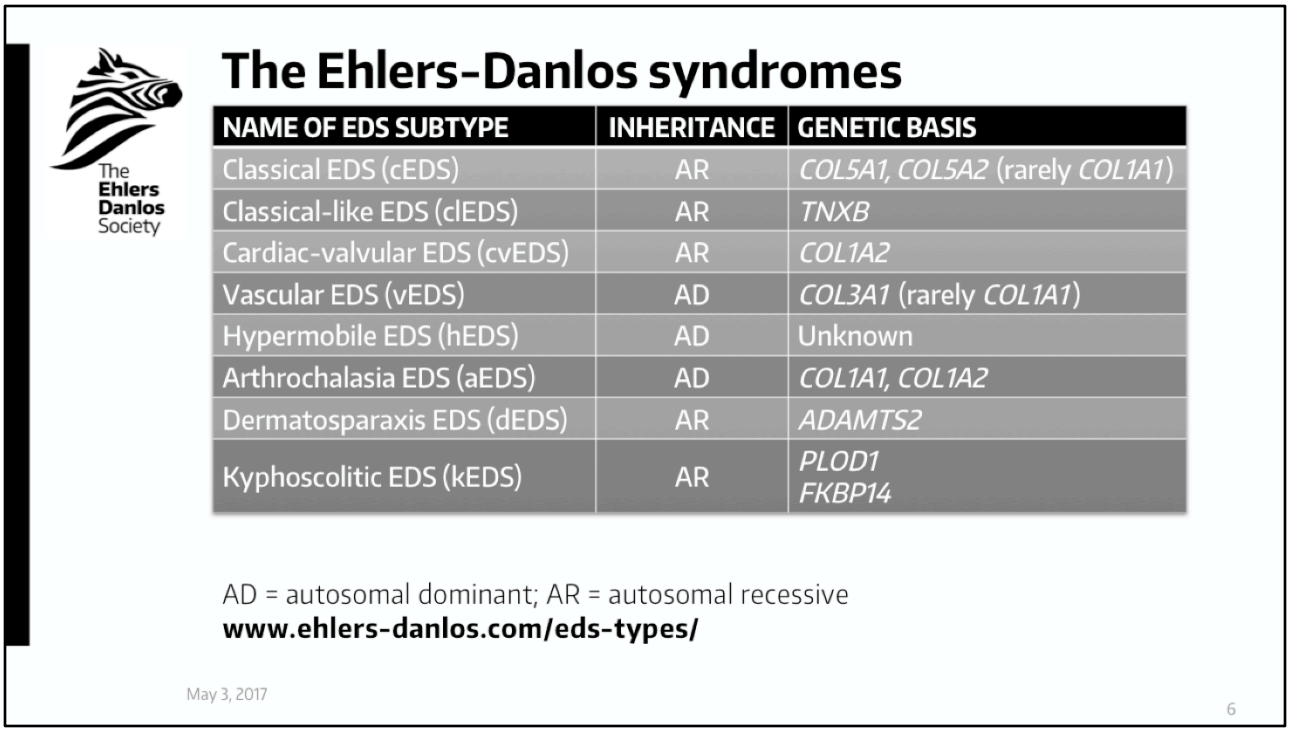

The
Ehlers
Danlos
Society
The Ehlers-Danlos Syndromes
3



The Ehlers-Danlos syndromes are a group of connective tissue disorders that can be inherited and are varied, both in how they affect the body and in their genetic causes. They are generally characterized by joint hypermobility (joints that stretch further than normal), skin hyperextensibility (skin that can be stretched further than normal), and tissue fragility. EDS are known to affect men and women of every race and ethnicity.



Connective tissue is the material in the body that binds together, supports, and separates different tissues and organs. Found between other tissues everywhere in the body, it provides strength and flexibility, and helps perform general functions as well as specialized services. Connective tissue disorders disrupt these most fundamental processes and structures of the body, so resulting problems can be widespread, in a wide range of severities, and affect areas that might seem to be otherwise unrelated.



The Ehlers-Danlos syndromes are currently classified into thirteen subtypes. Each EDS subtype has a set of clinical criteria that help guide diagnosis; a patient's physical signs and symptoms will be matched up to the major and minor criteria to identify the subtype that is the most complete fit.

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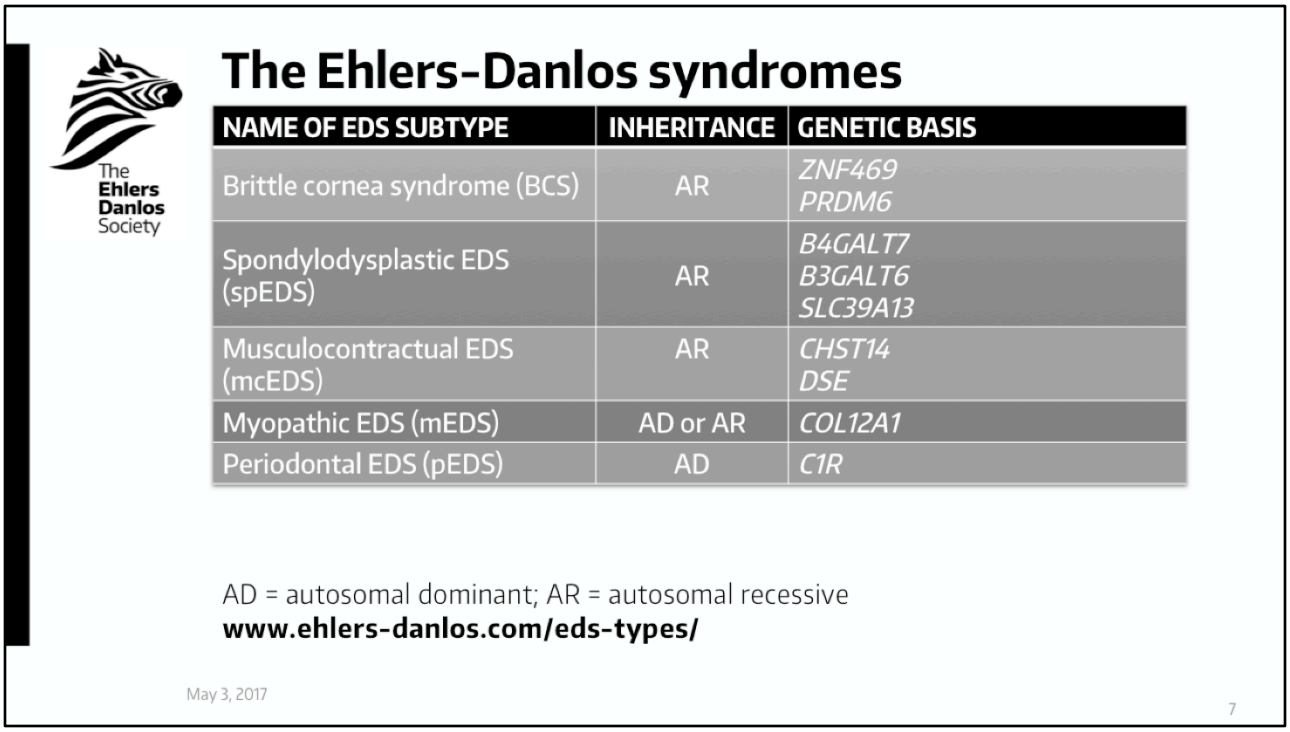
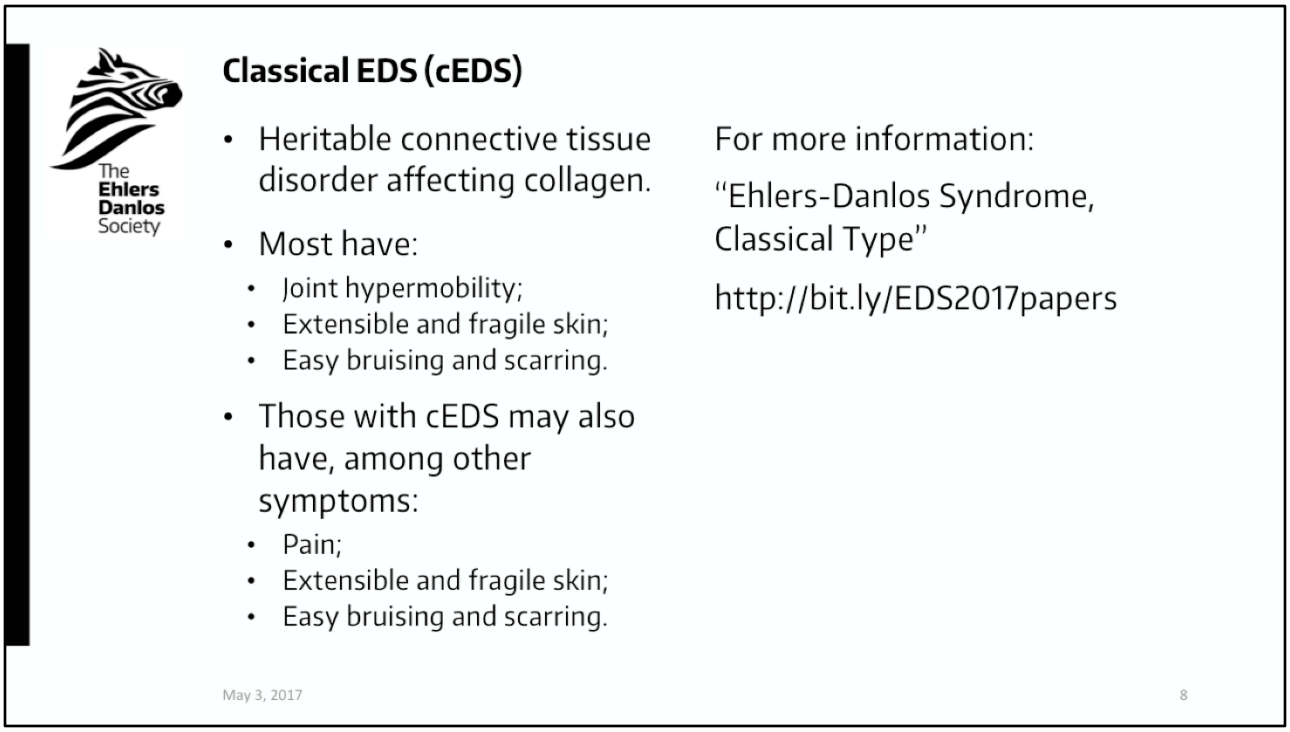
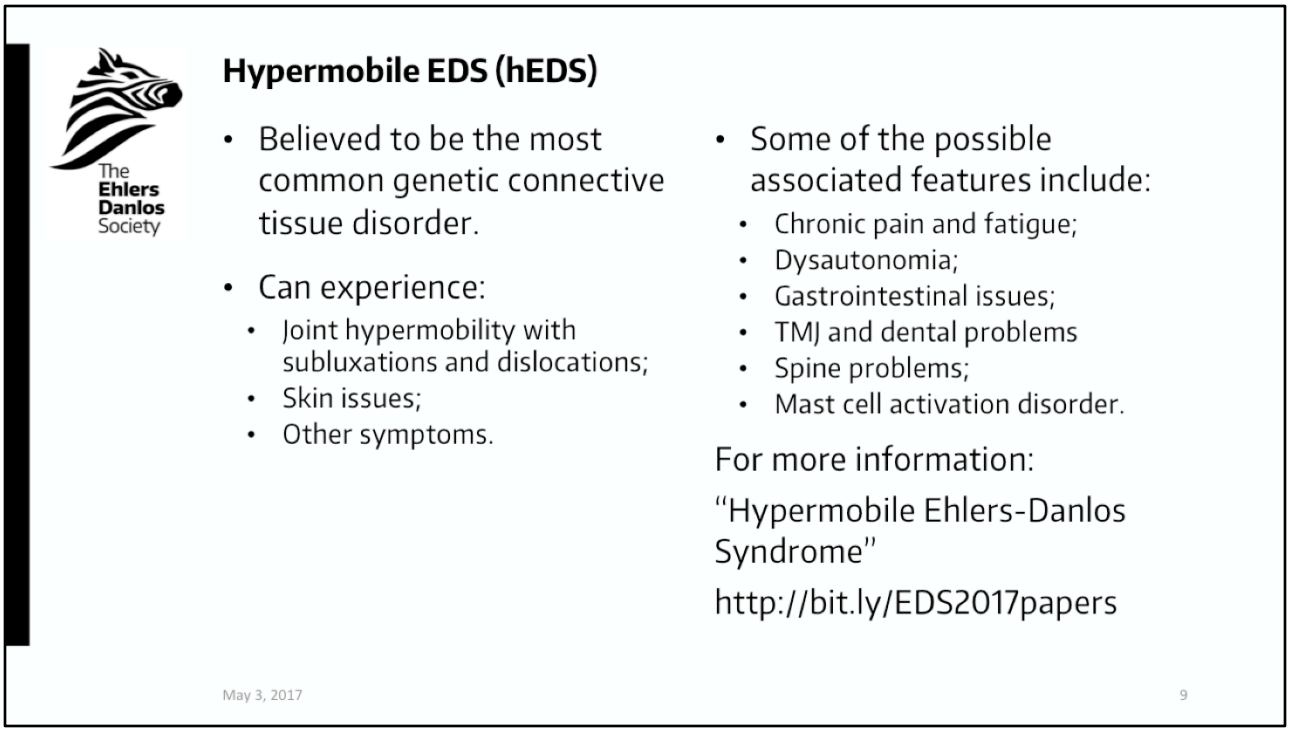
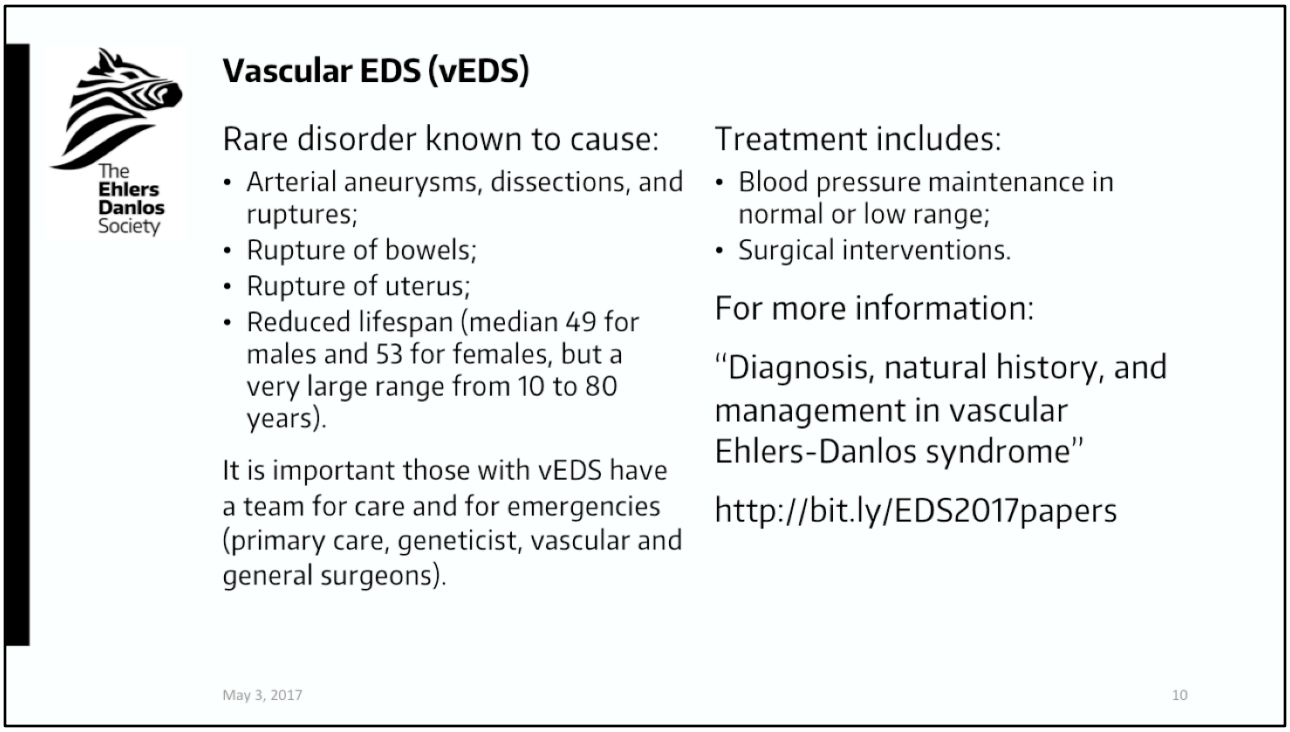

