

Hypermobile Ehlers–Danlos Syndrome (a.k.a. Ehlers–Danlos Syndrome Type III and Ehlers–Danlos Syndrome Hypermobility Type): Clinical Description and Natural History

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The hypermobile type of Ehlers–Danlos syndrome (hEDS) is likely the most common hereditary disorder of connective tissue. It has been described largely in those with musculoskeletal complaints including joint hypermobility, joint subluxations/dislocations, as well as skin and soft tissue manifestations. Many patients report activity-related pain and some go on to have daily pain. Two undifferentiated syndromes have been used to describe these manifestations—joint hypermobility syndrome and hEDS. Both are clinical diagnoses in the absence of other causation. Current medical literature further complicates differentiation and describes multiple associated symptoms and disorders. The current EDS nosology combines these two entities into the hypermobile type of EDS. Herein, we review and summarize the literature as a better clinical description of this type of connective tissue disorder. © 2017 Wiley Periodicals, Inc.

KEY WORDS: joint hypermobility; joint hypermobility syndrome; Ehlers–Danlos syndrome type III; Ehlers–Danlos syndrome hypermobility type

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INTRODUCTION

Hypermobile Ehlers–Danlos syndrome (hEDS; previously known as EDS type III according to the Berlin nosology [Beighton et al., 1988] and EDS hypermobility type in the Villefranche nosology [Beighton et al., 1998]) is a heritable connective tissue disorder (HCTD) primarily identified as having generalized joint hypermobility (GJH), related musculoskeletal manifestations, and a milder involvement of the skin, which lacks the degree of

cutaneous features typically observed in the classical and vascular types of EDS. Since the Villefranche nosology, the clinical description of hEDS in the medical literature has expanded considerably to include more features, such as chronic pain, chronic fatigue, dysautonomia, and anxiety among other associated symptoms.

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In a similar timeframe, joint hypermobility syndrome (JHS; also called hypermobility syndrome or benign joint hypermobility syndrome) has been further delineated since its original description [Kirk et al., 1967; Grahame et al., 2000]. The clinical spectrum of JHS is often clinically indistinguishable from hEDS according to an international panel of experts [Tinkle et al., 2009]. Subsequently, Castori et al. [2014] demonstrated the evolving natural history by studying multi-generational pedigrees and applying the then current diagnostic criteria for each (hEDS and JHS) concluding that both disorders may co-exist in the same pedigrees and could not be distinguished in the familial cases. It is, therefore, the consensus of the authors on behalf of the International Consortium on the Ehlers–Danlos Syndromes, based on the present state of our knowledge, that the two conditions are part of the same clinical spectrum ranging from apparently symptomatic GJH to the most disabled individuals fitting the new diagnostic criteria for hEDS.

Grouping all phenotypes comprised in this spectrum under the same heading may be misleading on both nosologic and therapeutic perspectives. Although it is reasonable that the congenitally “double-jointed” gymnast and the chronically disabled hEDS patient may share a strong genetic and pathophysiological background, to date, we have not any proof unequivocally demonstrating that they carry the same genetic trait, unless, perhaps, they are linked by a close blood relationship. But also in this case, as the molecular bases of these phenotypes remain unknown, we cannot exclude that these two individuals share a part only of the causative genetic milieu (i.e., oligogenic/polygenic disorder) in the absence of shared additional clinically or structurally relevant signs.

The new criteria of hEDS are stricter than the old Villefranche nosology [Beighton et al., 1988] and the Brighton criteria [Grahame et al., 2000]. This is intended to define a more homogeneous phenotype shared among patients who require long-term medical

attention for hEDS and to facilitate scientific identification of the underlying genetic cause(s) of the condition. Accordingly, some patients meeting the old Villefranche and Brighton criteria will not meet the new hEDS criteria. For all these individuals not showing a sufficiently convincing hEDS phenotype, some alternative labels within the above-mentioned spectrum are presented elsewhere in this issue (see “A Framework for the Classification of Joint Hypermobility and Related Conditions” by Castori et al., this issue).

Given the extreme variability within this spectrum and the age-influenced progression of the phenotype, some of these patients will probably remain under a relaxed program of follow-up in order to promptly detect the possible evolution into a full-blown hEDS phenotype.

METHODS

The Committee on hEDS of the International Consortium on the Ehlers–Danlos Syndromes met by telepresence or through electronic correspondence throughout 2015 and 2016 to discuss the nosology and clinical description of hEDS. The following reflects extensive literature review and the professional experience of the committee members as well as insights from various contributing members of the international effort on EDS through the Consortium.

CLINICAL DESCRIPTION

The below sections of this paper describing the phenotype and natural history of hEDS are extracted by the literature available on EDS hypermobility type, EDS type III and JHS (old nomenclature). To date, we are not sure that all available data will stand true for the newly defined hEDS. However, they are considered a good proxy for the delineation of the hEDS phenotype. In the following sections, the acronym hEDS is used as a substitute for EDS hypermobility type, EDS type III, and JHS, unless the distinction between these phenotypes is necessary for reasons of clarity.

Prevalence

Accurate prevalence estimation studies are still lacking for hEDS. Steinmann et al. [2002] reported a minimum prevalence of 1/5,000 for all types of EDS collectively. As hEDS likely represents 80–90% of cases of EDS, the prevalence is presumed not lower than 1/5,000. A much higher prevalence of 7.5/1,000 to 20/1,000 (0.75–2%) for “symptomatic” GJH has been proposed, considering that about 10% of individuals with GJH may develop related symptoms in their lifetime [Hakim and Sahota, 2006]. Others confirmed such an estimation [Hamonet et al., 2015]. A much higher prevalence for the association of JH and widespread pain is reported by Mulvey et al. [2013] and Morris et al. [2016]. Based on data obtained from a large epidemiological study undertaken on a population of 12,853, 3.4% had joint hypermobility and widespread pain which was been used as a proxy for hEDS [Mulvey et al., 2013]. Accordingly, hEDS is likely the most common systemic inherited connective tissue disorder in humans which translates in approximately 2 million in the United Kingdom, 10 million in the United States, 17 million in Europe, and 255 million affected worldwide. However, the diagnostic criteria proposed herein are more selective than the Villefranche nosology for EDS hypermobility type and the Brighton criteria for JHS, so the prevalence of hEDS under these criteria may be somewhat lower than some of these estimates.

Genetics

hEDS, for the most part, is inherited as an autosomal dominant disorder of connective tissue but other patterns of inheritance can be seen in some families; however, this may be confounded by non-penetrance, sex-influence as well as genetic heterogeneity. Unfortunately, unlike the other types of EDS, hEDS has no known genetic etiology responsible for any significant portion of this population. JH itself is multifactorial with age, gender, weight, training, and other aspects that influence this

phenotype. Twin studies have determined that the concordance of JH among dizygotic twins was 36% in 472 female twin pairs, whereas monozygotic twins had a concordance rate of 60% in 483 female twin pairs suggesting a strong genetic trait with multifactorial influences [Hakim et al., 2004].

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Various studies have suggested that hEDS is a phenotypically and presumably genetically heterogeneous disorder [De Wandele et al., 2013; Pacey et al., 2015a]. A minority of cases have been reported to be due to a haploinsufficiency of tenascin X (*TNXB*) [Zweers et al., 2003]. However, the haploinsufficiency was not penetrant in males and only partially in females (9 out of 14). *TNXB* lies near *CYP21A2*, the gene associated with congenital adrenal hyperplasia (CAH). The region contains several pseudogenes including those for *TNXB* and *CYP21A2*. Intragenic recombination and resultant microdeletion is a common cause of CAH. Merke et al. [2013] reported in several CAH individuals, an hEDS-like phenotype due to chromosomal microdeletion and coined the syndrome CAH-X. More recently, a novel missense variant of *TNXB* was shown in 10 individuals of seven families and was associated with the hEDS phenotype [Morissette et al., 2015]. Tenascin-X is an extracellular matrix protein and potentially can affect connective tissue in its various forms. However, the exact physiologic process remains unknown and heterozygous tenascin-X

deficiency accounts for only a small percentage of hEDS.

A few case reports have pointed to other genetic factors in hEDS. A collagen type III (*COL3A1*) variant was found in one family without the arterial or intestinal fragility typical of vascular EDS [Narcisi et al., 1994], but no subsequent reports of *COL3A1* mutation have been published in hEDS. More recently, a variant of the *LZTS1* gene was found in four families with a hEDS phenotype among 231 individuals evaluated, but the causal nature of these variants remains unexplored [Syx et al., 2015]. It is believed by many that the hEDS phenotype represents substantial genetic heterogeneity. With the wider use of whole exome or whole genome sequencing with strict phenotyping, it is expected that additional hEDS-related genes will be identified. Eventual identification of validated genetic etiologies will allow objective clinical testing and better delineation of the full phenotype.

