REVIEW ARTICLE

A Review of Hypermobile Ehlers-Danlos Syndrome

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Abstract

Ehlers-Danlos syndrome (EDS) is a rare connective tissue disorder that affects the collagen metabolism in which collagen deficiency occurs. According to the 2017 international classification of the EDS, 13 different subtypes are caused by pathogenic variants in 19 different genes that encode collagen and collagen-modifying proteins. Among the 13 subtypes of EDS, hypermobile EDS (hEDS) is the most common one. hEDS is formerly known as type III EDS. The cause of hEDS is idiosyncratic. Inheritance is autosomal dominant. The patients of hEDS have softness, stretchiness, fragility, bruisability, and poor wound healing when compared to normal patient. Hernias may also be more common in persons with hEDS who undergo abdominal surgery, such as laparotomy or C-section. Symptoms of hEDS include soft and elastic or stretchy skin, easy bruises, and persistent musculoskeletal pain. Three disease phases were proposed in a 2010 study: A "hypermobility" phase, a "pain" phase, and a "stiffness" phase. The prevalence rate of hEDS is 80–90% of all the cases of EDS. The cause of hEDS, which has a genetic inheritance pattern similar to Alzheimer's disease, is not known to be a gene mutation. The treatment of hEDS depends on signs and symptoms present in each patient, and treatment differs from patient to patient. There is no particular treatment for hEDS, and physical therapy is often recommended to strengthen muscles and improve joint stability. Pain medication such as physiotherapy, occupational therapy, orthopedic instruments, aquatic therapy, and cognitive behavioral therapy.

Key words: Bruises, collagen, connective tissue, Ehlers-Danlos syndrome, elasticity, hypermobile, mutations, pain

INTRODUCTION

Ehlers-Danlos syndrome (EDS) is a rare disorder of connective tissue that affects the collagen metabolism in which collagen deficiency or disordered deposition occurs.[1] Various body tissues such as skin, blood vessels, bones, and organs are composed of connective tissue. Among its components are cells, fibrous tissue, and a protein called collagen. Several types of EDS have been uncovered through biochemical and clinical research.[2] Although Van Meekeren's clinical characteristic of unusual skin extensibility has been the trademark of EDS, doctors have become increasingly aware of the extent to which the connective tissue abnormalities are widespread.[3] This syndrome has been studied for its skin and joint manifestations; however, the oral representations have been overlooked.[4]

As per available literature, the subtypes of EDS have been reorganized extensively. A Roman number was assigned to each of the eleven types of EDS based primarily on symptoms and inherited traits in the original classification (EDS I–XI).[5] According to the characteristics of each type, EDS was later divided into six subtypes.[6] According to the 2017 international classification of the EDS, 13 different subtypes are caused by pathogenic variants in 19 different genes that encode collagen and collagen-modifying

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proteins. EDS occurs in 13 classes, most of which are very rare.[7]

i. Classical EDS
ii. Classical-like EDS
iii. Cardiac-valvular EDS
iv. Vascular EDS
v. Hypermobile EDS (hEDS)
vi. Arthrochalasia EDS
vii. Dermatosparaxis EDS
viii. Kyphoscoliotic EDS
ix. Brittle cornea syndrome
x. Spondylodysplastic EDS
xi. Musculocontractural EDS
xii. Myopathic EDS
xiii. Periodontal EDS.

THE hEDS IS THE MOST COMMON TYPE

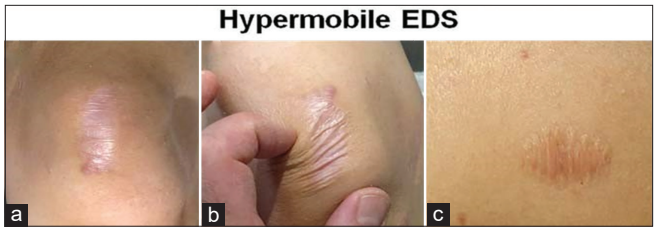
The hEDS is formerly known as type III EDS. In terms of the Berlin nosology (Beighton *et al*., 1988) and the Villefranche nosology (Beighton *et al*., 1998), it is primarily characterized by generalized joint hypermobility (GJH) Table 1.