The Ehlers Danlos Society
The Ehlers-Danlos syndromes
NAME OF EDS SUBTYPE
INHERITANCE
GENETIC BASIS
Brittle cornea syndrome (BCS)
AR
ZNF469
PRDM6
Spondylodysplastic EDS (spEDS)
AR
B4GALT7
B3GALT6
SLC39A13
Musculocontractual EDS (mcEDS)
AR
CHST14
DSE
Myopathic EDS (mEDS)
AD or AR
COL12A1
Periodontal EDS (pEDS)
AD
C1R
AD = autosomal dominant; AR = autosomal recessive
www.ehlers-danlos.com/eds-types/
May 3, 2017
7



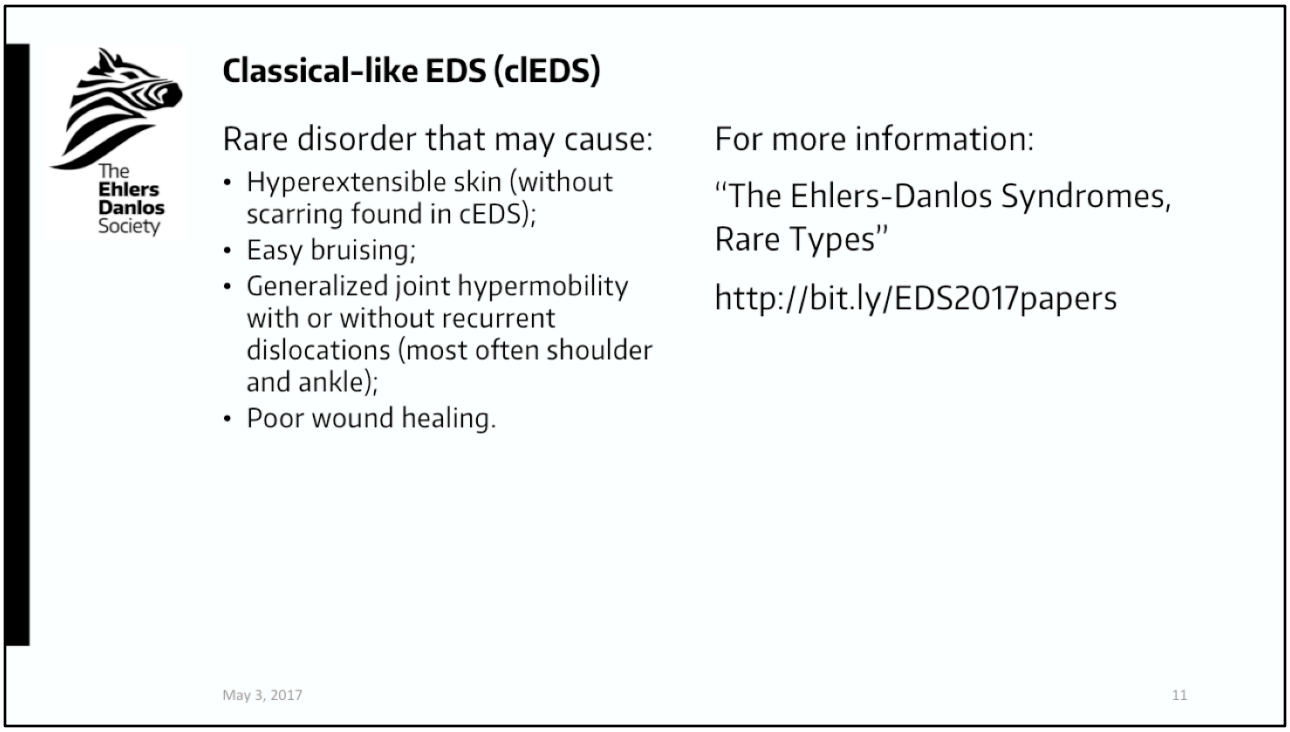
Classical EDS can be painful and disabling. It affects skin, wound healing, and joints. The effects often worsen over time as hypermobile joints can be unstable, causing painful dislocations, subluxations, arthritis, bursitis, tendonitis, and other musculoskeletal problems. Hyperextensible skin is easily torn and doesn't repair itself well, causing pain and disfiguring scarring.



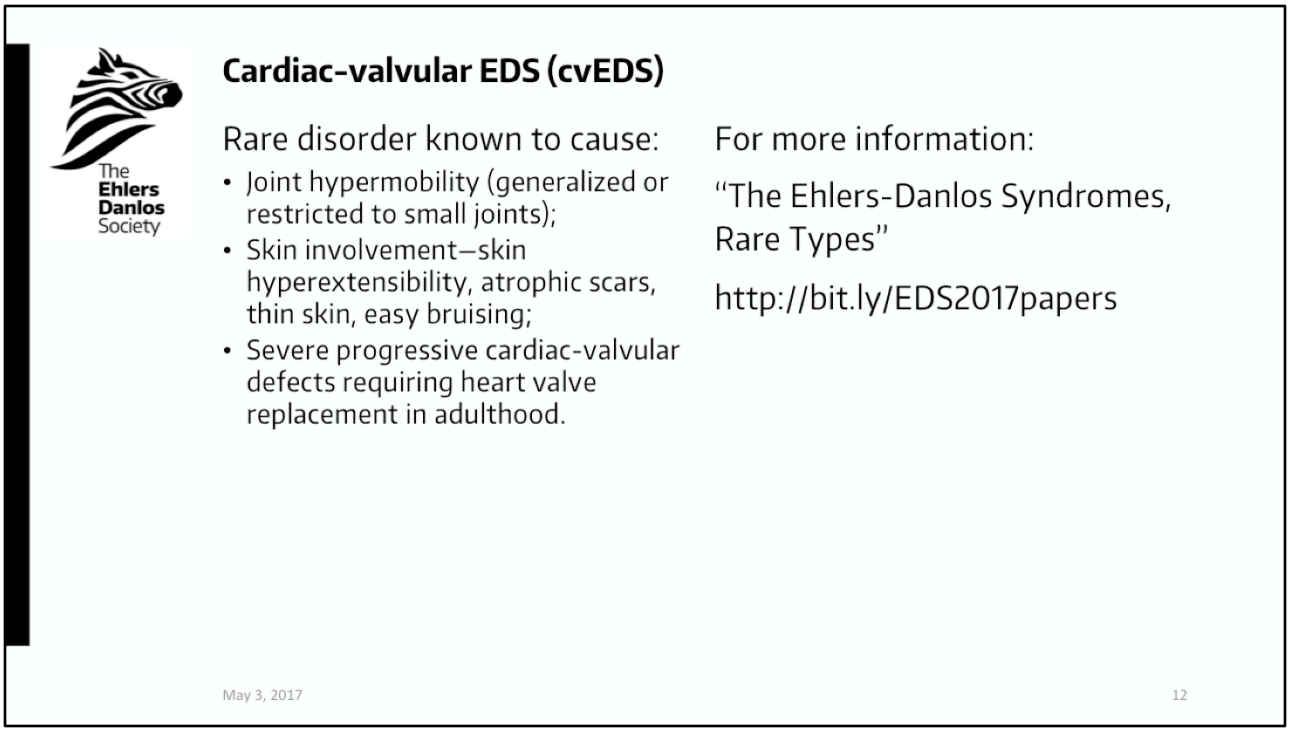
Hypermobile EDS evolves over time. The "hypermobility" phase (the first years of life) involves contortionism and propensity for sprains and dislocations; pain, often limited to lower limbs, also with fine motor or repetitive tasks; easy fatiguability may be a feature, together with voiding dysfunction. The "pain" phase (starting 2nd to 4th decade of life) includes more widespread and progressively worsening musculoskeletal pain, pelvic pain in women, and headache; exacerbation of fatigue; and is often associated with additional complaints. The "stiffness" phase (observed in a few adults and elderly only) results in general reduction of joint mobility; significant reduction in functionality due to disabling symptoms of pain and fatigue, and limitations from reduced muscle mass and weakness, prior injuries, and arthritis. Hypermobile EDS the only type without an identified distinctive cause.



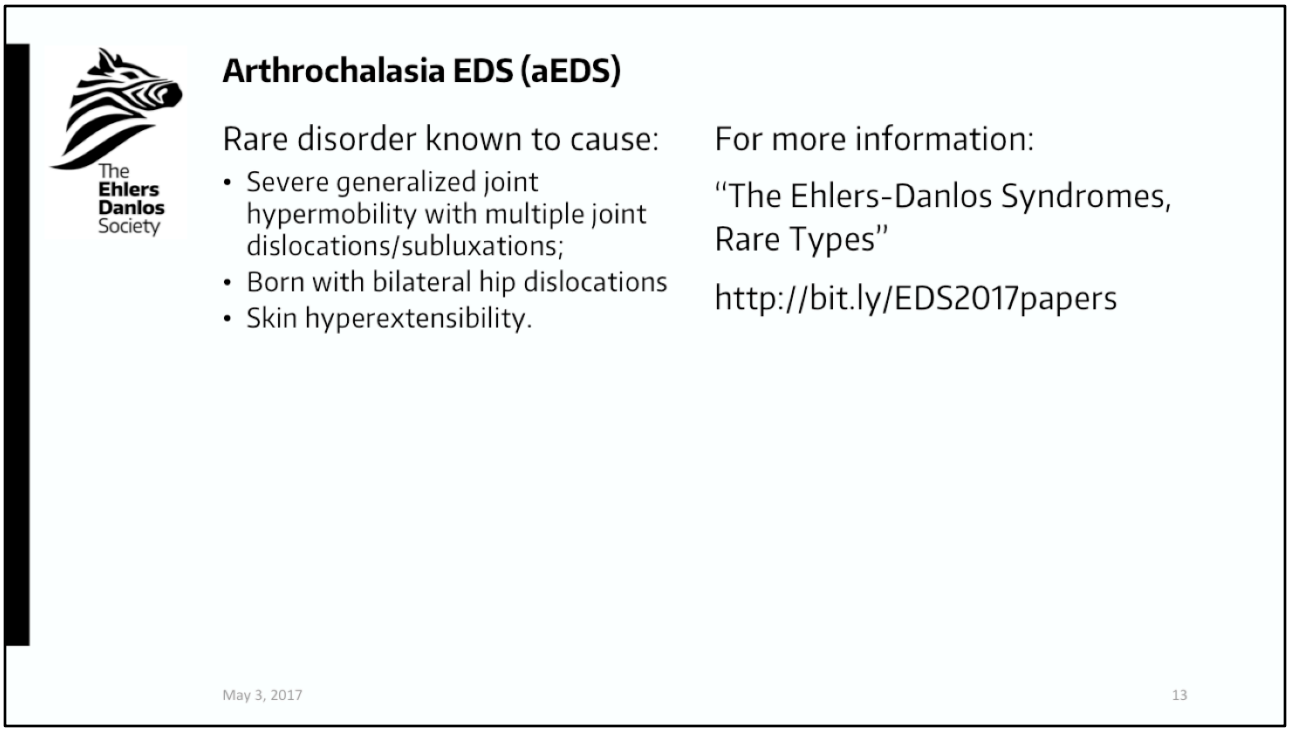
Vascular EDS is the most serious type due to the possibility of shortened lifespan, with median lifespans of 49 for men and 53 for women. Arterial rupture is the most common cause of sudden death. Even minor trauma can lead to extensive bruising and skin tears. Easy bruising is most often noticed in childhood, often accompanied by visibility of blood vessels through strikingly translucent skin. Additional features can include unusual bruising without identified cause, premature aging of hands and feet, early onset varicose veins, distinguishing facial features, including prominent eyes.