The Evolving Natural History

The Villefranche criteria for EDS hypermobility type and Brighton criteria for JHS were originally conceived for the diagnosis of two conditions perceived as distinct. However, they were subsequently recognized as separate tools for describing a single disorder [Tinkle et al., 2009; Castori and Colombi, 2015]. Such a dichotomy likely reflects the protean progression of the same entity. Anecdotally, many families were identified that had diagnoses of EDS hypermobility type and JHS in various family members usually segregated on age. The clinical identity between EDS hypermobility type and JHS was provisionally demonstrated in a single multiplex family with affected individuals fitting alternatively the Villefranche and Brighton criteria [Hermanns-Lê et al., 2012].

Definitive support to such a clinical overlap in families with EDS hypermobility type and JHS came from a study in 23 Italian pedigrees [Castori et al., 2014]. In these families, the formal diagnosis was influenced by age, with

children usually meeting the Villefranche criteria only and the elderly mostly ascertained by the Brighton criteria alone, while both diagnoses often coexisted in young adults and middle-aged affected members. This implied that the mean Beighton score, frequency (and distribution) of musculoskeletal pain, manifestations of skin involvement, and appearance of other complications were strongly influenced by age. Such a phenomenon seems not limited to the items included in the Villefranche and Brighton criteria, but also extends to other disease manifestations not originally considered, such as the gastrointestinal involvement [Castori et al., 2015a].

In an Italian study on disease progression with 21 hEDS patients, the existence of three “discrete” disease phases was proposed: a “hypermobility” phase, a “pain” phase, and a “stiffness” phase [Castori et al., 2010a]. Subsequent observations and speculations on the same ethnic group reinforced the concept and smoothed the rigid approach on three separate phases [Castori et al., 2011a, 2013, 2015b]. The three-step model can remain a prototypical description of the potential disease course, but not every patient experiences all three phases and the rate of transition between phases can be highly variable. The decrease of the Beighton score in the symptomatic individual may be considered a proxy for disease evolution in hEDS [Castori et al., 2011a, 2015b]. In cross-sectional studies on patients with different ages at diagnosis, a tendency of the Beighton score to turn “negative” (i.e., <5) around the fourth decade of life has been identified [Castori et al., 2011a].

The “hypermobility” phase dominates the first several years of life with contortionism and propensity for sprains and dislocations. Pain is often limited to lower limbs (i.e., persistent “growing pains”) but pain with fine motor or repetitive tasks such as handwriting is also commonly encountered [Gedalia et al., 1996; Murray and Woo, 2001]. Easy fatigability may be a feature, together with voiding dysfunction [Beiraghdar et al., 2013; Kajbafzadeh

et al., 2014]. Some hypermobile children experience developmental dyspraxia (or developmental coordination disorder), manifesting with mild hypotonia and non-specific developmental delay in gross and fine motor skills attainment [Adib et al., 2005; Kirby et al., 2005; Easton et al., 2014].

The “pain” phase is characterized by generalization and progressive chronicity of musculoskeletal pain, which is often diagnosed as fibromyalgia [Ting et al., 2012], summation of other forms of chronic pain, such as pelvic pain (in women) and headache, as well as exacerbation of fatigue. This phase typically starts in the second to the fourth decade of life and often associates with a variegated constellation of additional complaints, such as paresthesias, mixed and treatment-resistant functional gastrointestinal disorders, orthostatic intolerance, and pelvic dysfunction.

A generalized reduction of joint mobility dominates the “stiffness” phase, in which patients usually experience significant reduction in their functionality due to the combination of disabling symptoms (e.g., pain and fatigue) as well as motor limitations due to the coexistence of reduced muscle mass and weakness, defective proprioception, prior injuries, and arthritis. In this phase, observed in a few adults and elderly only, the symptomatology that appeared in the “pain” phase escalates and GJH is usually not appreciated.

hEDS is considered to be an autosomal dominant trait with variable expressivity. Yet, many studies point out a strong excess of affected females, at least in adults [Castori et al., 2010a]. The ratio ranges from 8–9:1 to ~2:1, depending upon how patients are selected. The lowest ratio was registered in familial cases only with the inclusion of affected relatives [Castori et al., 2014]. In early childhood, the male to female ratio of affected is similar. However, in the general population, as children enter puberty, joint mobility tends to increase in females and decrease in males [Fig. 1; Quatman et al., 2008]. The reason for the sex bias remains incompletely understood with speculation of a greater

influence of female sex hormones [Wolf, 2009; Shultz et al., 2012; Boyan et al., 2013]. hEDS is best defined as an autosomal disorder “influenced by sex,” with a predominance of symptoms in females. It should also be recognized that most chronic pain syndromes also have a female predominance, and this may be another contributing factor [Wijnhoven et al., 2006].

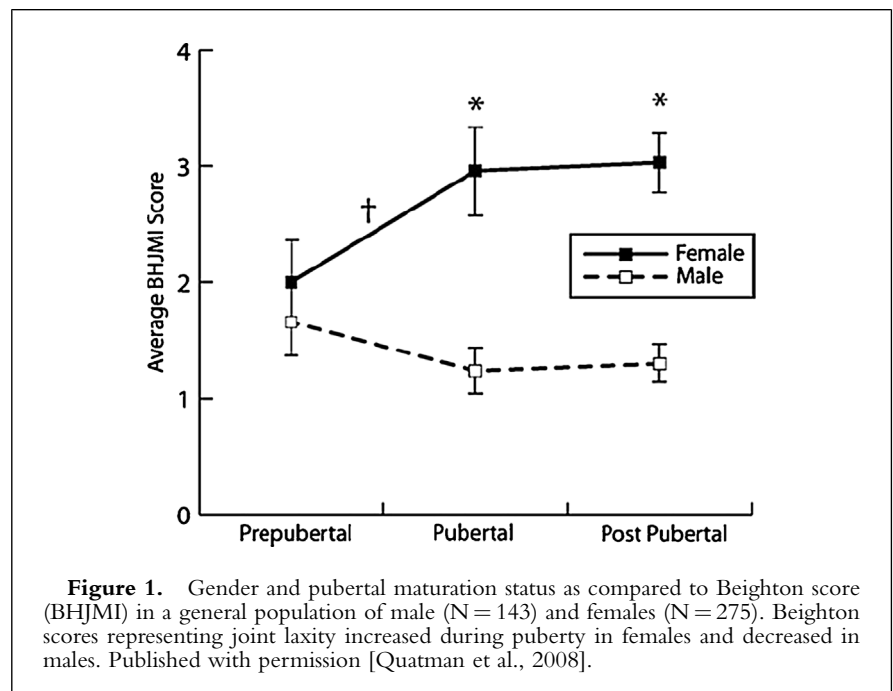
The phenotype of hEDS is one that evolves over time and has a gender bias that also changes over time. Previous attempts at diagnostic criteria (Villefranche and Brighton) have often not fully accounted for the natural transition from EDS hypermobility type to JHS with age within the above described disease evolution [Castori et al., 2013]. Such a nosological conundrum is solved by the use of unified diagnostic criteria.

Symptomatic Joint Hypermobility

Clinical problems associated with JH may present at any time of life. Syndromic or excessive JH can be difficult to diagnose in children, who are normally more flexible than adults [Tofts et al., 2009; Castori, 2012]. GJH is often diagnosed using the Beighton score (see also “Measurement properties of existing clinical assessment methods

for local and generalized joint hypermobility—a systematic review,” Juul-Kristensen et al., this issue), although this has major limitations in selected populations, such as the very young and the elderly [Dolan et al., 2003; Castori, 2012]. It can be asymptomatic, and is more common among dancers and elite athletes where it may confer a constitutional advantage [Day et al., 2011; Beighton et al., 2012]; however, it may predispose to higher injury rates [Briggs et al., 2009; Konopinski et al., 2015].