The cause is unknown of hEDS, as the gene that causes the condition has not been identified. Inheritance is autosomal dominant. This condition is characterized by manifested musculoskeletal symptoms and modest skin involvement, lacking its classical and vascular counterparts' skin characteristics.[8] HEDS patients have softness, stretchiness, fragility, bruisability, and poor skin wound healing compared to "normal" patients. However, it is mild in comparison to other types of EDS. When hEDS is diagnosed with a systemic component (rather than a local manifestation), the mild stretchiness of the skin is considered a systemic symptom. Stretch marks are not inevitable in hEDS; however, they often appear in persons with hEDS during adolescent growth spurts and are not necessarily due to rapid weight gain. The absence of stretch marks should not argue against a diagnosis of hEDS. In addition to these tissues, the protective coverings around organs may be lost because of hEDS. Weakness in this connective tissue in hEDS often results in a hernia (tissues or organs pushing through). Hernias may also be more common in persons with hEDS who undergo abdominal surgery, such as laparotomy or C-section.[9]

The most common symptoms of hypermobility include:

- Both major joints (elbows, knees) and minor joints (fingers, toes)
- Soft, smooth skin that is slightly elastic (stretchy) and easily bruises and persistent musculoskeletal pain.

The goal of treatment and management is to avoid severe problems while also alleviating associated signs and symptoms Table 2.[10]



PHASES OF HEDS

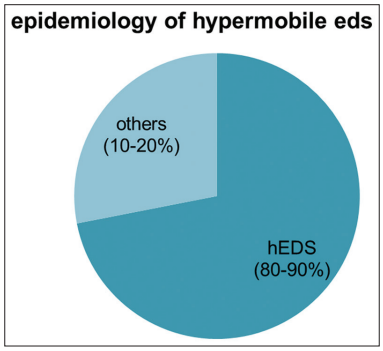
If a person has hEDS, it will likely affect them in different ways throughout their lifetime, and the person may be diagnosed with many other conditions known to occur in those with hEDS. For example, three disease phases were proposed in a 2010 study: A "hypermobility" phase, a "pain" phase, and a "stiffness" phase. Alternatively, existing studies have led to speculation that there is a natural transition from EDS-HT to GJH with age.

Existing studies show that children with hEDS who experience pain will be more likely to have pain limited to lower limbs (e.g., "growing pains") and pain caused by repetitive tasks such as handwriting in the school setting. Children with hEDS may have poor coordination. The "pain" phase is often accompanied by diagnosis with fibromyalgia or other long-term (chronic) pain conditions and perhaps chronic fatigue, typically starting in the second to fourth decade and accompanied by chronic pain, headaches, digestive system disorders, among others. The "stiffness" phase is seen in only a few persons, and, unfortunately for them, the symptoms of the "pain" phase may persist and escalate, and functionality may overall be significantly reduced.[11]

EPIDEMIOLOGY

The combined prevalence of all types of EDS appears to be at least 1 in 5,000 individuals worldwide, 80–90% of which are cases of hEDS. It is one of the most common subtypes, occurring in 1 out of every 10000 to 1 out of every 15000 people.

High estimates under the previous classification system give figures suggesting up to 2 million people in the UK, 10 million in the USA, 17 million in Europe, and 255 million worldwide have hEDS.[12]



ETIOLOGY

All of the genes listed below provide instructions on how to assemble collagen, except for ADAMTS2. In this gene, instructions are provided for making collagen-activating proteins. EDS can be caused by multiple genes,[13] although not a complete list:

- ADAMTS2
- COL1A1
- COL1A2
- COL3A1
- COL5A1
- COL6A2
- PLOD1
- TNXB.