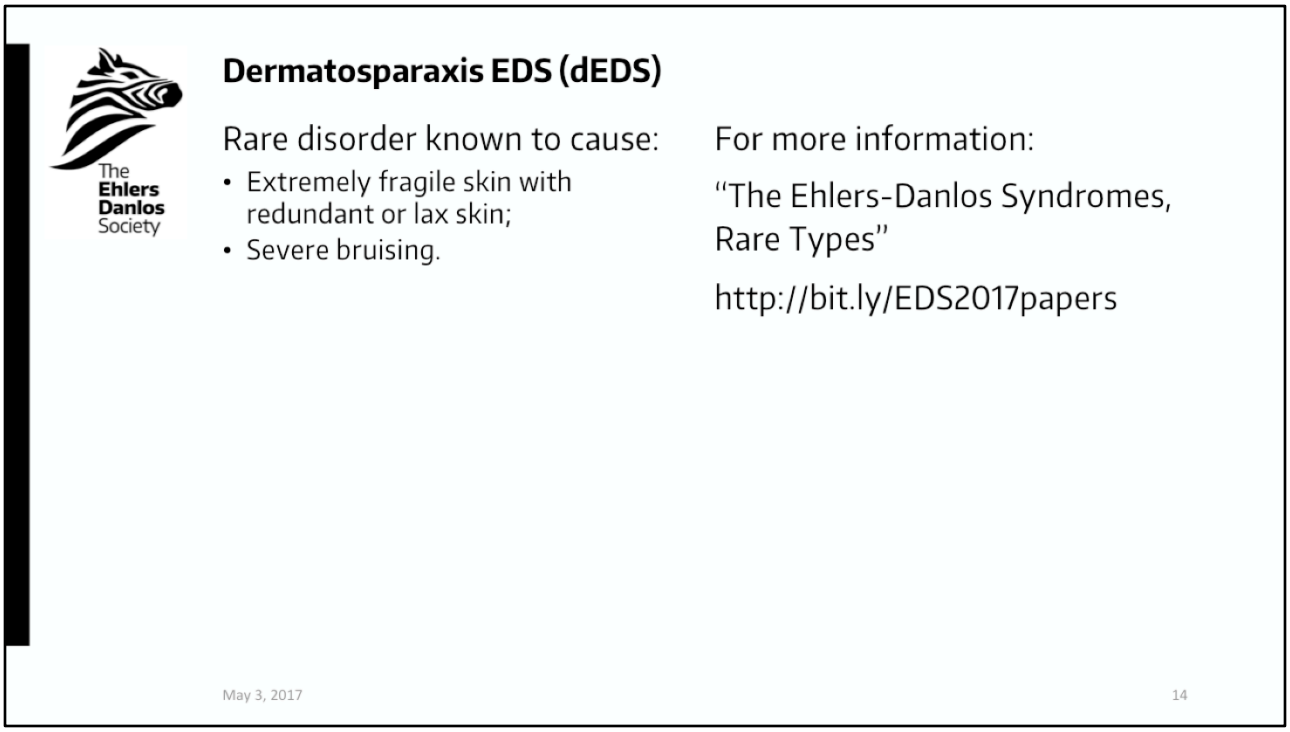
Classical-like EDS causes generalized joint hypermobility; hyperextensible, soft and/or velvety skin, but without the typical scarring seen in classical EDS.



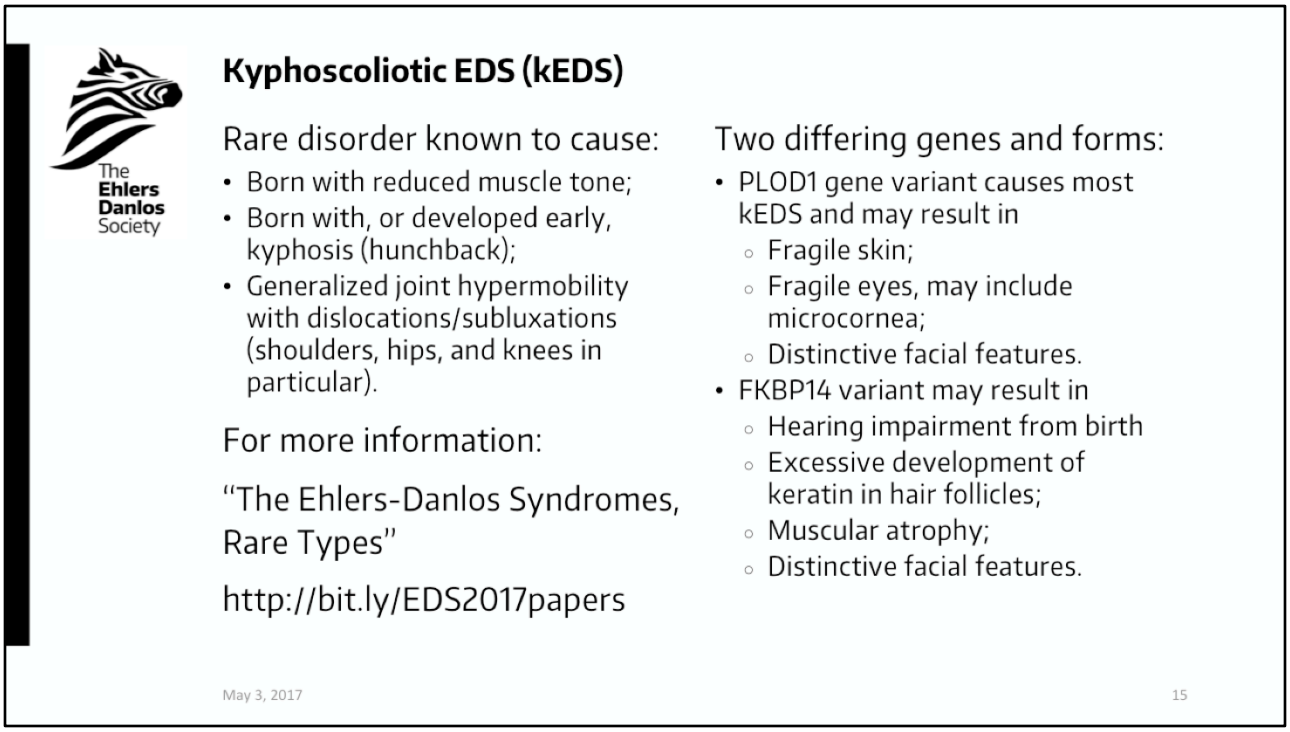
Cardiac-vulvular EDS presents with severe heart valve disease requiring valve replacement surgery. It may also involve variable skin hyperextensibility, atrophic scarring, joint hypermobility, and their often-associated complications and discomfort.



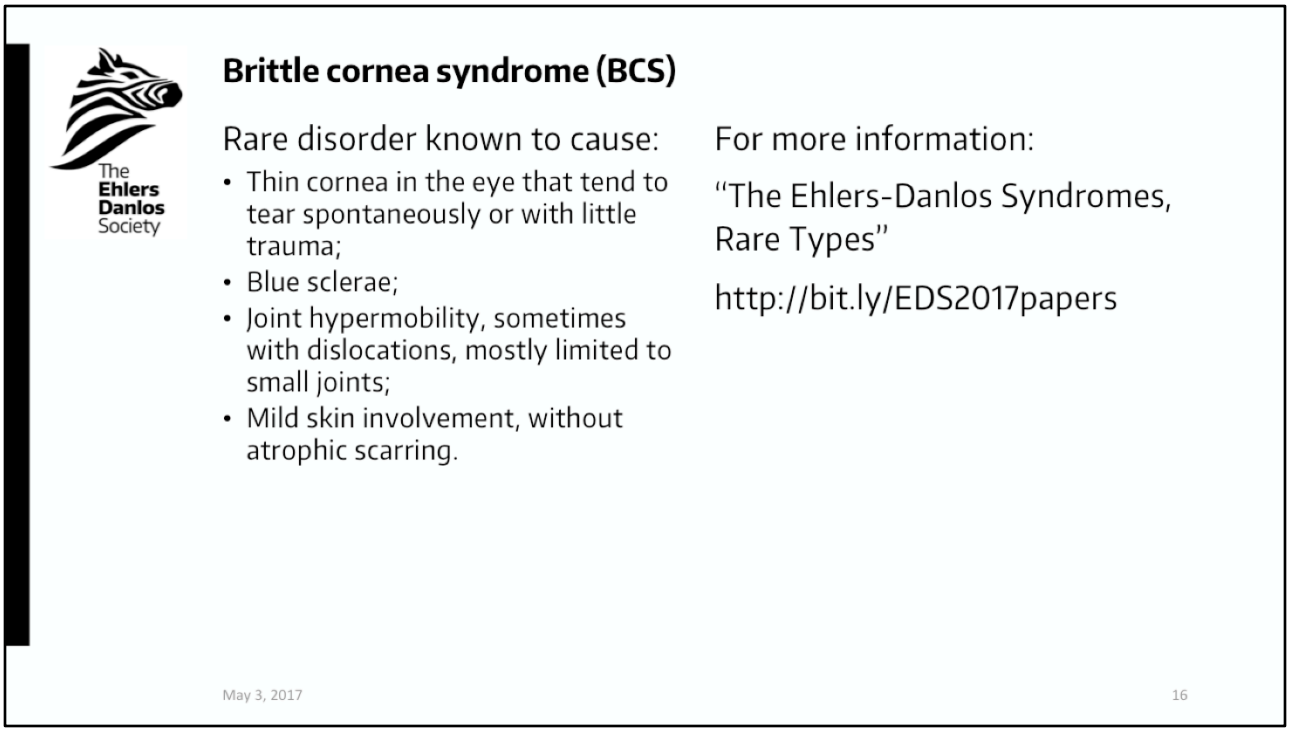
Arthrochalasia EDS is characterized by severe generalized joint hypermobility, bilateral hip dislocation present at birth, and recurrent subluxations and dislocations of both small and large joints. It can be both painful and disabling



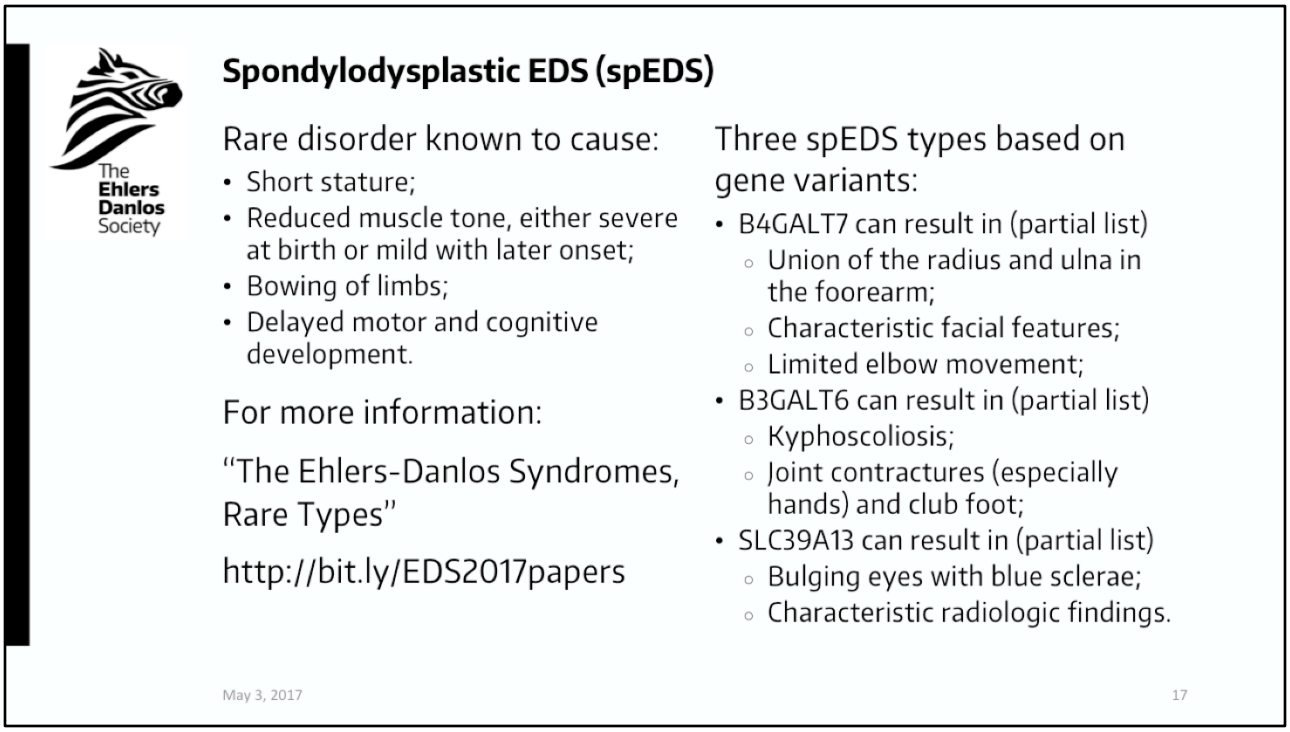
Dermatosparaxis EDS involves extreme skin fragility with redundant, almost lax skin, and a severe susceptibility of bruising.



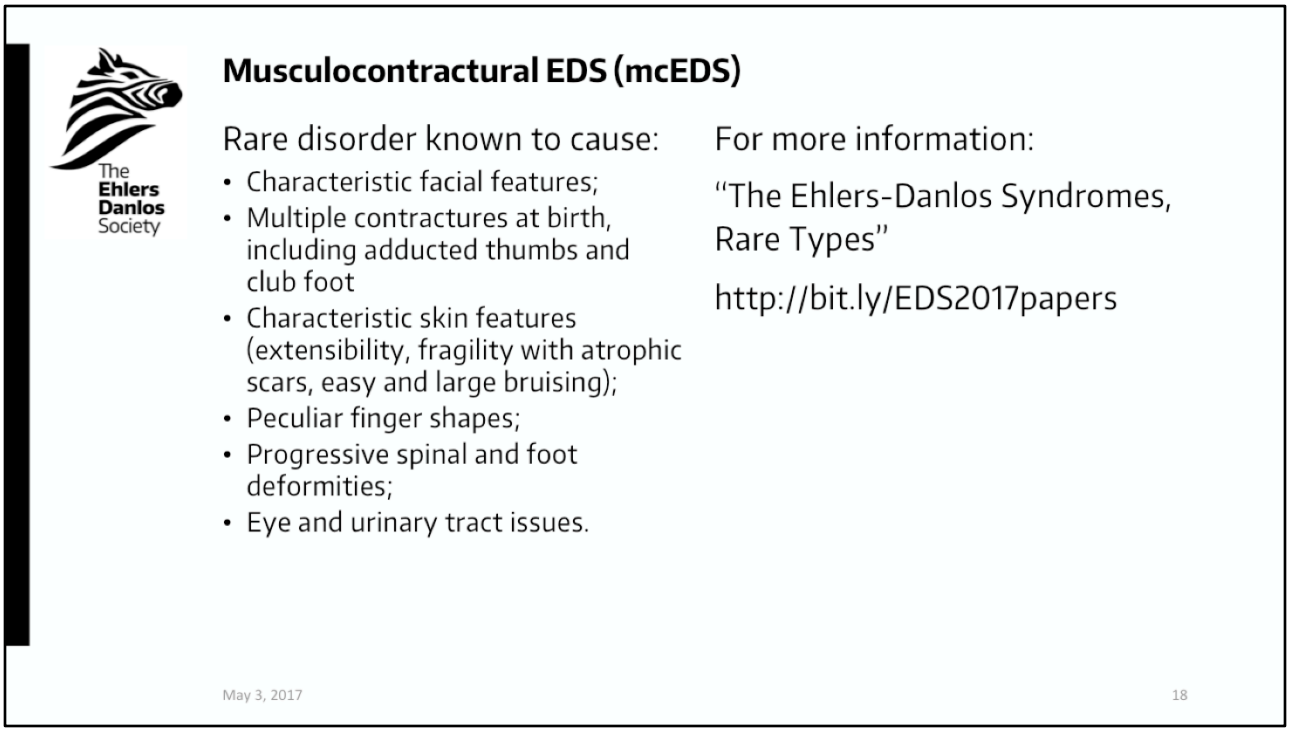
Kyphoscoliotic EDS caused by *PLOD1* results in abnormal spine curvature at birth, reduced muscle tone, and joint hypermobility; the *FKBP14* form is characterized by kyphoscoliosis, severe reduced muscle tone at birth with muscle atrophy, joint hypermobility, and congenital hearing loss, often resulting in chronic pain and disability.