When symptomatic, it often manifests in childhood or adolescence, along with associated features, but is often poorly recognized [Engelbert et al., 2003]. Adults may recall being flexible as a child, and being able to perform “party tricks” with their joints. The two more common patterns of presentation are with: (1) a limited number of painful and/or unstable joints or (2) chronic widespread musculoskeletal pain (which may have been diagnosed as fibromyalgia). In the former group, the more common problematic or unstable joints often presenting with recurrent subluxations/dislocations or pain are the shoulder, knee, and ankle [Tobias et al., 2013]. Iliotibial band syndrome (sometimes called “snapping hip”



syndrome) is also common, and is frequently perceived by the patient as hip instability, even though the sense of motion occurs over the greater trochanters and not in the groin. In the group with chronic widespread musculoskeletal pain, the pain distribution and descriptions often overlap with fibromyalgia to such an extent that it can be virtually impossible to distinguish [Ofluoglu et al., 2006; Ting et al., 2012]. It is important to recognize that there are many causes for both localized and widespread joint or musculoskeletal pain, and that the presence of pain alone without associated JH is insufficient to establish a diagnosis of EDS. Over time, many patients lose their former joint laxity, while others remain hypermobile [Castori, 2012]. This reduction in JH over time further complicates the diagnostic evaluation of chronic pain patients over approximately age 40.

In common with other chronic pain syndromes, there may also be overlapping diagnoses such as chronic fatigue, irritable bowel syndrome, temporomandibular joint dysfunction, sleep disturbance, as well as depression and anxiety. The specific associated impairments and their severity can vary markedly, and are not necessarily associated with the degree of joint laxity. Higher rates of anxiety and depression have been noted in GJH, hEDS, and JHS since 1994 [Lumley et al., 1994; Mallorqui-Bagué et al., 2015]. Distress, kinesiophobia, and individuals' coping strategies and behavioral responses are more likely to predict impairment and quality of life (QoL) than the intensity of pain [Celletti et al., 2013]. Physical deconditioning can exacerbate joint laxity, contributing to an ongoing cycle of deconditioning, weakness, joint instability, and worsening pain [Castori, 2012].

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Pain

The specific underlying cause(s) and mechanism(s) of pain in EDS, and in particular hEDS, are not well understood, but both acute and chronic pain are common manifestations and often contribute to disability [Rombaut et al., 2010, 2011a,b, 2012; Voermans et al., 2010a,b; Castori et al., 2012a; Murray et al., 2013]. Nociceptive pain directly related to affected muscles, joints, and connective tissue is frequent. Neuropathic pain, characterized by allodynia and/or typical quality descriptors, such as electrical, burning, numb, or tingling, is also common. Anatomic imaging (e.g., for impingement of the central spine or foraminal nerve roots) and functional electrodiagnostic studies (e.g., nerve conduction studies or electromyography) are often negative even in the face of subjective symptoms highly suggestive of a neuropathic etiology. Skin biopsy may reveal reduction of intradermal nerve fiber density, suggestive of small fiber neuropathy [Cazzato et al., 2016].

Some potential etiologies of pain include spasm of muscles, tendons, and other connective tissue; direct trauma due to joint instability; and nerve entrapment [Granata et al., 2013]. Osteoarthritis, secondary to joint instability, is also a likely factor. Central sensitization, generalized hyperalgesia, chronic regional pain syndrome, and similar systemic or regional pathogenic mechanisms may contribute in later stages [Castori et al., 2013; Rombaut et al., 2015; Scheper et al., 2015, 2016a; Di Stefano et al., 2016]. See

also “Pain Management in the Ehlers–Danlos Syndromes” by Chopra et al., this issue.

Skin and Fascia

The Ehlers–Danlos syndromes are primarily due to disorders of connective tissue matrix proteins, in particular, but not exclusively collagen (see also “The Ehlers–Danlos Syndromes: The New” by Malfait et al., this issue). It is presumed that the genetic determinants of hEDS are also likely of collagen or collagen-related genes. The dermis comprises 70% dry-weight collagen so that the skin presents itself as a visible, palpable, and readily accessible organ for the study of collagen-related genetic aberrations. The skin in hEDS is different from normal skin and these differences constitute an important aid to diagnosis. In hEDS, the skin texture is characteristically soft, silky, or velvety to the touch. It may be semi-transparent so that veins and tendons are more easily visible than normal, but this is subtle in comparison with the skin transparency of vascular EDS.

The skin in hEDS is also hyperextensible. The technique used is important in obtaining reliable results. The stretchiness is subtle in hEDS and can easily be overlooked if the clinician is anticipating the degree of stretch seen in classical EDS. The “rubber glove skin test” may distinguish between hEDS skin and normal, by raising a skin fold on the dorsum of the hand in patients with hEDS, the skin is seen to stretch over a much wider area than is normal, extending to the wrist and beyond. However, the clinical evaluation of skin laxity follows that outlined in the new diagnostic criteria for hEDS (see also “The 2017 International Classification of the Ehlers–Danlos Syndromes” by Malfait et al., this issue).

The hEDS skin is more fragile than normal, but much less so than in the other types of EDS. Easy bruising is common but poorly defined. Wound healing may be impaired with the production of mildly atrophic scars, which may be wider than the original wound and/or sunken below the

surface of the surrounding skin. Again, the degree of atrophic scarring in hEDS is less severe than in and usually distinguishable from the other types of EDS (Fig. 2). However, its occurrence may be exacerbated by the use of local or systemic steroids [Jacks and Zirwas, 2016].

Striae atrophicae often appear during the adolescent growth spurt usually between the ages of 11–13 years and not necessarily associated with rapid weight gain; however, this can also be seen in adolescents without an underlying connective tissue disorder as well [Feldman and Smith, 2007]. By contrast, striae

gravidarum may be minimal or non-existent in some as skin of the mature hEDS female is inherently stretchy so that the elastic limit is never reached despite the enlarging maternal abdomen.

Other important collagen-bearing tissues may also fail in hEDS due to their inherent fragility. Cerebrospinal fluid (CSF) leaks, spontaneous or induced, are a possible cause of orthostatic headaches. One case-control study of patients with spontaneous CSF leak reported a greater than expected frequency (16/50) of patients with classical EDS, hEDS, or an unclassified hereditary disorder of connective tissue [Reinstein et al., 2013], while a similar study found no increase in features of hereditary connective tissue disorders between patients with spontaneous intracranial hypotension and controls [Liu et al., 2011].

Both of the musculotendinous support of the diaphragm and the pelvic floor can fail mechanically leading to hiatal hernia [Nelson et al., 2015] or pelvic floor weakness further leading to uterine/rectal prolapse, rectocele, cystocele, and/or enterocele [Veit-Rubin et al., 2016]. Fascial weakness can lead to hernias in the inguinal, femoral, or umbilical areas or at sites of previous surgical incisions as after abdominal surgery [Nazem et al., 2013].

Fatigue

Fatigue is common among adolescents in general, affecting approximately one-third of the general population and can interfere with activities of daily living including school performance and attendance [Kizilbash et al., 2014; Sleep Working Group et al., 2014]. However, chronic fatigue defined as fatigue lasting longer than 6 months, occurs in ~1% of adolescents in the general population [Werker et al., 2013]. The entity chronic fatigue syndrome (CFS) occurs more commonly in women and particularly in those over 45 years of age but is often underdiagnosed [Yancey and Thomas, 2012; Wright Clayton, 2015]. It can be associated with impaired memory, cognitive deficits, muscle pain, joint pain,