The cause of hEDS, which has a genetic inheritance pattern similar to Alzheimer's disease, is not known to be a gene mutation.[14]

SYMPTOMS

The signs and symptoms of hEDS vary but may include:

- Joint hypermobility affecting both large (elbows, knees) and tiny (fingers, toes) joints
- Frequent joint dislocations and subluxations (partial dislocation), often affecting the shoulder, kneecap, or temporomandibular joint (the joint that connects the lower jaw to the skull)
- Soft, smooth skin that may be slightly elastic (stretchy) and bruises easily
- Chronic musculoskeletal (muscle and bone) pain
- Early-onset osteoarthritis
- Osteoporosis
- Gastrointestinal issues such as dysmotility, bloating, nausea, vomiting, heartburn, constipation, or hiatal hernia (which can also cause problems such as heartburn or reflux)
- Dysfunction of the autonomic nervous system
- Cardiovascular abnormalities such as mitral valve prolapse (MVP) or aortic root dilatation (enlargement of the blood vessel that distributes blood from the heart to the rest of the body)
- Increased risk of pelvic prolapse, painful menstruation (dysmenorrhea), and painful intercourse (dyspareunia) in women
- Increased risk of pregnancy complications such as premature rupture of membranes or rapid labor and delivery (<4 h) Figure 1.

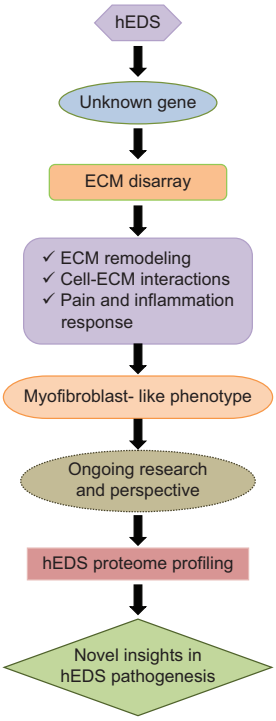
CLINICAL CHARACTERISTICS

Clinical distinction between the hypermobile and classic types of EDS is sometimes very difficult. With the exception of skin and soft-tissue complications, much of the information in this section is derived from publications that collectively analyzed individuals with hypermobile and classic EDS, without specifying whether there was any difference in manifestations between the two types.

hEDS is generally considered the least severe type of EDS, although significant complications, primarily musculoskeletal, do occur. Clinical variability is substantial. Most individuals who seek medical care are female. Pain and major joint complications are much less common among affected males. This bias may result from differences between men and women with respect to pain perception and inherent joint stability, as well as the effects of sex hormones.

PATHOPHYSIOLOGY

The pathophysiology of hEDS includes mutations in those genes which cause EDS that can alter the production or processing of collagen or proteins that can interact with collagen. Mutations in those genes cause EDS that can alter the production or processing of collagen or proteins that can interact with collagen. The diagnosis of hEDS should include three strict criteria: Criteria-1 is measured using Beighton score, Criteria-2 must have connective tissue disorder according to certain features, and Criteria-3: All these prerequisites must be met: Absence of unusual skin fragility, exclusion of other heritable, and acquired connective tissue disorders including autoimmune rheumatologic conditions. Differential diagnosis includes several disorders that share common characteristics with EDS. For example: cutis laxa, Marfan syndrome, Loeys-Dietz syndrome, Menkes disease, and Pseudoxanthoma elasticum are worth consideration in diagnosis. Complications of hEDS may include joint hypermobility, loose, unstable joints that dislocate easily, joint pain and clicking joints, extreme tiredness (fatigue), and problem with bladder control.



DIAGNOSIS

To diagnose this subtype, three strict criteria must be met. The purpose of this review is not to go into detail about the diagnostic components of these criteria.

Criteria 1

Measured by a Beighton score and a questionnaire for GJH (small and large joints).