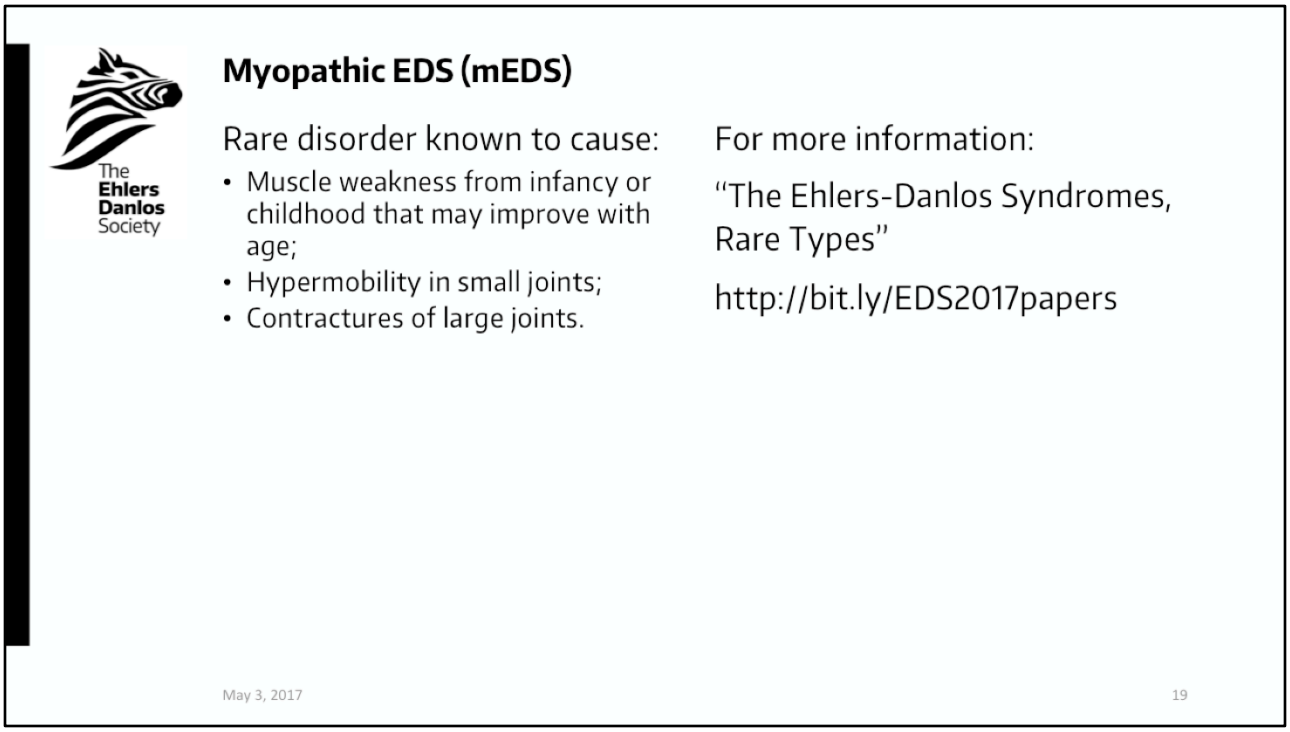
Brittle cornea syndrome (BCS) produces thin, fragile cornea, with an increased risk for spontaneous corneal rupture, and too often, blindness or severe vision loss.



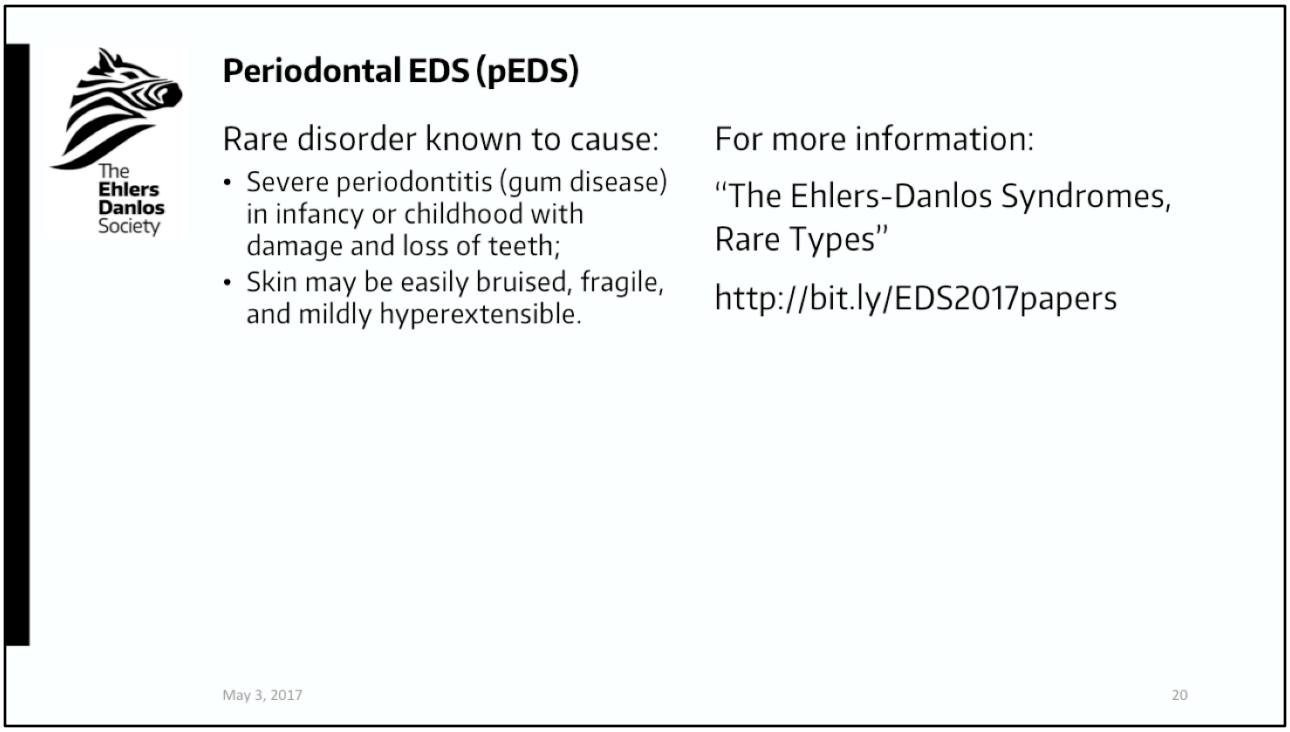
Spondylodysplastic EDS is caused by one of three gene variants. It can be one of the most severe and disabling forms of Ehlers-Danlos. *B4GALT7* produces short stature and mild intellectual disability. The *B3GALT6* form results in characteristic head and facial features; abnormal spine curvature; joint hypermobility and deformed, rigid joints; short stature; osteoporosis with multiple fractures; and cognitive delay through brain atrophy, leading to intellectual disability. *SLC39A13* is characterized by moderate short stature; hyperelastic, velvety, thin skin with an easily visible venous pattern, and bruisability which leads to atrophic scars; slender, tapering fingers, wrinkled palms, and considerable atrophy; and distal joint hypermobility which later results in contractures.



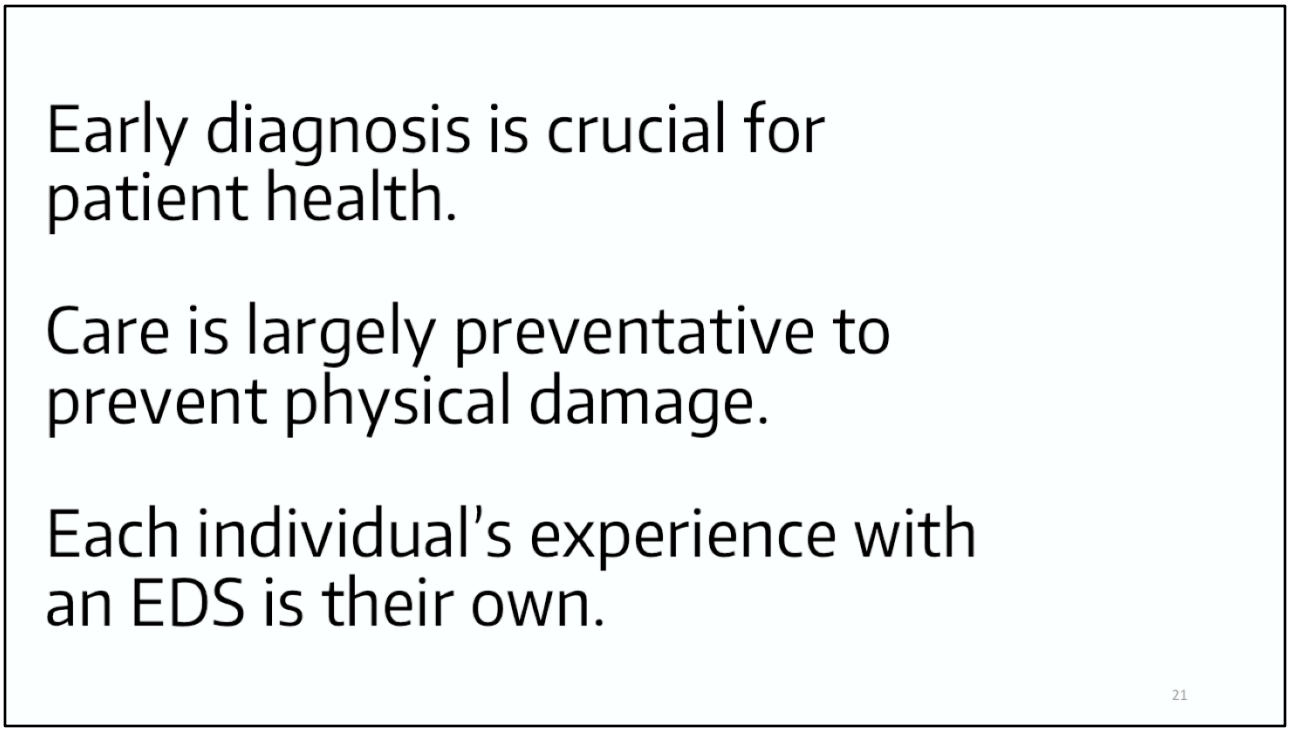
Musculocontractural EDS results in distinctive head and facial features; multiple deformed and rigid joints at birth, including adducted thumbs and club foot; characteristic skin features including fine palmar creases; peculiar finger shapes; progressive spinal and foot deformities; large subcutaneous hematomas; and ophthalmological and urogenital involvement.



Myopathic EDS involves muscle weakness that is present in infancy or childhood and is associated with proximal large joint rigidity and distal joint hypermobility. The muscle weakness tends to get better with age until young adulthood with some deterioration in the 4th decade.

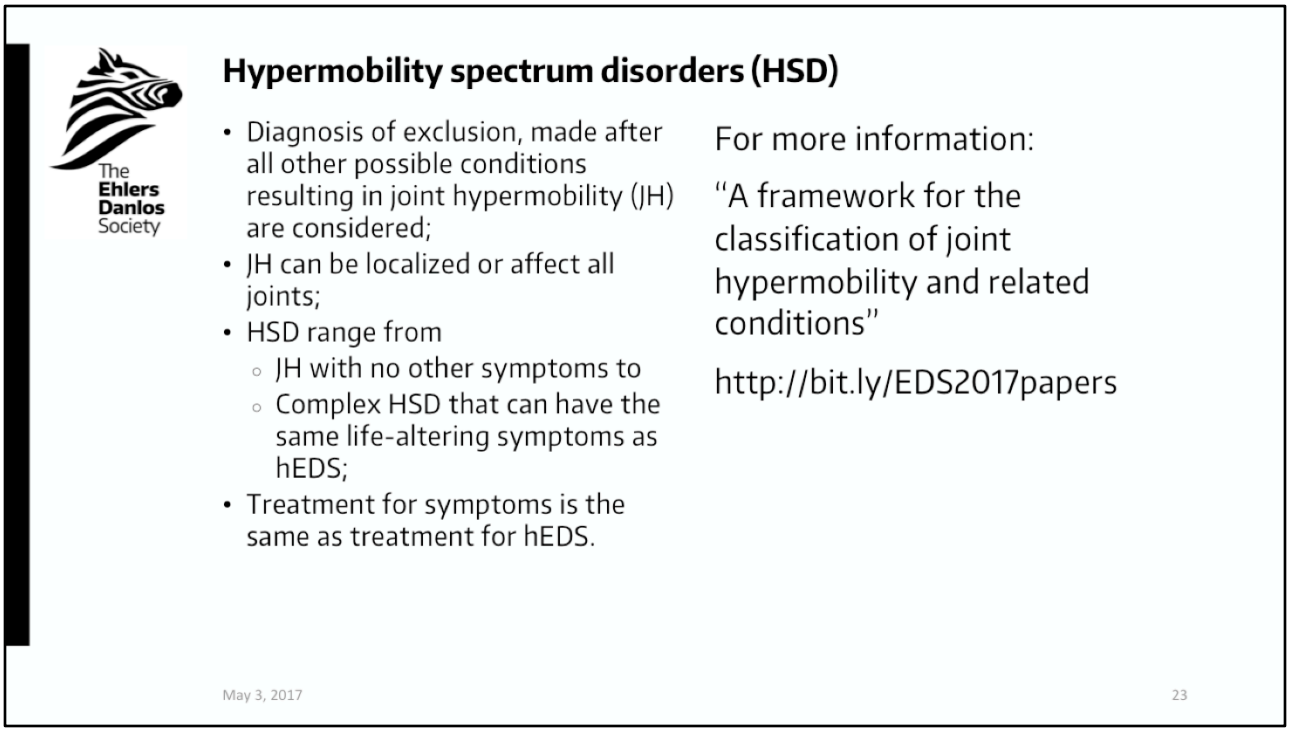


Periodontal EDS results in early-onset inflammation of the tissue around teeth, with extensive gum destruction and loss of teeth starting in childhood or adolescence.