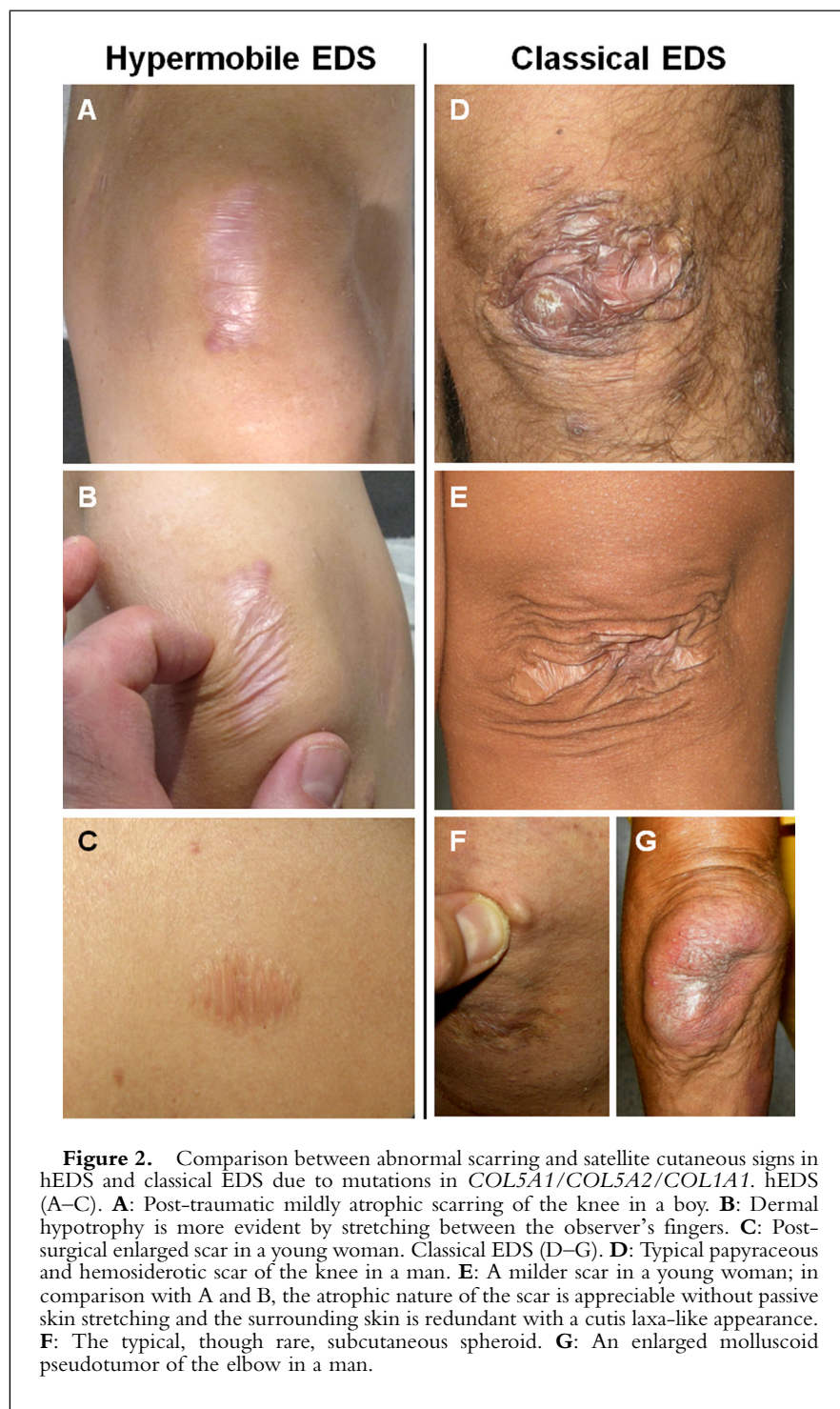


Figure 2. Comparison between abnormal scarring and satellite cutaneous signs in hEDS and classical EDS due to mutations in *COL5A1*/*COL5A2*/*COL1A1*. hEDS (A–C). **A:** Post-traumatic mildly atrophic scarring of the knee in a boy. **B:** Dermal hypotrophy is more evident by stretching between the observer’s fingers. **C:** Post-surgical enlarged scar in a young woman. Classical EDS (D–G). **D:** Typical papyraceous and hemosiderotic scar of the knee in a man. **E:** A milder scar in a young woman; in comparison with A and B, the atrophic nature of the scar is appreciable without passive skin stretching and the surrounding skin is redundant with a cutis laxa-like appearance. **F:** The typical, though rare, subcutaneous spheroid. **G:** An enlarged molluscoid pseudotumor of the elbow in a man.

headaches, non-restorative sleep, post-exertional malaise, as well as psychological issues [Fossey et al., 2004; Nijs et al., 2006; Meeus et al., 2007]. The etiology of the chronic fatigue (syndrome) is multifactorial and includes infectious agents, immune dysregulation, allergies, endocrinopathy, nutritional deficiency, and abnormally low blood pressure often associated with postural orthostatic tachycardia syndrome (POTS) or neurally mediated hypotension (NMH) [Kanjwal et al., 2010; Werker et al., 2013; Kizilbash et al., 2014].

Fatigue is one of the most common complaints among those with hEDS [Gazit et al., 2003; Maeland et al., 2011; De Wandele et al., 2013; Murray et al., 2013]. Chronic fatigue in hEDS includes bodily and mental fatigue which only minimally improves with rest and often fits well into the diagnostic criteria of CFS [Castori et al., 2011b]. In a small series of 12 EDS patients (six classical EDS; six hEDS), Rowe et al. [1999] characterized that all had chronic fatigue, post-exertional malaise, and unrefreshing sleep, whereas 92% had impaired cognition/memory; 83% with polyarthralgia and headache; and 58% with muscle pain. Sore throat and lymphadenopathy occurred in the minority at 25%. In a subsequent study of 58 consecutive children with CFS, Barron et al. [2002] described GJH was significantly more common in the CFS population than in healthy controls. In 273 EDS patients, pain and fatigue comprised 31% of the functional impairment with fatigue having a slightly greater impact overall [Voermans et al., 2010a].

The fatigue in hEDS, as in the general population, is under recognized [Rombaut et al., 2015] and may increase in prevalence with age [Castori et al., 2011a]. Like in the general population, fatigue in hEDS is multifactorial with contributing factors including pain, sleep disturbance, dysautonomia, medications, and/or allergies. It has been associated with greater pain, functional impairment, and psychological distress as well as decreased QoL [Voermans et al., 2010b; Ali Zekry et al., 2013;

Scheper et al., 2013; Pacey et al., 2015a, b; Hershenfeld et al., 2016].

Fatigue may also be a factor in musculoskeletal pain and injury. Exercise to the point of physical fatigue has been shown to alter kinematics, postural stability, and coordination, which may increase the risk of direct injury and also the risk of falls causing secondary injury [Sparto et al., 1997; Dickin and Doan, 2008]. A study of 30 EDS patients, five of whom had hEDS, showed correlation between fatigue and objectively measured muscle weakness [Voermans et al., 2011]. Exercise-induced fatigue increases knee laxity [Skinner et al., 1986], which may also increase the risk of knee injury. Fatigue is also associated with reduced ground reactive force during gait, suggestive of decreased proprioception [Celletti et al., 2012], which could also increase the risk for falls and injury. Severity of fatigue also correlated with kinesiophobia in hEDS and, therefore, became an activity-limiting factor [Celletti et al., 2013].

In conclusion, fatigue and especially chronic, debilitating fatigue is common in hEDS. Fatigue decreases muscle control and coordination, can inhibit physical activity, and may increase risk for injury. The fatigue is mental as well as physical, leading to impaired cognition and memory recall. It is also associated with multiple comorbidities linked to pain, sleep disturbance, anxiety and depression, as well as decreasing function and QoL. See also “Guidelines on the Assessment and Management of Chronic Fatigue in Ehlers–Danlos Syndrome” by Alan Hakim et al., this issue.

Cardiovascular

Mild dilation of the aortic root may develop in up to one-third of children or young adults [Wenstrup et al., 2002; McDonnell et al., 2006; Atzinger et al., 2011], but is unlikely to progress and typically does not require any specific treatment [Atzinger et al., 2011]. Baseline echocardiography is not recommended based on these findings alone but depend on other symptoms and differential diagnoses upon presentation.

POTS, NMH, and orthostatic intolerance are common manifestations in hEDS [Rowe et al., 1999; Gazit et al., 2003; Mathias et al., 2011]. Head-up tilt test may or may not establish a specific etiology, but often does not affect therapeutic decision-making and, therefore, may not be necessary. See also “Guidelines on the Assessment and Management of Cardiovascular Dysregulation in Ehlers–Danlos Syndrome” by Hakim et al., this issue.

Mitral valve prolapse (MVP) was previously considered a common feature of EDS and many other HCTDs, but that was prior to the establishment of more rigorous criteria for the diagnosis of MVP. Since then, some studies show no increase in the frequency of clinically significant MVP [Dolan et al., 1997, McDonnell et al., 2006, Atzinger et al., 2011] and others show an MVP frequency of 28–67% among hEDS patients [Camerota et al., 2014; Kozanoglu et al., 2016]. Increased prevalence of mitral and tricuspid insufficiency has also been reported [Camerota et al., 2014]. Since the mitral valve relies upon collagen for its tensile strength, and myxomatous MVP is characterized by disruption of the collagen layer with expansion of glycosaminoglycans within the middle layer of the valve [Delling and Vasan, 2014], it is reasonable to still consider MVP as a potential clue for hEDS, but the true clinical significance is not yet known.