Criteria 2

Components must have at least two of the following properties (A&B, A&C, B&C, or A&B&C):
Feature A-systemic manifestations of a more generalized connective tissue disorder (a total of 5 out of 12 must be present)

- Skin that is unusually soft or silky
- Extensibility of the skin that is unusually soft or velvety
- Unexplained striae, such as striae distensae or rubrae, in the back, groynes, thighs, breasts, and abdomen in adolescents, men, or prepubertal women without a history of considerable weight gain or loss.
- Piezogenic papules in the heel on both sides
- Abdominal hernia(s) recurrent or numerous (e.g., umbilical, inguinal, crural)
- Atrophic scarring involves at least two locations without producing true papyraceous and hemosideric scars, as observed in classic EDS.
- Pelvic floor, rectal, and uterine prolapse in children, men, or nulliparous women who do not have a history of morbid obesity or other known predilections
- Crowded teeth and a high or narrow palate
- Arachnodactyly as defined by at least one of the following: I on both sides, a positive wrist sign (Steinberg sign); (ii) on both sides, a positive thumb sign (Walker sign).
- 1.05 arm span-to-height
- Mild or severe MVP based on a detailed echocardiographic criterion
- Z-score > +2 aortic root dilatation

Feature B-positive family history, with one or more first-degree relatives independently meeting the current diagnostic criteria for hEDS.
Feature C-musculoskeletal complications (must have at least 1 of 3):

- Musculoskeletal pain in 2 or more limbs, recurring daily for at least 3 months
- Chronic, widespread pain for ≥3 months
- Recurrent joint dislocations or frank joint instability, in the absence of trauma (a or b).
    a. Three or more atraumatic dislocations in the same joint or two or more atraumatic dislocations in two different joints occurring at other times
    b. Medical confirmation of joint instability at two or more sites not related to trauma.

Criteria 3

All these prerequisites must be met: Absence of unusual skin fragility, exclusion of other heritable, and acquired connective tissue disorders including autoimmune rheumatologic conditions and exclusion of alternative diagnoses that may also include joint hypermobility due to poor muscle tone (hypotonia) and/or connective tissue laxity.[15]

DIFFERENTIAL DIAGNOSIS

Several disorders share some characteristics with EDS. For example, in cutis laxa, the skin is loose, hanging, and wrinkled. In EDS, the skin can be pulled away from the body but is elastic and returns to normal when let go. In Marfan syndrome, the joints are very mobile and similar cardiovascular complications occur. People with EDS tend to have a "Marfanoid" appearance (e.g., tall, skinny, long arms and legs, "spidery" fingers). However, physical appearance and features in several types of EDS also have characteristics including short stature, large eyes, and the appearance of a small mouth and chin, due to a small palate. The palate can have a high arch, causing dental crowding. Blood vessels can sometimes be easily seen through translucent skin, especially on the chest. The genetic connective tissue disorder, Loeys-Dietz syndrome, also has symptoms that overlap with EDS.[11]

In the past, Menkes disease, a copper metabolism disorder, was thought to be a form of EDS. People are not uncommonly misdiagnosed with fibromyalgia, bleeding disorders, or other disorders that can mimic EDS symptoms. Because of these similar disorders and complications that can arise from an unmonitored case of EDS, a correct diagnosis is important.[16] Pseudoxanthoma elasticum is worth consideration in diagnosis.[17]

PROGNOSIS

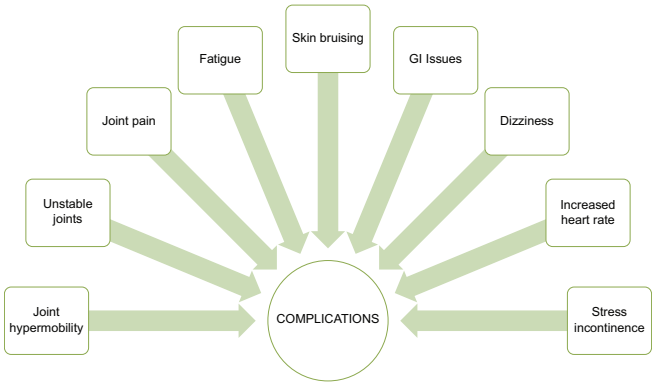
The long-term outlook (prognosis) for people with hEDS depends on the severity of the condition and the signs and symptoms present. Although this form of EDS does not typically impact life expectancy, musculoskeletal (muscle and bone) pain and joint instability can have a significant impact on daily function and quality of life.[18]