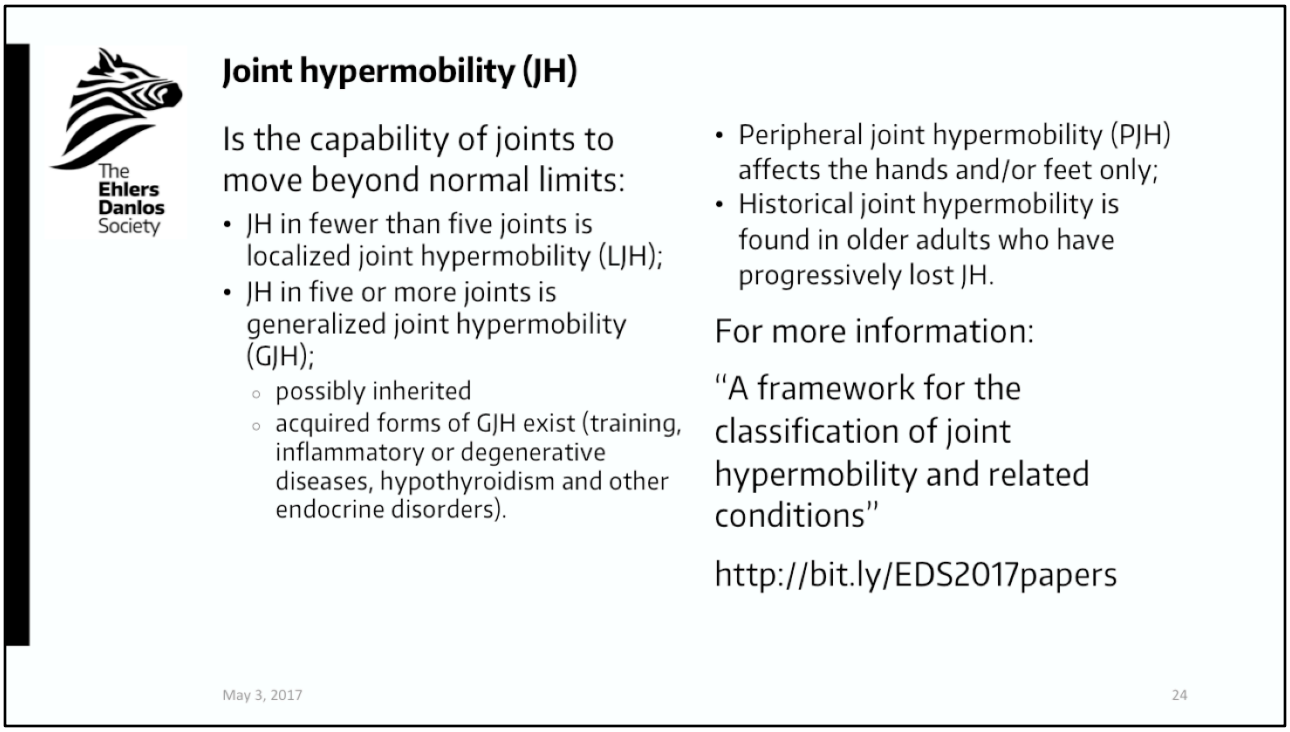
Early diagnosis is crucial to positive patient health. Symptoms can be treated as they arise. Care is largely preventative, to support and manage EDS with the intent of keeping damage as minimal as possible. Specifics have to be tailored to those symptoms exhibited in the person with EDS, as an individual's experience with an EDS is their own, and may not necessarily be the same as another person's experience.


The
Ehlers
Danlos
Society
The Hypermobility Spectrum Disorders
22



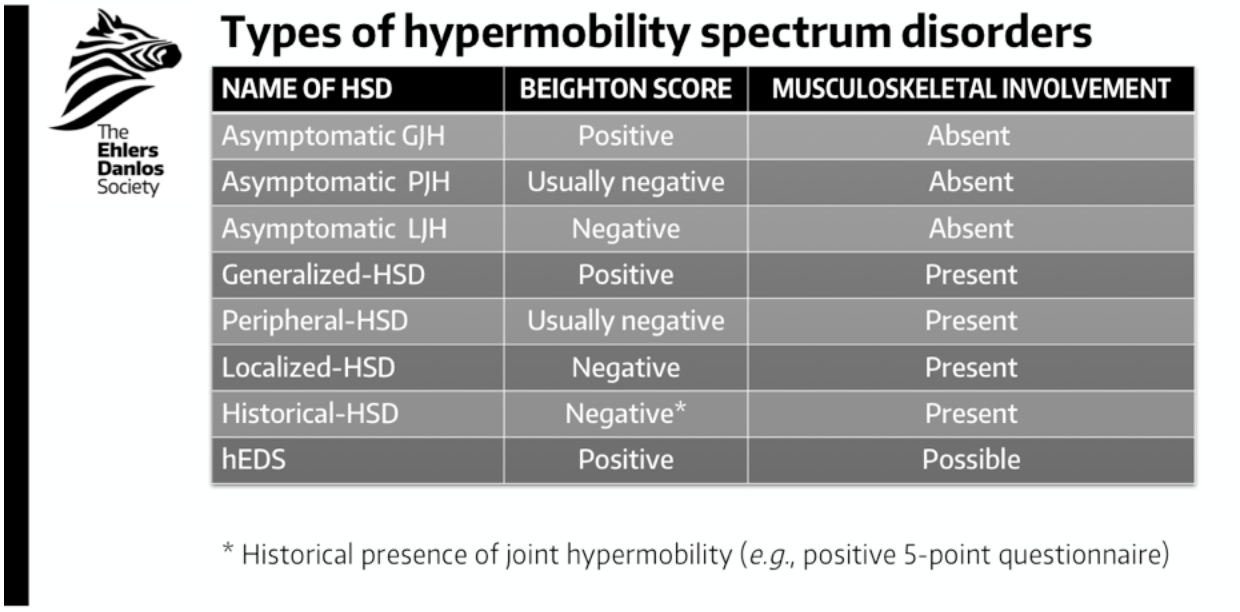
Hypermobility spectrum disorders are a group of conditions related to joint hypermobility. HSD are intended to be diagnosed after other possible answers are excluded, such as any of the Ehlers-Danlos syndromes including hypermobile EDS. HSD, just like hypermobile EDS, can have significant effects on health. Whatever the problems that arise, whatever the diagnosis, it is important that these effects are managed appropriately and that each person is treated as an individual. HSD and hypermobile EDS can be equal in severity, but more importantly, both need similar management, validation, and care.

The essential difference between HSD and hEDS lies in the stricter criteria for hEDS compared to the HSD and reflects the more likely hereditary and/or systemic nature of hEDS compared to HSD. The term HSD relates, in fact, to a wide range of musculoskeletal manifestations that can be considered "secondary to" the underlying JH. But treatment is more important than labels.



Joint hypermobility is a term to describe the capability of joints to move beyond normal limits. It can exist by itself or be a part of a more complex diagnosis. Those with joint hypermobility in a couple of joints (fewer than five) have localized joint hypermobility. Those of us with joint hypermobility in five or more joints are described as having generalized joint hypermobility. Unlike localized joint hypermobility, generalized joint hypermobility is more often something we're born with and possibly inherited, although acquired forms of generalized joint hypermobility exist (training such as dance, widespread inflammatory or degenerative diseases of the joints, musculoskeletal tissues, and nerves, and hypothyroidism and other endocrine disorders).

There are other types of joint hypermobility. Peripheral joint hypermobility is a form of that affects the hands and/or feet only. It is common in infants, toddlers, and children, in whom it is usually mild or has no serious effect. Another is proposed for older adults who have progressively lost JH, called historical joint hypermobility.



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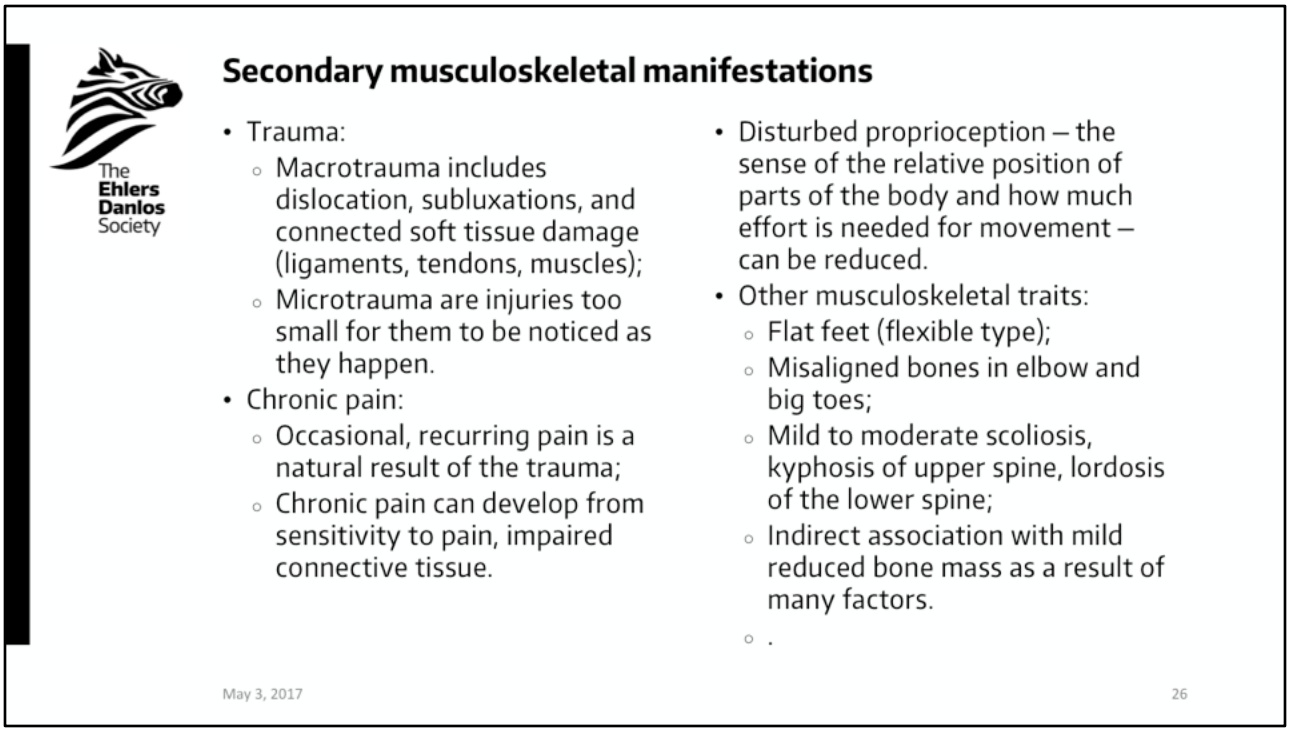


Joint hypermobility can be symptomless apart from the unusual mobility, but there is a series of other symptoms that result from that mobility. These should be evaluated for a diagnosis of HSD (and treated, of course).

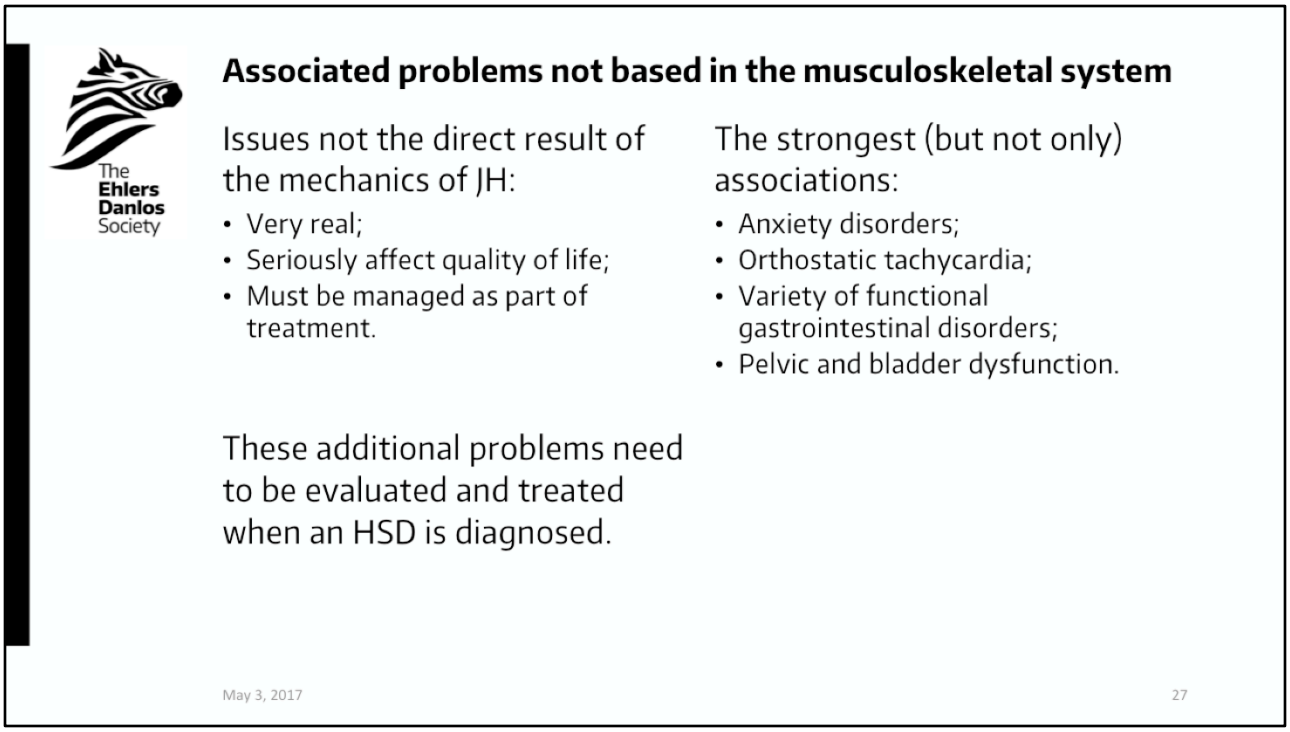
Trauma: Macrotrauma includes dislocation, subluxations, and connected soft tissue damage (ligaments, tendons, muscles). It can cause acute pain and loss of joint function. Microtrauma are injuries too small for them to be noticed as they happen. Over time, they may make one susceptible to recurrent or persistent pain, and possibly early joint degeneration like osteoarthritis.