Gastrointestinal Disorders

Systematic attention on gastrointestinal involvement in hEDS started in 2004 with the study by Hakim and Grahame [2004], who found a wide range of functional complaints in adults. The relevance of gastrointestinal manifestations in hEDS is increasing in both scientific and clinical perspectives. In fact, while the link between a congenital laxity of the soft connective tissue and gut diseases is still unclear as is the role of comorbidities and concurrent medications, its better understanding will certainly help better delineate patients' complaints, which remain without specific management protocols. In a recent

review on this topic, a total of 42 works were identified exploring the relationship between hEDS or GJH with gastrointestinal disorders [Castori et al., 2015a]. Among them, 12 were specifically addressed for better defining the spectrum of gastrointestinal symptoms in syndromic patients [Manning et al., 2003; Hakim and Grahame, 2004; Castori et al., 2010b, 2011a; Zarate et al., 2010; Danese et al., 2011; Mastoroudes et al., 2013a; De Wandele et al., 2013, 2014a; Kovacic et al., 2014; Fikree et al., 2015; Pacey et al., 2015b], and various clinical reports on single complications and/or surgical treatment in EDS [Douglas and Douglas, 1973; Defuentes et al., 2004; Sardeli et al., 2005; Chen and Jao, 2007; Reinstein et al., 2012; Dordoni et al., 2013; Fogel, 2013; Plackett et al., 2014].

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Based on these publications, gastrointestinal involvement in hEDS may have functional and morphological manifestations, although most papers were focused on the former. Collectively, functional features may be observed in 1/3 to 3/4 of the patients with an increasing rate by age. Manifestations variably include gastroesophageal reflux, heartburn, bloating, recurrent abdominal pain, irritable bowel syndrome, constipation, and diarrhea [Maeland et al., 2011]. Dysphagia may be a further common complaint in hEDS, but the literature is scanty except for an early

report highlighting a high prevalence of speech, voice, and swallowing disorders in a heterogeneous group of EDS patients [Hunter et al., 1998]. Zarate et al. [2010] provisionally identified dysphagia in 14.3% of their JHS patients.

Constipation with or without other features of voiding dysfunction is usually the earliest sign of gastrointestinal involvement, which tends to manifest with multiple, sometimes severely disabling symptoms at any age. Repeated evidence indicates that gastrointestinal involvement aggregate with other chronic symptoms and, then, is more commonly encountered in the complex patient [De Wandele et al., 2013; Fikree et al., 2015; Pacey et al., 2015b]. Standard investigations are usually carried out without severe complications in hEDS, but they often have negative or inconsistent results. Functional tests, including esophageal manometry, 24-hr pH-metry, gastric emptying study, small bowel manometry, and colorectal transit study, may lead to positive results although these too are sometimes intermittent [Zarate et al., 2010].

More recently, rectal evacuatory disorder has been confirmed by anorectal manometry in 60% of the cases from a mixed population of 30 classical EDS, hEDS, and vascular EDS patients [Nelson et al., 2015]. Treatment of functional GI complaints in hEDS is problematic due to the absence of tailored strategies and an apparent resistance to pharmacologic treatments at standard dosages/regimens. The exclusion of common comorbidities, such as celiac disease, lactose intolerance, and *Helicobacter pylori* infection, is reasonable at first examination. Preliminary results suggest an increased rate of celiac disease [Danese et al., 2011; Laszkowska et al., 2016] and eosinophilic esophagitis [Abonia et al., 2013] in hEDS, but additional studies are required to determine the significance of these potential associations.

Morphological findings with a presumed higher rate in hEDS compared to the general population may include abdominal hernias, rectal prolapse, ptosis of internal organs, diaphragmatic hernias, and intestinal

intussusceptions. Systematic data are available for abdominal hernias [Harrison et al., 2016] and rectal prolapse [Manning et al., 2003] only, while all other features are described in single reports only and their relationship with hEDS remains to be further scrutinized. Abdominal hernias occur in up to one-fifth of the patients; the chance of occurrence increases with age, and their surgical treatment seems effective under standard procedures [Harrison et al., 2016]. Rectal prolapse is observed in more than one tenth of women [Mastoroudes et al., 2013b]. It can occur in nulliparous women but its rate is highest in those who underwent episiotomy but has been associated with JH and pelvic floor dysfunction [Lammers et al., 2012]. The rate of rectal prolapse in men and children with hEDS remains unknown, as such an association has been reported in single case reports only [Douglas and Douglas, 1973; Chen and Jao, 2007]. See also “Gastrointestinal Involvement in the Ehlers–Danlos Syndromes” by Fikree et al., this issue.

Dysautonomia

The first evidence for a tight link between hEDS and autonomic dysfunction was published by Rowe et al. [1999], who studied eleven pediatric patients (classical EDS and hEDS) all showing either POTS or NMH. Four years later, Gazit et al. [2003] found orthostatic hypotension, POTS, and uncategorized orthostatic intolerance in 21 out of 27 (78%) JHS adults. More specifically, this study revealed a greater drop in systolic blood pressure during hyperventilation and a greater increase in systolic blood pressure after a cold pressor test in patients compared to controls. The authors suggested the existence of alpha- and beta-adrenergic hyper-responsiveness in hEDS. The concept was reinforced by Hakim and Grahame [2004], who demonstrated, for the first time, a significant increase of the rate of systemic dysautonomic symptoms in hEDS.

More recently, a study focused on hEDS found an increase of the physiological heart rate variability, a greater

blood pressure fall during Valsalva maneuver and a smaller initial systolic blood pressure increase during tilt in a cohort of 39 hEDS women compared to controls [De Wandele et al., 2014b]. This study also highlighted POTS as the most prevalent autonomic profile in hEDS and identified sympathetic neurogenic dysfunction as the most likely explanation for dysautonomia in this condition, although connective tissue laxity and vasoactive medication may also play a role.

Cardiovascular dysautonomia can easily explain orthostatic intolerance, palpitations, tachycardia, and atypical chest pain, as well as a series of neurological secondary manifestations, including fatigue, dizziness, fainting, syncope, memory, and concentration troubles. A primary sudomotor involvement was recently demonstrated in hEDS with a significant reduction of sweat volume production [De Wandele et al., 2014b]; a finding that can explain dry skin and mucosa. A possible wider involvement of the autonomic nervous system could contribute to other relatively common features of hEDS that affect the gastrointestinal and urinary systems, such as gut dysmotility and underactive/overactive bladder. The link between abdominal symptoms and dysautonomia, possibly via an increased visceral sensitization, still needs additional research [Farmer et al., 2014]. Dysautonomia could be also a pathogenic contributor to selected psychological traits of hEDS, as recently proposed [Eccles et al., 2015]. General assessment strategy and treatment of POTS are available in Mathias et al. [2011]. Minor adaptations specifically addressed for hEDS were also published [Castori et al., 2012a]. See also “Guidelines on the Assessment and Management of Cardiovascular Dysregulation in Ehlers–Danlos Syndrome” by Hakim et al., this issue; as well as “Gastrointestinal Involvement in the Ehlers–Danlos Syndromes” by Fikree et al., this issue.

Bone Mass

Osteoporosis and osteopenia are considered features of the rare kyphoscoliotic

and arthrochalasis types of EDS as well as the classic-like EDS with propensity to arterial rupture [Beighton et al., 1998]. See also “Ehlers–Danlos Syndromes: Rare Types” by Malfait et al., this issue. Reports of reduced bone mass in the more common EDS variants, mainly classical and hypermobile types, remains controversial.

Coelho et al. [1994] described four adults with classical EDS and bone mineral density (BMD) values persistently below 1 standard deviation consistent with osteopenia. In this very limited series, they found that bone mass appears reduced in EDS, predominantly affecting trabecular bone, but the degree of involvement is less marked than other HCTDs. In the same year, Deodhar and Woolf [1994] reported EDS as a diagnosis among seven adults referred for low bone density (one with classical EDS and the others with less defined phenotypes which may have included hEDS). Similarly, reduced bone mass was also demonstrated at the calcaneum by ultrasound and previous fractures were 10 times more common in EDS than general population (86.9% vs. 8.7%) [Dolan et al., 1998]. In this work, the cause of reduced bone mass in EDS was considered multifactorial with a possible contribution of reduced mobility and proprioceptive defect. However, Carbone et al. [2000] did not confirm this finding in 23 hEDS adults. The authors also noted that the femoral neck BMD was significantly reduced as compared to controls but once age, weight and activity-level were corrected for, the difference became not significant. More recently, Mazziotti et al. [2016] found no significant difference in BMD among 52 EDS patients (37 hEDS). However, a surrogate radiographic marker for vertebral fracture was more prevalent in the EDS group as compared to controls. If the fractures are true (patients only report chronic low back pain) then this observation is not likely due to reduced BMD but mechanical stress of the hypermobile spine. Critics of the above-mentioned studies have speculated that those patients with EDS were often less active and this should be taken into account in comparing bone density. Overall, there is no convincing evidence

that hEDS is associated osteoporosis or fragility fractures, especially in children. Such persons should be evaluated for other underlying disorders as outlined in the American Academy of Pediatrics Guideline [Flaherty et al., 2014]. The bone fragility disorder, osteogenesis imperfecta, as well as the EDS/osteogenesis imperfecta overlap (see EDS rare types, this issue), have JH and may be mistaken for hEDS [Castori, 2015].