COMPLICATIONS

People with hEDS may have:

- Joint hypermobility
- Loose, unstable joints that dislocate easily

- Joint pain and clicking joints
- Extreme tiredness (fatigue)
- Skin that bruises easily
- Digestive problems, such as heartburn and constipation
- Dizziness and an increased heart rate after standing up
- Problems with internal organs, such as MVP or organ prolapse
- Problems with bladder control (stress incontinence).[13]



MANAGEMENT

The treatment of hEDS depends on the signs and symptoms present in each person. No cure for EDSs is known, and treatment is supportive. For example, physical therapy is often recommended to strengthen muscles and improve joint stability. Assistive devices such as braces, wheelchairs, or scooters may be necessary depending on the severity of joint instability.[19] Aquatic therapy promotes muscular development and coordination. With manual therapy, the joint is gently mobilized within the range of motion and/or manipulations. If conservative therapy is not helpful, surgical joint repair may be necessary. Medication to decrease pain or manage cardiac, digestive, or other related conditions may be prescribed. To decrease bruising and improve wound healing, some people have responded to vitamin C. Special precautions are often taken by medical care workers because of the sheer number of complications that tend to arise in people with EDS.

To evaluate baseline echocardiogram aortic root diameter is adjusted for age and body surface area. Significant aortic enlargement and/or other cardiac abnormalities should prompt consideration of alternative diagnoses.

PAIN MEDICATIONS

Comfortable writing utensils and a low-stress mattress serve an important role in reducing musculoskeletal pain. Pain management is tailored to the individual. Gastrointestinal and psychological complications are likewise managed per an individual's needs. In addition to physical therapy and low-resistance exercise, calcium and vitamin D can help maximize bone density. DEXA bone density scans should be conducted every other year.[20]

Pain medications may be prescribed to manage severe musculoskeletal (muscle and bone) pain. Affected people may be monitored for the development of osteopenia (low bone density) and aortic root dilatation (enlargement of the blood vessel that distributes blood from the heart to the rest

Table 1: Representing classification of EDS on a different basis

Villefranche classification (genetic basis): Defective collagen	EDS classification
Classical (AD): type V Collagen	cEDS AD
Hypermobility (AD): Unknown	clEDS AR
Vascular (AD): type III collagen	cvEDS AR
Kyphoscoliosis (AR): deficiency of lysyl hydroxylase	vEDS AD
	hEDS AD
Arthrochalasia (AD): Type I collagen	aEDS AD
Dermatosparaxis (AR): Type I collagen processing	dEDS AR
	kEDS AR
	BCS AR
	spEDS AR
	mcEDS AR
	mEDS AD or AR
	pEDS AD

AD: Autosomal dominant, AR: Autosomal recessive, EDS: Ehlers-Danlos syndrome, cEDS: Classical EDS, clEDS: Classical-like EDS, cvEDS: Cardiac-valvular EDS, vEDS: Vascular EDS, hEDS: Hypermobile EDS, aEDS: Arthrochalasia EDS, dEDS: Dermatosparaxis EDS, kEDS: Kyphoscoliotic EDS, BCS: Brittle Cornea Syndrome, SEDS: Spondylodysplastic EDS, mcEDS: Musculocontractural EDS, mEDS: Myopathic EDS, pEDS: Periodontal EDS