Chronic Pain: Occasional, recurring pain is a natural result of the trauma, but chronic pain can develop—perhaps because of unusual sensitivity to pain (called hyperalgesia), perhaps because of an impaired connective tissue function (as suggested by the discovery of small fiber neuropathy in adults with classical, hypermobile, and vascular EDS).

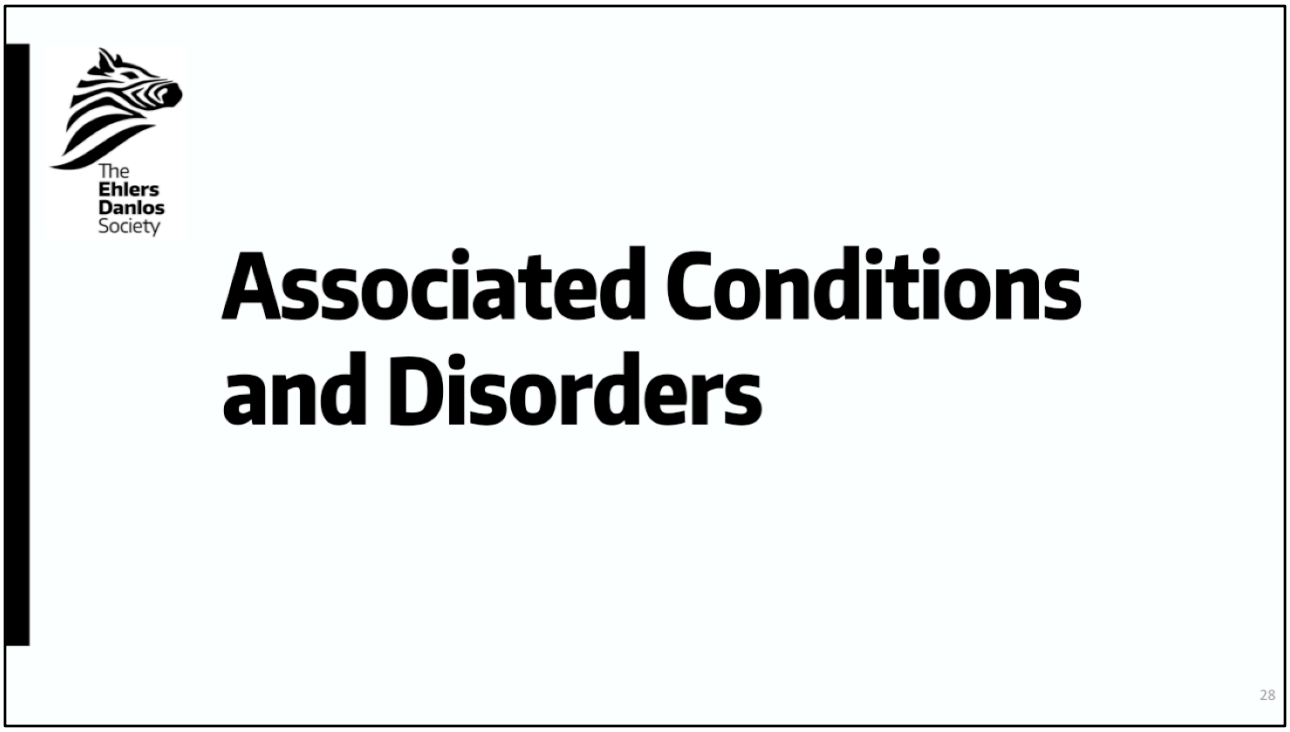
Disturbed Proprioception: Proprioception is the sense of the relative position of parts of the body and how much effort is needed for movement, and it can be reduced. Not understanding where joints are

and how much muscle strength it takes to use them can lead to a cycle that increasingly limits abilities to manage every day life.

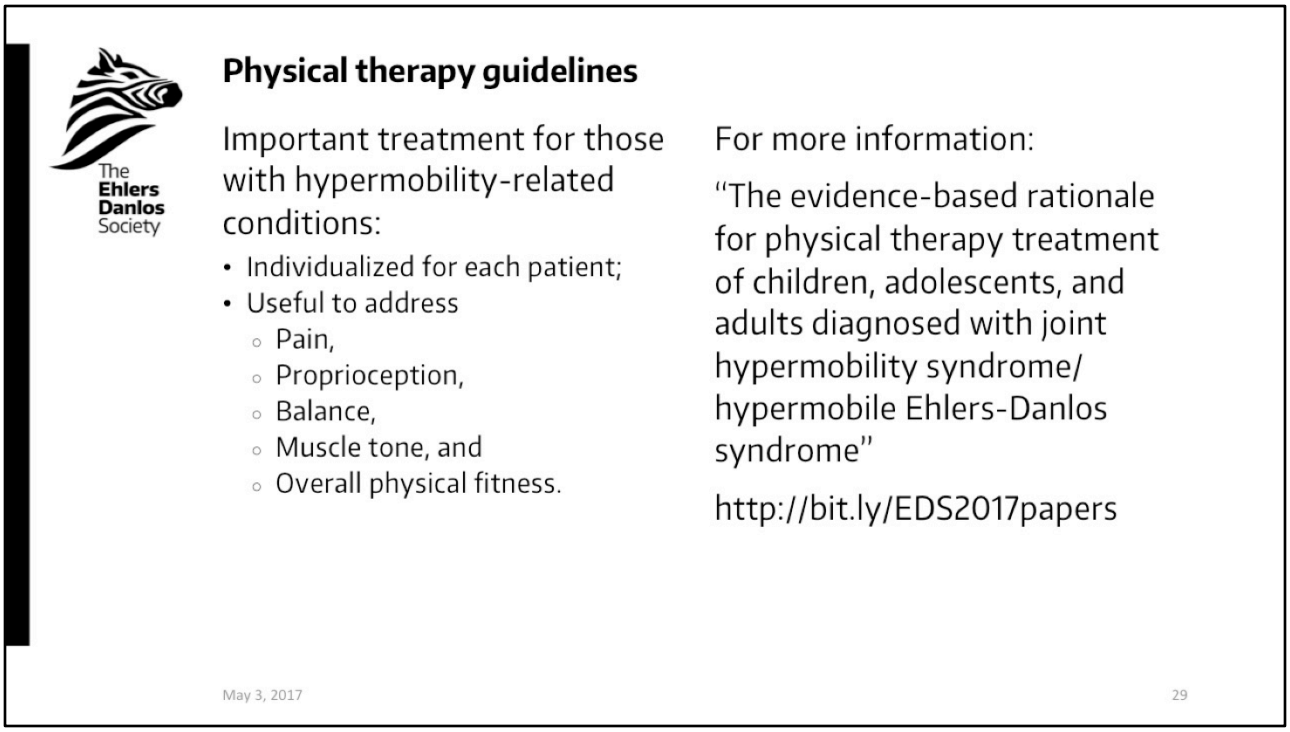
Those with generalized joint hypermobility often have other minor musculoskeletal physical traits, which may be the result of the interactions between “softer” musculoskeletal tissues and mechanical forces during growth. These include: flat feet of the flexible type, misaligned bones in the elbow and big toes, mild to moderate scoliosis (side to side curvature of the spine), kyphosis (outward curvature) of the upper spine and lordosis (inner curvature) of the lower spine. There may be an indirect association with mild reduced bone mass as a result of many factors including the lack of proprioception, muscle weakness, and resulting reduced activity.



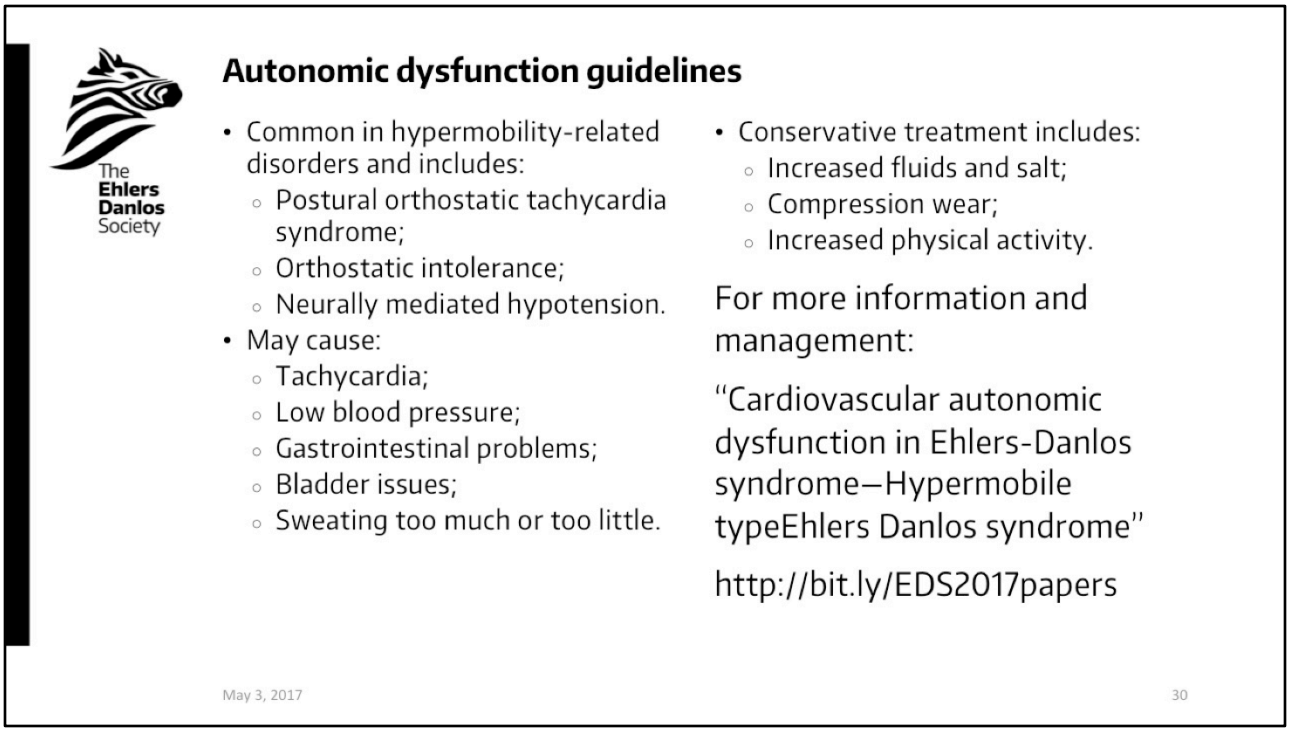
There can be quite a few issues that are not the direct result of the mechanics of joint hypermobility. These associations are very real; they seriously affect quality of life and they need to be managed as part of treatment. The strongest (but not only) associations noted so far are anxiety disorders, orthostatic tachycardia, a variety of functional gastrointestinal disorders, and pelvic and bladder dysfunction. These additional problems need to be evaluated and treated when an HSD is diagnosed.



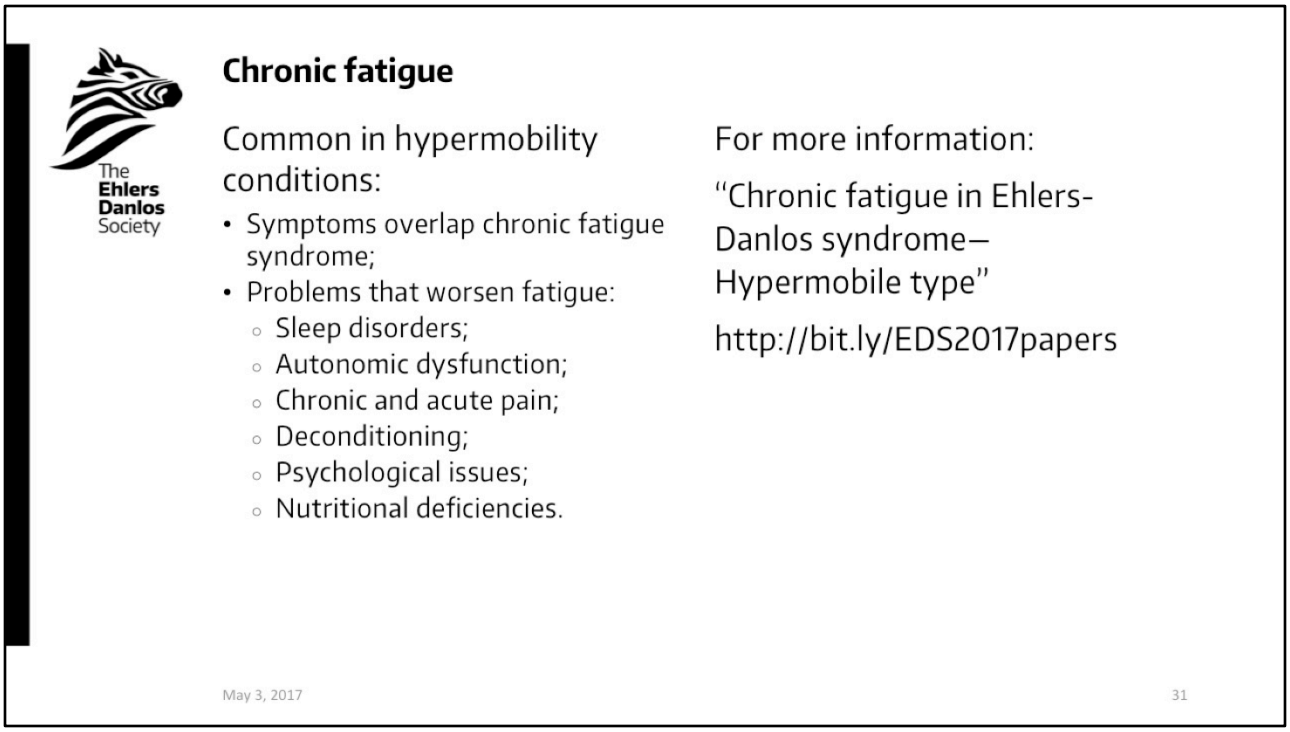
There are multi-systemic disorders that often are part of having an EDS, and more specifically hypermobile EDS. While research has shown there is an association between these disorders and EDS, there is not yet proof that they're caused by the genes that result in EDS. Whatever the relationship, recognition and treatment of these associated conditions is an important part of living with an EDS or HSD.