The association between GJH and BMD was further investigated in three additional studies. Reduced BMD by ultrasound and lower excretion of urinary hydroxylsilypyridinoline cross-links and lysylpyridinoline cross-links were demonstrated in 15 children with “symptomatic” GJH compared to 95 healthy prepubertal children [Engelbert et al., 2003]. By contrast, another study suggests that a high Beighton score may be a marker of fitness, reduced rate of knee osteoarthritis and increased (rather than reduced) hip BMD in postmenopausal women [Dolan et al., 2003]. A third study showed reduced BMD (mild osteopenia) in 23 premenopausal hypermobile women compared to controls by DXA at some sites but not others [Gulbahar et al., 2006].

As expected from the early literature and the nosologic confusion among EDS, GJH, and JHS, the published data may be hard to apply to “pure” hEDS and, then, translated in clinical practice. In the above-mentioned studies, it is unclear if hEDS is associated with osteoporosis in adults, especially premenopausal women. An increase in fractures or risk of bone fragility fractures was not well-established. There is no evidence at present to suggest that children or infants have a lower bone mass in hEDS nor that they are predisposed to fragility fractures.

Osteoarthritis

Osteoarthritis (OA) has been postulated as a long-term consequence of JH [Scott et al., 1979]. It is possible that an increase in the prevalence of OA is due to the same underlying collagenopathy or by repetitive trauma that commonly occurs in JH and altered joint mechanics

[Bird et al., 1978; Grahame, 1989; Klemp, 1997]. Knee hypermobility is common among patients with knee OA [Dolan et al., 2003; van der Esch et al., 2006; Güreer et al., 2016]. In a study of 34 patients with severe thumb (carpometacarpal) OA, 62% had generalized JH [Jonsson and Valtysdottir, 1995]. In a small series of 24 EDS patients with a mean age of 16 years, 16% already had radiographic evidence of trapezium-metacarpal OA [Gamble et al., 1989]. In that same study, 66% had evidence of subluxation and 29% with dislocation. This association adds evidence that joint hypermobility and presumably altered joint biomechanics may increase the susceptibility of such joints to OA [Wolf, 2009].

Headaches

Much like headaches in the general population, headaches in hEDS vary by type and severity [Jacome, 1999; Murray et al., 2013; Neilson and Martin, 2014; Castori et al., 2015c]. Headache itself has been shown to occur in a larger portion of EDS patients (multiple types of EDS) as compared to historical controls [Sacheti et al., 1997]. It is a frequent complaint among those having hEDS as well [Jacome, 1999; Maeland et al., 2011; Murray et al., 2013; Hamonet et al., 2015]. More specifically, migraines were seen at a greater frequency and disability compared to a control population [Hakim and Grahame, 2004; Bendik et al., 2011; Puledda et al., 2015].

Rozen et al. [2006] described new daily persistent headaches in a series of 12 patients of which 11 demonstrated cervical spine hypermobility. Further work revealed that 10 of the 11 with cervical spine hypermobility showed GJH. Headache due to CSF leak has been demonstrated in a few case reports and affects a very small minority of hEDS patients but can cause significant disability [Reinstein et al., 2013]. Craniocervical junction instability is thought to be linked to cervicogenic and Chiari-like headaches [Milhorat et al., 2007]. This instability or simply the musculature strain throughout the

upper body can cause widespread spasms and muscular tension leading to headaches as well. Temporal headaches, unilateral or bilateral, may again be related to muscular dysfunction but involving the temporomandibular joint. Such headaches can be associated also with ear symptoms such as pain, sense of fullness, or tinnitus. Those patients with dysautonomia, orthostatic intolerance, or POTS can also complain of intense pounding headaches. Medications and medication-overuse can also be responsible for headaches in this population. As in the general population, individual patients often suffer from more than one type of headache, making both the etiology of the headache and the intervention less certain.

Temporomandibular Joint and Dental Issues

Several studies have linked temporomandibular joint (TMJ) hypermobility to temporomandibular joint dysfunction (TMD), including in children [Adair and Hecht, 1993]. Nosouhian et al. [2015] characterized 69 patients with TMJ hypermobility and found that a maximal mouth opening (MMO) of <55 or >65 mm, was associated with more TMJ discomfort than an intermediate degree of MMO. TMJ hypermobility was more common in women than men, and increased MMO was also correlated with more TMJ sounds (“clicks” or “pops”) and more pain in the masticatory muscles. The jaw in hEDS is often also hypermobile until such time that damage occurs in the TMJ, which will further limit MMO. Jaw sounds, locking, dislocation, bruxism, and temporal headaches are also frequently described in this population. Indeed, Murray et al. [2013] found that a significant portion of 466 adults with hEDS self-reported TMD as a major issue.

Westling [1992] studied 360 patients with TMD. Among that group, a subset analysis of 74 females with GJH were compared to 73 age and gender matched controls. Using stepwise regression analysis, the study was able to

show a significant association of GJH and TMD.

In a recent national study in Finland involving 6227 participants, TMJ pain was often associated with palpable pain of the neck and shoulder musculature, widespread pain, chronic illness, and female gender [Sipilä et al., 2011]. Given that those with hEDS often have most if not all of the additional variables, it would suggest that TMD in this population is complex, common, and must use a more holistic approach to treat.

The oral mucosa in hEDS is often friable and easily injured giving rise to episodes of painless bleeding [Hagberg et al., 2004; Berglund and Björck, 2012]. The lingual or labial frenulum may be hypoplastic or altogether absent [Machet et al., 2010]. Periodontitis may also be common. However, periodontal disease with early-onset and widespread tooth loss is thought to represent another form of EDS, the periodontal type [Rahman et al., 2003], that has been recently associated with defects in complement type 1 [Kapferer-Seebacher et al., 2016] (see also “Ehlers–Danlos Syndromes: Rarer Types” by Malfait et al., this issue). Many patients report being less responsive to local anesthetics during dental procedures [Arendt-Nielsen et al., 1990; Hakim et al., 2005]. A Swedish study utilizing a self-reported oral health questionnaire showed that mucosal problems in different areas of the body were reported by 206/223 (92%) women, and that 75% of respondents with hypermobility type self-reported problems with their oral mucosa [Berglund and Björck, 2012].

The teeth in hEDS are described with slightly altered morphology with higher cusps and deeper fissures of the premolars and molars with shortened roots. Enamel hypoplasia has also been described as well as tooth fracture (unclear if fracture intrinsic to the tooth or due to bruxism or similar mechanical pressures) [De Coster et al., 2005]. With the use of orthodontia, it is a common anecdotal experience that the teeth will migrate faster than expected and, unfortunately, migrate back toward their pre-treatment location after the removal of the orthodontic appliance. See also

“Oral and Mandibular Manifestations in Ehlers–Danlos Syndrome” by Mitakides and Tinkle, this issue.

Spine

Postural kyphosis is commonly encountered in those with hEDS [el-Shahaly and el-Sherif, 1991]. This is thought to be primarily due to loose ligamentous structure and poor postural ergonomics. Scoliosis is also common occurring in up to half of all patients [Ainsworth and Aulicino, 1993; Stanitski et al., 2000; Adib et al., 2005; Czaprowski, 2014; Stern et al., 2016]. The scoliosis is acquired, often mild as well as flexible and may continue to progress beyond the adolescent period but most do not require intervention.

The spine is a series of joints, the most mobile of which involves the craniocervical junction. Multiple connective tissue disorders have been reported to have craniocervical instability including Marfan [Herzka et al., 2000], Loeys-Dietz [Rodrigues et al., 2009], and EDS [Milhorat et al., 2007]. Cervical hypermobility has been associated with headaches and hEDS [Rozen et al., 2006]. In a large series of patients presenting with signs of Chiari type I (neck pain, gait disturbance, numbness and tingling of the hands and feet, dizziness, dysphagia, and speech difficulties), Milhorat et al. [2007] described nearly 13% had features consistent with hEDS. Compared to the other patients with Chiari-like symptoms, the patients with hEDS were more likely to have a reduction of the basion-dens interval, clival-axial angle, clival-atlas angle, and the atlas-axial angle as well as an enlargement of the basion-dens interval—all of which are concerning for excessive laxity or instability. There was also an increase in retro-odontoid pannus formation, a pathophysiologic process thought to represent abnormal stress of the transverse ligament. A portion of these patients did not have radiologic findings of Chiari and were labeled as Chiari Type 0, a controversial label. Moreover, the Chiari-like symptoms of headache and dysautonomia are common in hEDS and the vast majority

are not likely attributable to dysfunction at the craniocervical junction. See also “Neurologic Manifestations in the Ehlers–Danlos Syndrome” by Henderson et al., this issue.