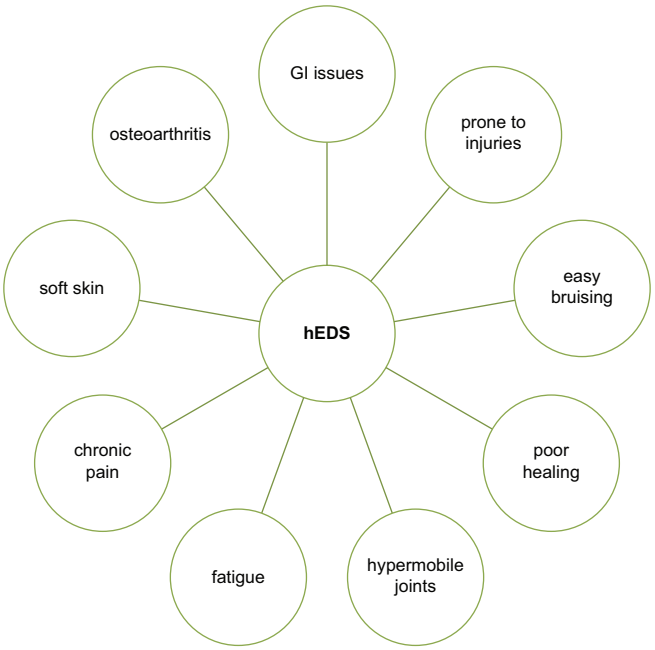


Figure 1: Symptoms of hEDS. hEDS: Hypermobile Ehlers-Danlos syndrome

of the body). Cannabinoids and medical marijuana have shown some efficacy in reducing pain levels.[21]

Table 2: EDS types grouped according to the underlying genetic defect

EDS type	IP	GENE	Protein
Group A: Disorders of collagen primary structure and collagen processing			
cEDS	AD	Major: COL5A1, COL5A2 Rare: COL1A1	COLLV COLLI
vEDS	AD	COL3A1	COLLIII
aEDS	AD	COL1A1, COL1A2	COLLI
dEDS	AR	ADAMTS2	ADAMTS-2
cvEDS	AR	COL1A2	COLLI
Group B: Disorders of collagen folding and collagen cross-linking			
kEDS	AR	PLOD1 FKBP14	LH1 FKBP22
Group C: Disorders of structure and function of myomatrix			
clEDS	AR	TNXB	Tenascin X
mEDS	AD/AR	COL12A1	COLLXII
Group D: Disorders of glycosaminoglycan biosynthesis			
spEDS	AR	B4GALT7 B3GALT6	β4GalT7 β3GalT6
mcEDS	AR	CHST14 DSE	D4ST1 DSE
Group E: Disorders of complement pathway			
pEDS	AD	CIR CIS	Clr Cls
EDS type molecularly unsolved			
hEDS	AD	Unknown	Unknown

AD: Autosomal dominant, AR: Autosomal recessive, EDS: Ehlers-Danlos syndrome, cEDS: Classical EDS, clEDS: Classical-like EDS, cvEDS: Cardiac-valvular EDS, vEDS: Vascular EDS, hEDS: Hypermobile EDS, aEDS: Arthrochalasia EDS, dEDS: Dermatosparaxis EDS, kEDS: Kyphoscoliotic EDS, SEDS: Spondylodysplastic EDS, mcEDS: Musculocontractural EDS, mEDS: Myopathic EDS, pEDS: Periodontal EDS

A physiotherapist can teach you exercises to help strengthen your joints, avoid injuries, and manage pain. Myofascial release (any physical therapy modality that reduces spasm) provides short-term relief of pain, lasting hours to days. An occupational therapist can help you manage daily activities and give advice on equipment that may help you. Usable methods may include posture re-education, muscle release, joint mobilization, trunk stabilization, and manual therapy for overworked muscles. Psychological counseling and cognitive behavioral therapy (CBT) may be useful if you are struggling to cope with long-term pain. For certain types of EDS, regular scans carried out in hospital can detect problems with internal organs. Genetic counseling can help you learn more about the cause of your condition, how it is inherited, and what the risks are of passing it on to your children.