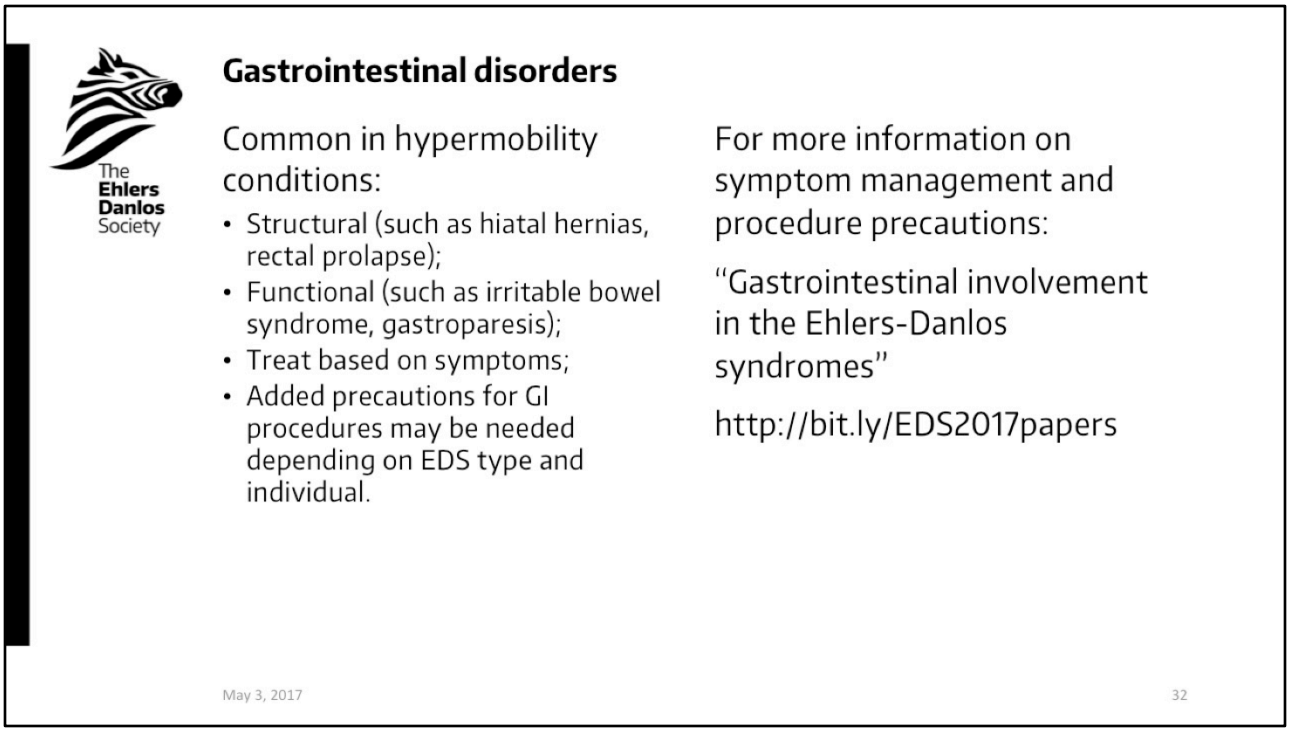
Physical therapy is an important treatment for those with hypermobility-related conditions like EDS or HSD. Physical Therapy should be individualized for each patient. Therapists may need to address a patient's pain, proprioception, balance, muscle tone, and physical fitness.



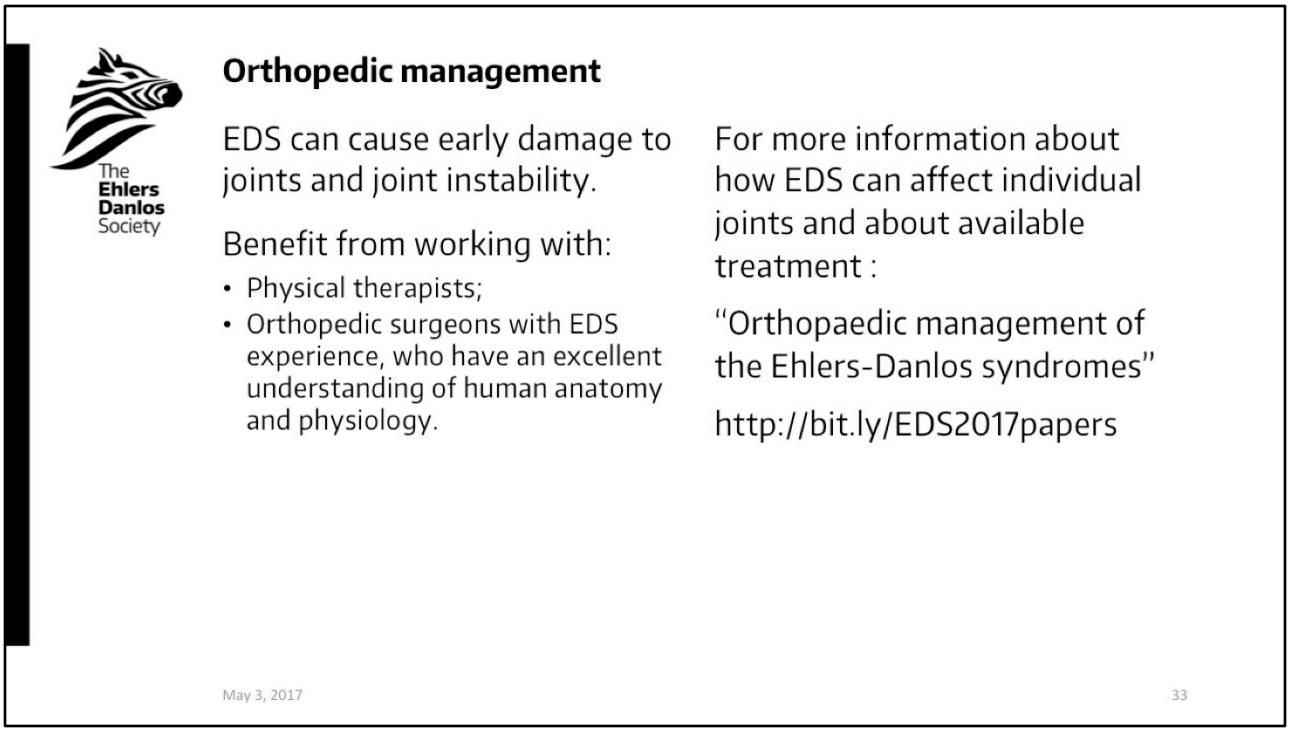
Autonomic dysfunction, including postural orthostatic tachycardia syndrome (POTS), orthostatic intolerance (OI), and neurally mediated hypotension (NMH) are common in those with Hypermobile EDS and other hypermobility-related conditions. Autonomic dysfunction may cause tachycardia, low blood pressure, gastrointestinal problems, bladder issues, and sweating too much or too little. Conservative treatment includes increased fluids and salt, compression wear, and increased physical activity. Conservative treatment may not be enough for everyone with autonomic dysfunction so medication may be needed.



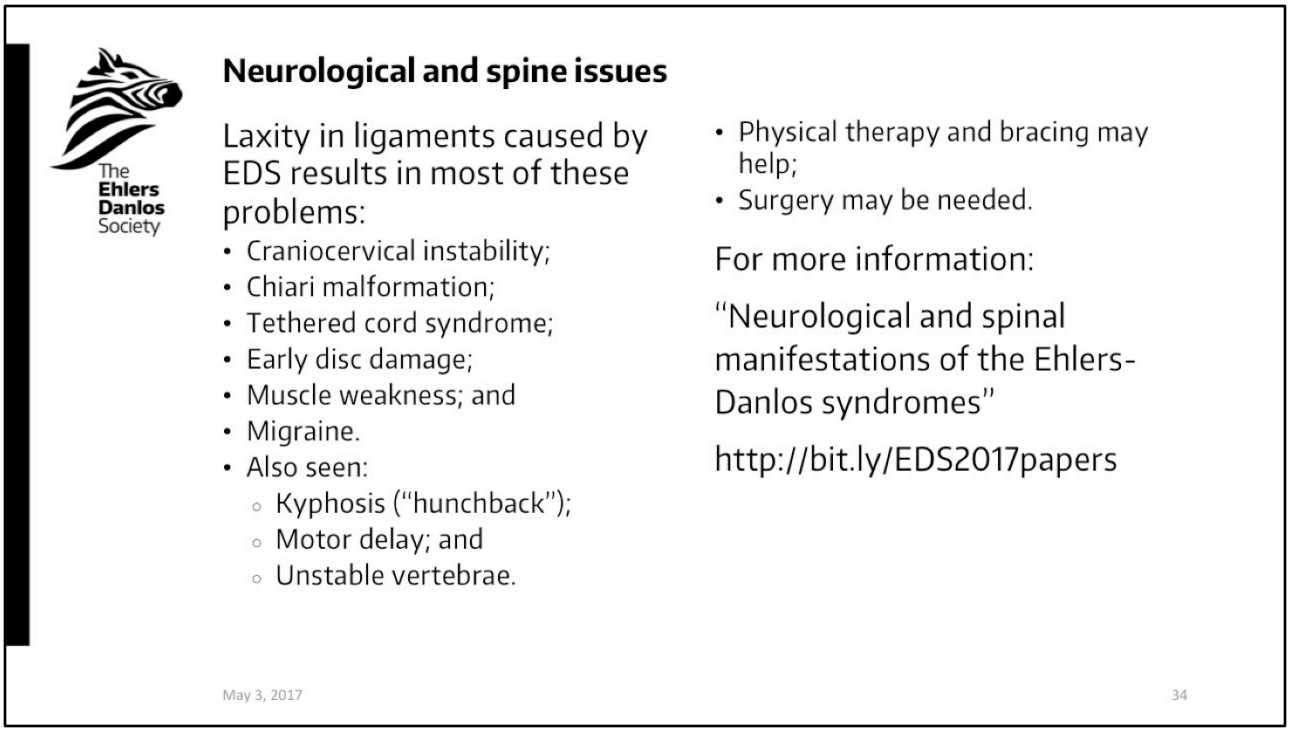
Chronic fatigue is common in EDS. Symptoms often overlap chronic fatigue syndrome. It is likely some patients with chronic fatigue syndrome are misdiagnosed and really have EDS. Problems that commonly worsen fatigue in EDS are sleep disorders, autonomic dysfunction, chronic and acute pain, deconditioning, psychological issues, and nutritional deficiencies.



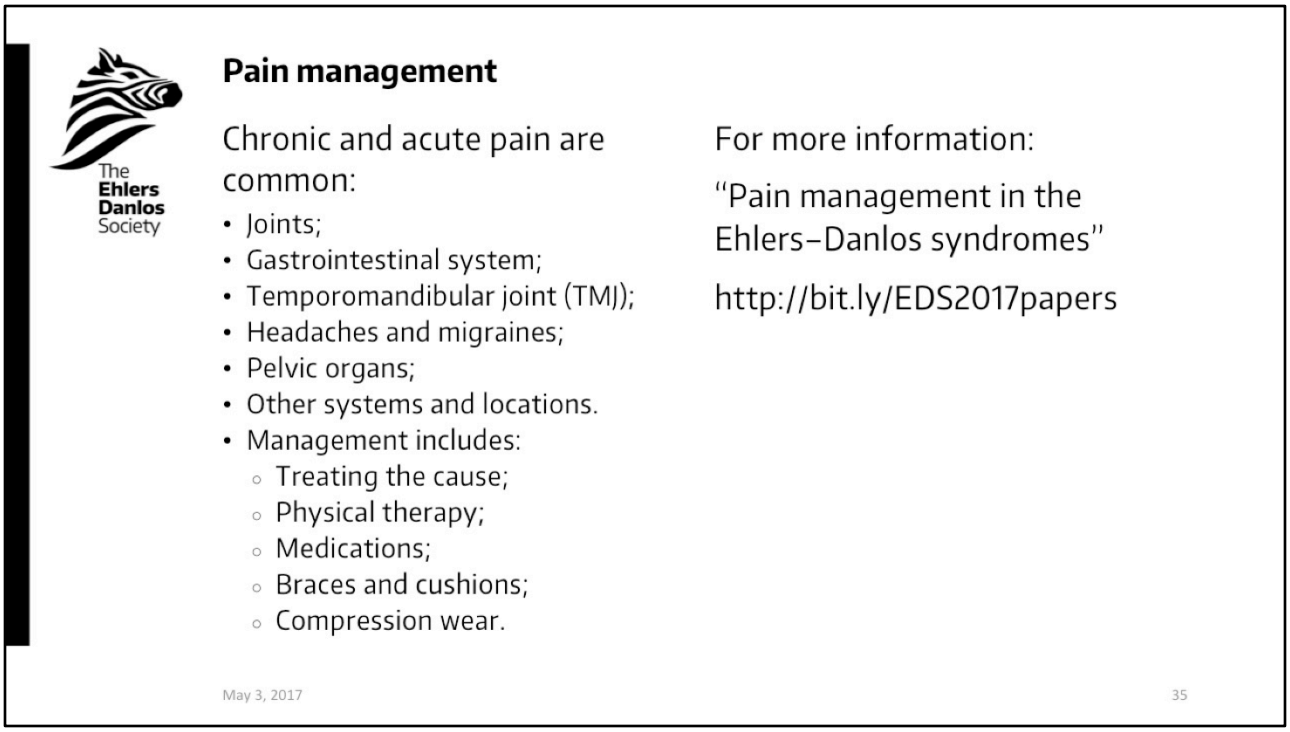
Gastrointestinal issues are common in EDS. They may be structural, such as hiatal hernias or rectal prolapse, or they may be functional, such as Irritable Bowel Syndrome (IBS) or Gastroparesis. Patients are treated based on their symptoms. Some precautions are needed for those with EDS when having Gastrointestinal procedures.