Similarly, laxity of the lumbar spine increases movement and decreases stability. Kim et al. [2013] showed that young males with GJH had excessive lumbar segmental motion which was associated with increased low back pain, disability, and limited physical activity. Lumbar hypermobility is also an underlying risk factor for degenerative disc disease [Nef and Gerber, 1998] and facet fractures [Mazziotti et al., 2016].

Gynecologic Issues

Gynecologic complaints from patients with hEDS are commonly encountered. In a study with 223 women with EDS, 67% self-reported mucosal problems with their genital area [Berglund and Björck, 2012]. Heavy menstrual bleeding (menorrhagia) was reported by 26–76% of hEDS females [Ainsworth and Aulicino, 1993; Hugon-Rodin et al., 2016]. Painful intercourse was also reported by 30–57% of women with EDS and hEDS [McIntosh et al., 1995; Castori et al., 2010a; Hugon-Rodin et al., 2016].

Pelvic Dysfunction

Pelvic floor disorders include urinary incontinence (UI), pelvic organ prolapse (POP), and other sensory and emptying abnormalities. Childbirth has a very substantial impact on a woman’s probability of developing pelvic floor disorders. It has been reported that about a third of women have UI after childbirth [Hallock and Handa, 2016]. In addition to parity, a positive family history of prolapse increases a woman’s risk of prolapse, even among nulliparous women [Buchsbau et al., 2006; Buchsbau and Duecy, 2008].

Several case-control studies in the past suggested that hEDS is associated with pelvic floor disorders [Al-Rawi and Al-Rawi, 1982; Norton et al., 1995; McIntosh et al., 1996; Aydeniz et al., 2010]. However, most of these studies

have not controlled for childbirth history or age and included patients affected by various types of EDS.

Castori et al. [2012c] found that POP represented a common late-onset complication in women with hEDS. Interestingly, most (90.9%) prolapses occurred in women with positive history for episiotomy. The reason(s) as to why episiotomy associates with POP in hEDS is unknown.

The largest prospective case-control study to date to address these issues was published in 2013 and involved 120 women [Mastoroudes et al., 2013a,b]. Sixty women diagnosed with JHS, according to the Brighton criteria, were recruited from a tertiary referral hypermobility clinic. Controls were recruited from hospital personnel. All women in the study group were matched with healthy control women according to age, parity and ethnicity. Both groups completed specific health and QoL questionnaires. Objective assessment of POP was undertaken. The prevalence of UI in those with hEDS were significantly higher than in controls (73.3% vs. 48.3%) as was voiding difficulties. The impact of UI on QoL was also statistically significant. Objective findings of prolapse of the anterior vaginal wall were more severe than in controls.

However, another recent study [Derpapas et al., 2015] reported a lack of strong association of JH with UI or POP. The study involved 270 women scheduled to undergo urodynamic investigations. JH was not assessed clinically but was based on the self-completed five-part JH questionnaire. Women underwent a full gynecological history and examination. The prevalence of reported JH in this study was 31.1%; however, the researchers did not find a strong association between JH and any UI subtype. They reported a trend toward higher prolapse staging in women with JH, which becomes significant only after adjustment for the confounding negative association between age and JH.

As childbirth has a very substantial impact on a woman’s probability of

developing pelvic floor disorders, such as UI and POP, pregnancy remains a source of anxiety to patients and their doctors.

Pregnancy and Childbirth

Several pregnancy-related complications have been more commonly reported in women with hEDS in some studies but as often, not substantiated in others. In an online survey of EDS patients (N = 497), self-reported infertility was more commonly encountered in women with hEDS [Hurst et al., 2014] although this was not reproduced by others [Castori et al., 2012b; Hugon-Rodin et al., 2016; Sundelin et al., 2017]. Premature birth has been reported as more common among patients with EDS than in the general population, but this appears to be primarily among women with classic EDS; it is unclear if there is an increased risk for preterm birth specifically in the hEDS population as the few studies are conflicting [Sorokin et al., 1994; Lind and Wallenburg, 2002; Castori et al., 2012b; Hurst et al., 2014]. Some works report that miscarriage is increased in hEDS [Ainsworth and Aulicino, 1993; Hurst et al., 2014; Hugon-Rodin et al., 2016] but not in other studies [Sundelin et al., 2017].

In a comprehensive study, Castori et al. [2012c] collected a set of gynecological and obstetric features in 82 women with hEDS attending two Italian centers. All patients were originally assessed by physical examination and questionnaire administration focused on collecting information about selected aspects of their gynecological and obstetric history. Only post-pubertal women meeting diagnostic criteria for the hypermobility type of EDS or JHS were included. Other HCTDs were excluded clinically. The study did not include gynecological examination. A total of 93 pregnancies were registered among the 82 women with at least one pregnancy. In this study, fertility was overall preserved, as were mean age at menarche and menopause, rate of pregnancy/woman and of spontaneous abortion that were

comparable with those in the Caucasian population.

EDS-related symptom evolution during pregnancy seemed unpredictable as 40% of patients reported worsening symptoms (especially gastrointestinal complaints, asthenia, and pain), 13% of patients improved, and the symptoms were unchanged in the remaining 47%. Preterm delivery due to premature rupture of the membrane was reported in 10% pregnancies, which is not different from the general population, and none of which led to major complications. Rapid labor occurred in more than 1/3 of the cases.

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The risk of intra- and post-partum hemorrhages was 1/5 irrespective to the delivery modality. They reported a high rate of abnormal scar formation in both Caesarean and vaginal delivery with episiotomy. In all cases, hemorrhages were always successfully managed without life-threatening complications and no internal organ/vascular accidents were registered after Caesarean. It was reassuring that all delivery options showed a very limited number of local and systemic short-term complications. In this sample, the group did not find any life-threatening complication related to local and general anesthesia.

It has long been recognized that joint laxity increases over the course of pregnancy, allowing the bony pelvis to adapt to accommodate vaginal birth [Calguneri et al., 1982]. The same

phenomenon occurs in women with hEDS, which may lead to increased joint instability later in pregnancy.

A large study was conducted to investigate the association between JH, obstetrical outcomes, and pelvic floor disorders [Knoepp et al., 2013]. It involved 587 parous women (participants in a longitudinal cohort study of pelvic floor disorders after childbirth). Their obstetrical histories were obtained from review of hospital records. Pelvic floor disorders were assessed using validated questionnaires and a structured examination for prolapse. JH and pelvic floor disorders were evaluated at enrollment (5–10 years after first delivery). The main weakness of this study was the inclusion criteria. The researchers defined JH as Beighton score ≥ 4 and did not use the Brighton or Villefranche criteria. They compared obstetrical outcomes and pelvic floor disorders between women with and without JH. JH was diagnosed in 46 women (7.8%) and was associated with decreased odds of caesarean after complete cervical dilation or operative vaginal delivery. In this study, anal sphincter laceration was less likely to occur in women with JH and was not associated with any pelvic floor disorder. Although this study did not address the issues related to hEDS specifically, the results are quite reassuring for women with asymptomatic hypermobility as JH seem to facilitate spontaneous vaginal birth but does not appear to be a risk factor for pelvic floor disorders in the first decade after childbirth.

Urinary System

De Kort et al. [2003] evaluated 89 families of children with GJH. The children with GJH showed an increase in daytime and nighttime urinary incontinence as well as urinary tract infections (UTIs). Voiding dysfunction was also significantly associated with GJH in children but this is unclear if this is secondary to constipation [Kajbafzadeh et al., 2014]. Adib et al. [2005] evaluated 125 children with a diagnosis of hEDS and catalogued their multisystem disorders. UTIs and urinary tract

dysfunction were more common in girls than controls. Vesicoureteral reflux was also more common in children with hEDS as compared to the control population [Beiraghdar et al., 2013].

Sleep Disturbance

Sleep is a restorative process for the body. During the deeper stages of non-rapid eye movement sleep, the body regenerates tissue, builds bone and muscle, and positively affects the immune system. Sleep deprivation is considered unhealthy leading to fatigue, a decrease immune response, poor muscle coordination, susceptibility to injury, impaired cognition and memory, increased pain, moodiness, and depression [Owens, 2014]. Insomnia can be reported as delayed sleep (sleep-onset) or due to sleep fragmentation (sleep-maintenance). Sleep deprivation due to sleep maintenance insomnia has been related to impairment of the endogenous pain inhibitory function and therefore increases spontaneous pain and pain amplification [Smith et al., 2007].