SURGERY

The instability of joints, leading to subluxations and joint pain, often requires surgical intervention in people with EDS. Instability of almost all joints can happen but appears most often in the lower and upper extremities, with the wrist, fingers, shoulder, knee, hip, and ankle being most common.[22]

Common surgical procedures are joint debridement, tendon replacements, capsulorrhaphy, and arthroplasty. After surgery, the degree of stabilization, pain reduction, and people's satisfaction can improve, but surgery does not guarantee an optimal result; affected peoples and surgeons report being dissatisfied with the results. The consensus is that conservative treatment is more effective than surgery,[23] particularly since people have extra risks of surgical complications due to the disease. Three basic surgical problems arise due to EDS – the strength of the tissues is decreased, which makes the tissue less suitable for surgery; the fragility of the blood vessels can cause problems during surgery; and wound healing is often delayed or incomplete.[24] If considering surgical intervention, seeking care from a surgeon with extensive knowledge and experience in treating people with hEDS and joint hypermobility issues would be prudent.[25]

Table 3: Management of hEDS

Pain management	Medication	Surgery
• Physiotherapy • Occupational therapy • Orthopedic instruments • Aquatic therapy • Cognitive behavioral therapy	• NSAIDs • Acetaminophen • Opioids • Lidocaine • Tricyclic antidepressants • Anticonvulsants • Selective norepinephrine reuptake inhibitors • Benzodiazepines • Topical capsaicin	• Joint debridement • Tendon replacements • Capsulorrhaphy • Arthroplasty • Surgery does not guarantee an optimal result

hEDS: Hypermobile Ehlers-Danlos syndrome, NSAIDs: Non-steroidal anti-inflammatory drugs

Prolotherapy, in which saline and/or other irritants are injected in tendons or around joints to induce scar formation and increase stability, has not been objectively studied. It is probably safe and probably subject to the same limitations as orthopedic surgery. Anesthetic/corticosteroid injections for localized areas of pain and acute inflammation are often helpful but cannot be repeated indefinitely. "Dry needling" without injection of any material sometimes provides similar benefit. Anesthetic nerve blocks can provide temporary relief of neuropathic pain. These are sometimes followed by surgical nerve root destruction and/or implantable stimulators (sensory or motor), with variable results. Constant intrathecal delivery of anesthetic and/or opioid medication may reduce the need for oral/systemic medications but should only be considered as a last resort.

Local anesthetics, arterial catheters, and central venous catheters cause a higher risk of bruise formation in people with EDS. Some people with EDS also show a resistance to local anesthetics.[26] Resistance to lidocaine and bupivacaine is common, and mepivacaine tends to work better in people with EDS. Special recommendations for anesthesia are given for people with EDS. Detailed recommendations for anesthesia and perioperative care of people with EDS should be used to improve safety. Surgery in people with EDS requires careful tissue handling and a longer immobilization afterward.

MEDICATIONS

Non-steroidal anti-inflammatory drugs (NSAIDs) may help if the pain is caused by inflammation. However, long-term use of NSAIDs is often a risk factor for gastrointestinal, renal, and blood-related side effects. It can worsen symptoms of mast cell activation syndrome, a disease that may be associated with EDS. Acetaminophen can be used to avoid the bleeding-related side effects of NSAID's. Opioids have shown efficiency in some EDS cases for the management of both acute and chronic pain. Lidocaine can be applied topically after subluxations and painful gums. It can also be injected into painful areas in the case of musculoskeletal pain.[27] If the pain is neuropathic in origin, tricyclic antidepressants in low doses (typical doses are nortriptyline 25–150 mg or trazadone 50–300 mg every evening), anticonvulsants (gabapentin should be up to at least 1200 mg/3x/day, pregabalin at least 300 mg), and selective norepinephrine reuptake inhibitors (venlafaxine, desvenlafaxine, duloxetine, and milnacipran) can be used· Benzodiazepines may offer some short-term reduction in muscle spasm but are poor choices for long-term muscle relaxation and carry high risk of tolerance, dependency, and addiction. Topical lidocaine as a cream or patch is sometimes useful for localized areas of pain. Topical capsaicin is of questionable utility but is safe. Magnesium, either topically as Epsom salt baths or orally in any form, may also reduce muscle spasm and pain Table 3.[28]

CONCLUSION

There is very limited evidence to guide the use of physical and mechanical therapies for lower limb problems in children with Hypermobility Spectrum Disorder and Hypermobile Ehlers Danlos Syndrome. Mechanical therapies have not been evaluated in RCTs and results of the two RCTs of physical therapies do not definitively guide physical therapy prescriptions.

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