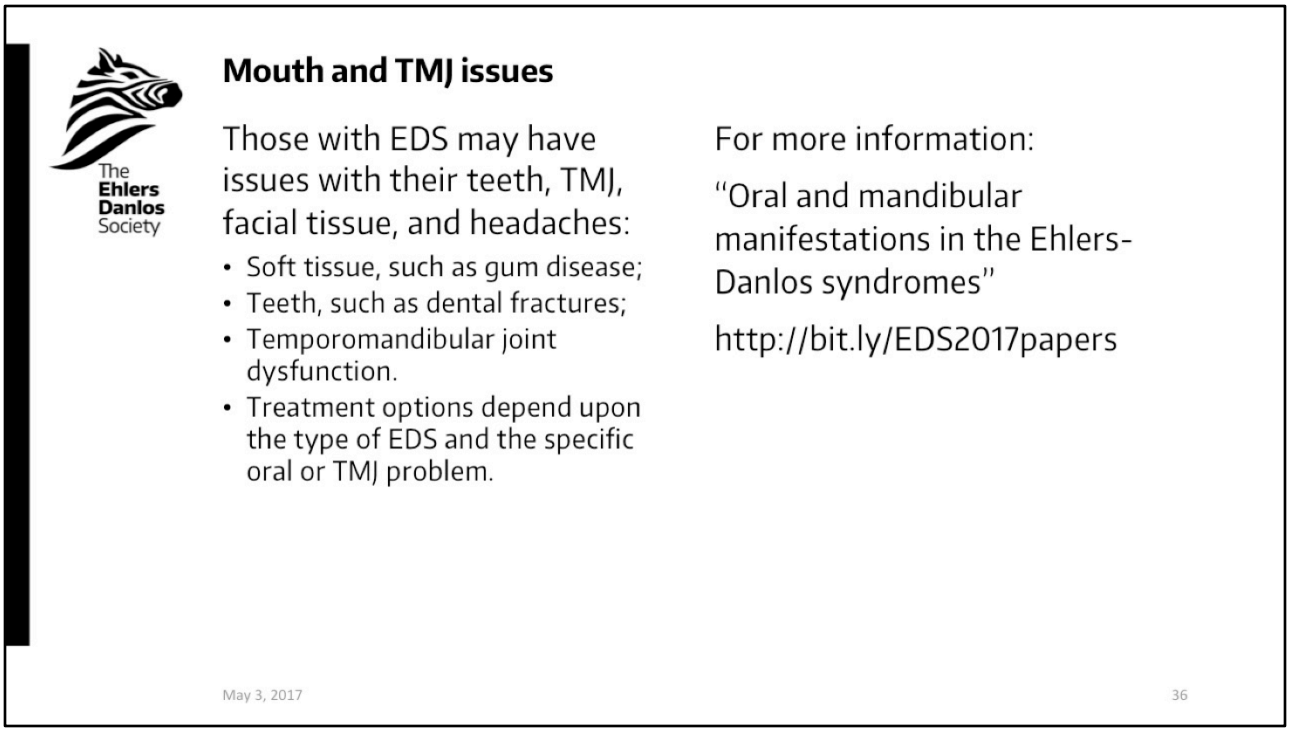
EDS can cause early damage to joints and joint instability. EDS patients benefit from working with Physical Therapists and, sometimes, Orthopedic Surgeons who have an excellent understanding of human anatomy and physiology.



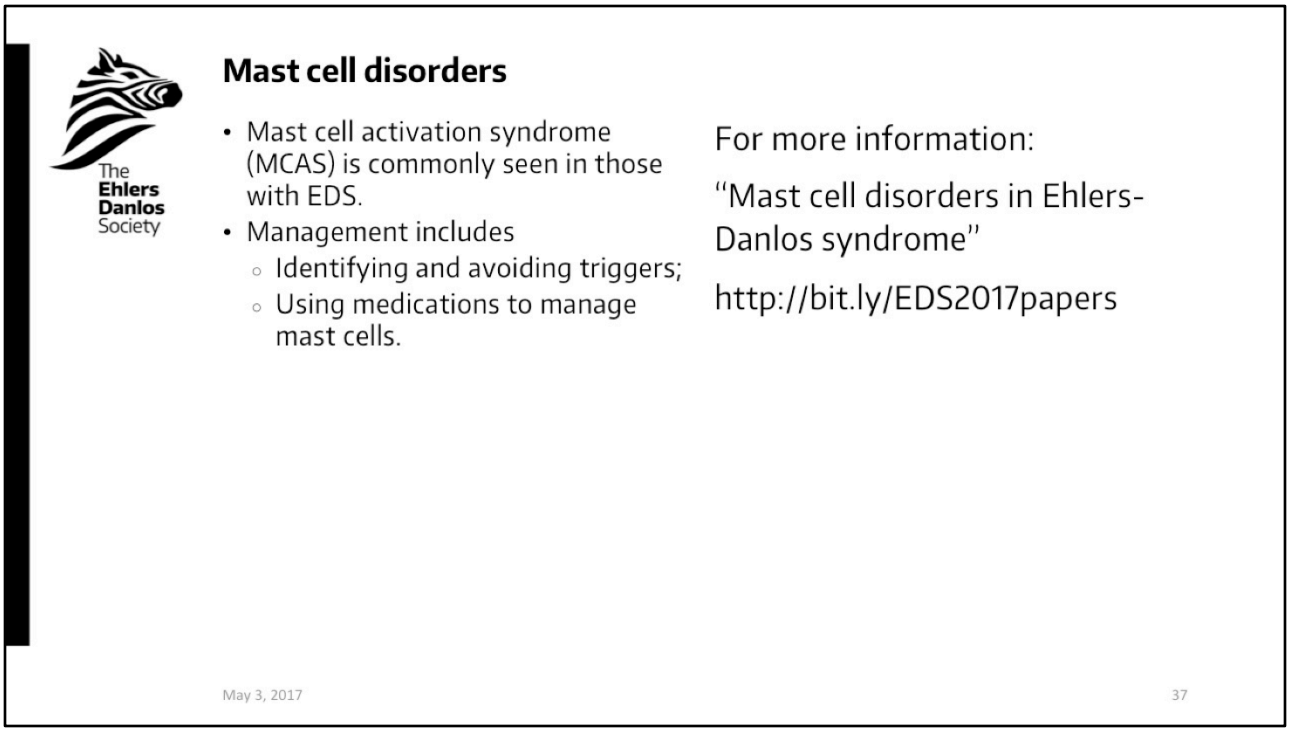
Those with EDS may experience craniocervical instability, Chiari malformation, tethered cord syndrome, early disc damage, muscle weakness, and migraine. Also seen in those with EDS are kyphosis ("hunchback"), motor delay, and unstable vertebrae. Laxity in ligaments caused by EDS results in most of these problems. Physical therapy and bracing may help though surgery may be needed for some.



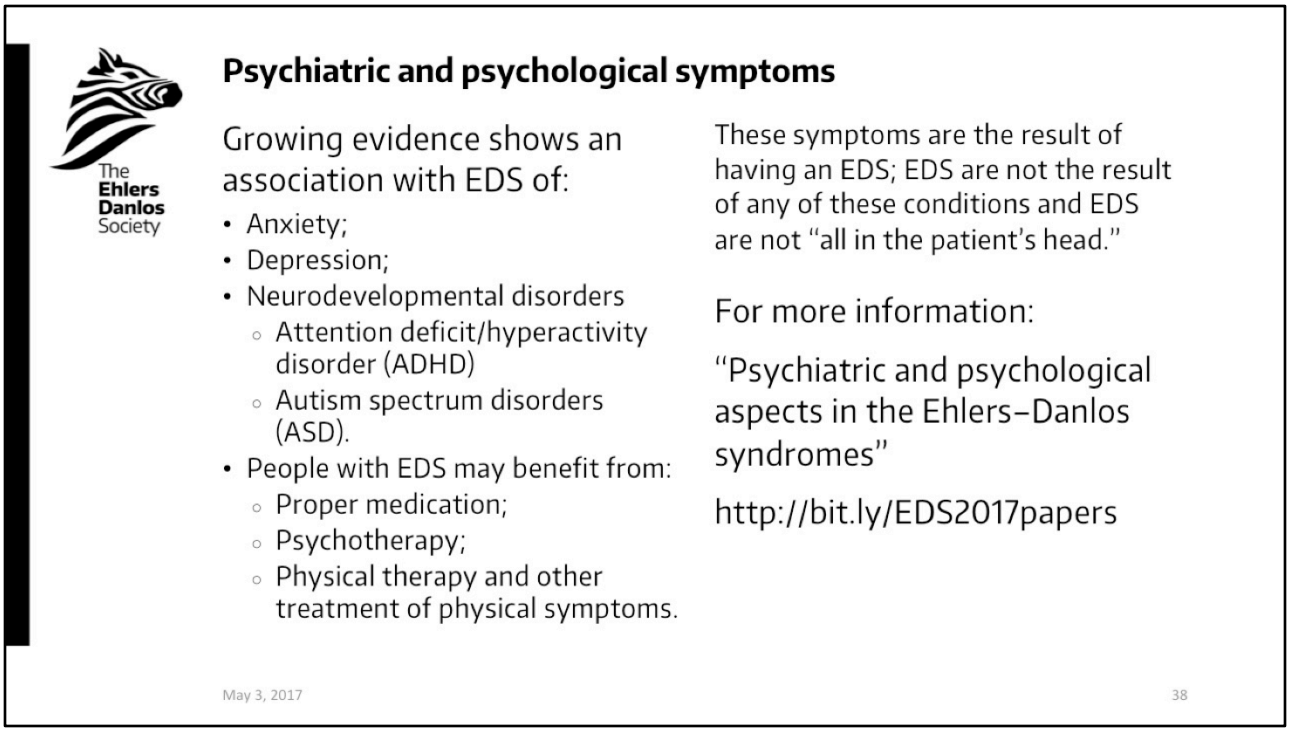
Chronic and acute pain are common in EDS. Those with EDS may have pain in joints, gastrointestinal system, temporomandibular joint (TMJ), head (headaches and migraines), pelvic organs, and more. Management includes treating the cause of the pain. It also can include physical therapy, medications, braces, cushions, and compression wear.



Those with EDS may have issues with their teeth, TMJ, facial tissue, and headaches. EDS can cause problems in the soft tissue such as gum disease, in the teeth such as dental fractures, and issues in the temporomandibular joint. Treatment options depend upon the type of EDS and the specific oral or TMJ problem.



Mast cell disorders, especially mast cell activation syndrome (MCAS), are commonly seen co-morbidly in those with EDS. Management includes identifying triggers and avoiding them as well as using medications to manage mast cells.



Growing evidence shows an association with EDS and anxiety, depression, and neurodevelopmental disorders such as Attention Deficit/Hyperactivity Disorder (ADHD) or Autism Spectrum Disorders (ASD). Please note these are the result of having an EDS; EDS are not the result of any of these conditions and EDS are not the result of a person's psychological problems. Many patients with EDS may benefit from proper medication and psychotherapy to manage these conditions in addition to physical therapy and other treatment options to treat the physical symptoms of EDS.

Thank you for your interest in learning about Ehlers-Danlos syndromes and hypermobility spectrum disorders.

For more information, visit
www.ehlers-danlos.com

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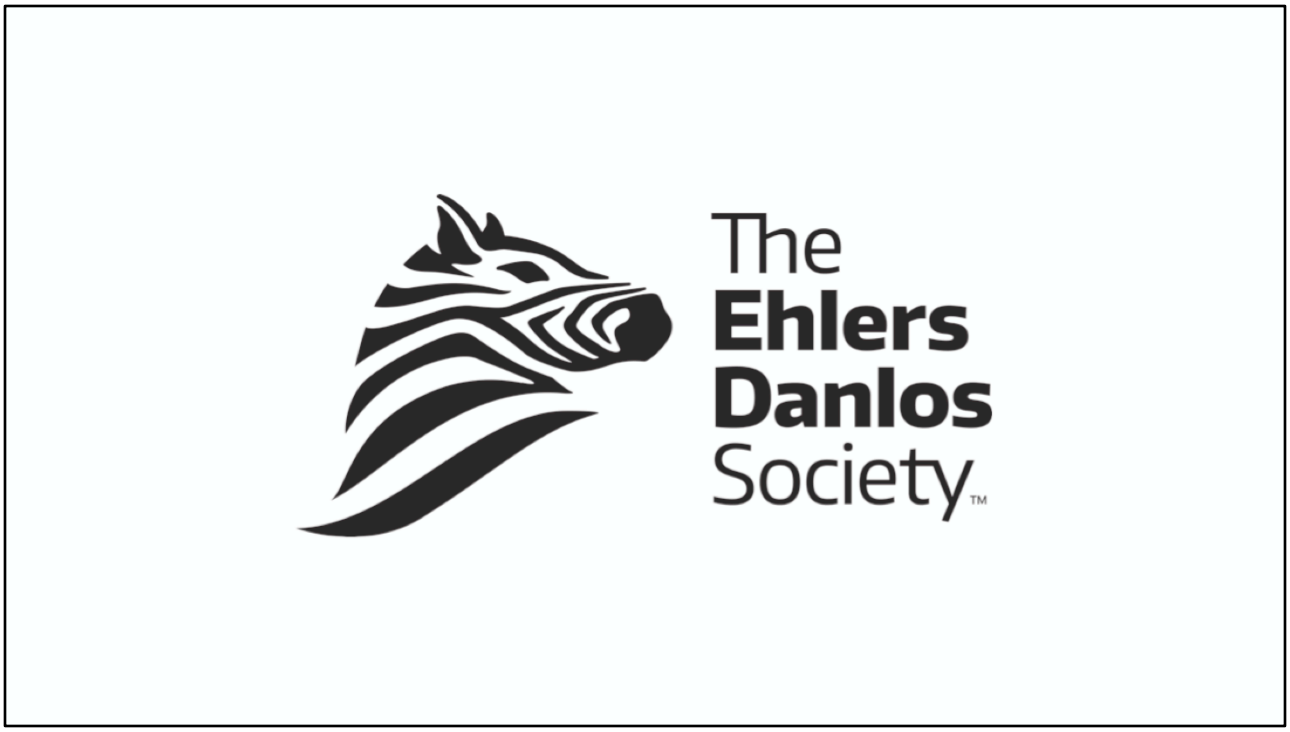
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