Many patients with hEDS report poor sleep including insomnia and unrefreshing sleep [Verbraecken et al., 2001; Hakim and Grahame, 2004; Murray et al., 2013]. In a study of 115 patients with hEDS, Albayrak et al. [2015] found a significant decrease in sleep quality as compared to controls. Comorbid conditions such as restless legs syndrome and sleep apnea have been described in small series of patients with hEDS [Guilleminault et al., 2013]. However, of the 34 patients with EDS, only one was described as having hEDS but details on the diagnostic criteria were not described. Fibromyalgia is also a common comorbidity [Ofluoglu et al., 2006; Ting et al., 2012] and is strongly associated with sleep disturbance, including abnormal sleep architecture [Dauvilliers and Touchon, 2001; Besteiro Gonzalez et al., 2011]. Many other factors may also interfere with sleep in this population including pain, dysautonomia, poor sleep hygiene, and medications [Voermans et al., 2010b].

Mast Cell Activation Disorder

Mast cell activation syndrome (MCAS) refers to an increased number of mast cells, increased mast cell mediators (e.g., histamine, tryptase, etc.), or both. The clinical symptoms of MCAS include flushing, pruritis, hypotension, asthma, diarrhea, abdominal bloating, and cramping. The diagnosis of MCAS is increasingly recognized in the general population [Afrin et al., 2016] and is likely among those with hEDS as well. It remains unclear if MCAS is more common in hEDS or perhaps represents a phenocopy of hEDS (with similar joint laxity and multi-system involvement). Those with EDS report a higher incidence of food sensitivities suggestive of histamine reaction [Berglund, 2015]. Regardless of any possible association, the presence of MCAS in hEDS might complicate the known symptoms of POTS, chronic fatigue, and gastrointestinal manifestations. Elevated serum tryptase, a marker of MCAS, followed a dominant inheritance pattern that overlapped with a “hypermobile connective tissue phenotype” in eight of nine studied families [Lyons et al., 2014]. Subsequent evaluation of 35 families with elevated serum tryptase showed this phenotype to be due to increased copy number of the alpha-tryptase gene, *TPSAB1* [Lyons et al., 2016]. See also “Mast Cell Activation Syndrome in Ehlers–Danlos Syndrome” by Seneviratne et al., this issue.

Psychiatric

Psychological dysfunction and emotional problems, including depression, anxiety, affective disorder, low self-confidence, negative thinking, hopelessness, and desperation, are also common among those with EDS [Hagberg et al., 2004; Castori et al., 2010b; Baeza-Velasco et al., 2011; Branson et al., 2011; Rombaut et al., 2011a; Berglund et al., 2015; Sinibaldi et al., 2015; Hershenfeld et al., 2016]. These problems may exacerbate the pain experience, as well as other organ system manifestations (especially

gastrointestinal and autonomic). This can lead to avoidance behavior, exacerbation of dysfunction and disability, and marginalization. Resentment, distrust, and hostility between the patient, family, and healthcare team may develop. To be ignored, being assigned a psychological and/or psychiatric explanation, not being respected and treated as an object could have consequences such as mistrusting health-care and create difficulties in encounters with care [Berglund et al., 2010]. Equally, to ignore or avoid confronting the presence of significant comorbid psychological problems can lead to suboptimal treatment. See “Psychiatric and Psychological Aspects in the Ehlers–Danlos Syndromes” by Bulbena et al., this issue.

Quality of Life

In a national cohort of 134 patients, functional gastrointestinal disorders correlated with a poorer QoL in EDS patients [Zeitoun et al., 2013]. When comparing SF-36 scores as a measure of QoL in EDS in a Swedish population study, the EDS group reported significantly lower scores [Berglund et al., 2015]. Also, probable anxiety on the Hospital Anxiety and Depression Scale was rated as 74.8% and probable depression was rated as 22.4%. Physical pain, psychological discomfort, and handicap has considerable impact on health-related QoL in EDS. Adults with hEDS reporting neck and shoulder pain had a significant association with generalized pain and a decreased health-related QoL [Johannessen et al., 2016]. Children with hEDS and fatigue experienced poor health-related QoL [Pacey et al., 2015b]. In 38 hEDS patients, baseline QoL was significantly reduced and worsened with experiences in physical therapy and iatrogenic injury [Bovet et al., 2016]. A recent meta-analysis revealed significant disability related to pain, fatigue, and psychological distress in hEDS [Scheper et al., 2016b]. These results indicate a lower quality of health in those with EDS than in the general population.

MANAGEMENT

Assessment of a person with or suspected of having hEDS is based on symptoms. Musculoskeletal symptoms should be approached conservatively. Physical therapy, education, and pacing are paramount [Simmonds and Keer, 2007]. “The Evidence-Based Rationale for Physical Therapy Treatment of Children, Adolescents and Adults Diagnosed with Joint Hypermobility Syndrome/Hypermobility Ehlers Danlos Syndrome” by Engelbert et al., this issue. Frank joint instability should be evaluated by orthopedics or other well-qualified personnel. Symptoms of orthostatic intolerance, tachycardia with palpitations, and/or near-syncope should be also treated conservatively by fluid and salt intake along with education and the appropriate exercise. Syncope should be evaluated further by specialists such as neurology or cardiology for concerns of arrhythmia, seizure disorder, cardiomyopathy, and so on.

The management of hEDS includes treatment of acute/emergency manifestations (e.g., dislocations), attenuation of chronic symptoms (e.g., pain and fatigue), as well as primary and secondary prevention of acute and chronic complications. Acute complications are usually managed far away from the reference center and treatment follows guidelines and procedures applied in the general population. As many patients with hEDS have multiple symptoms, a coordinated effort is required as other specialists (if needed) are incorporated into the medical team. The approach should be holistic focusing on the complications, the desire(s) of the patient, QoL and functionality, as well as the psychological aspects.

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Pain

Primary prophylaxis and treatment of nociceptive pain relies upon physical approaches to improve joint stability and prevent or reduce myofascial spasm. Although there is only limited evidence, avoidance of joint hyperextension may not be necessary [Pacey et al., 2013]. High impact and resistance exercise should be minimized, but regimens need to be individualized and this is not a strict contraindication. Myofascial release, stretching, and other mechanical techniques to reduce spasm can provide up to 24 hr of pain reduction. Joint stabilization is best achieved by working on muscle tone (the resting state of muscle contraction) and proprioception, with only gentle attention to strength (voluntary force exerted at will) [Simmonds and Keer, 2007; Palmer et al., 2014]. Exercises should be low resistance, with very gradual increase in repetitions but not resistance. Water-based exercise is often a good choice for some individuals because water reduces effective body weight and protects against impact. Exercise regimens are often initiated with formal physical therapy, but once learned by the patient, can and should be continued indefinitely, independent of formal instruction or supervision. It is important to understand that physical therapy should be done by experienced and learned professionals as many patients commonly report increased pain and decreased QoL with improper exercise regimens [Bovet et al., 2016]. It often takes several months of routine toning exercise to halt progressive deterioration in pain, and it may be several years before substantial reduction in pain is recognized.

Scheduled use of multiple medications together is often more effective than as-needed use of one or two medications at a time. Systemic

non-opioid oral analgesics should be maximized first, including both acetaminophen and either a non-steroidal anti-inflammatory (NSAID) or cyclooxygenase-2 (COX2) inhibitor. NSAIDs may be helpful after episodes of dislocation or subluxation or as an addition during flares of pain. Topical agents such as lidocaine, NSAIDs and/or custom compounded creams can also be helpful. Where allowed by law, cannabinoids can be considered, but the treatment effect must be measured against potential long-term consequences [Mandelbaum and de la Monte, 2017]. Muscle relaxants may help to reduce myofascial spasm and nociceptive pain [Abdel Shaheed et al., 2017; Chou et al., 2016]. Benzodiazepines can be considered for cautious short-term muscle relaxation, but are poor choices for long-term use due to loss of muscle-relaxing effect over time, in addition to problems with tolerance, dependency, and sometimes addiction. Neuropathic pain often requires one or more of a tricyclic antidepressant, serotonin-norepinephrine reuptake inhibitor, and/or an anti-epileptic drug. Topical lidocaine and capsaicin may also provide some benefit. Opioids are rarely needed for the treatment of chronic musculoskeletal pain [NGC, 2013] and are no higher than third line agents for neuropathic pain [Finnerup et al., 2015]. Opioids and tramadol are best reserved for acute pain episodes or for patients whose pain is inadequately managed on all of the above medications, require close monitoring, and should be added on to the above regimen in the lowest possible doses rather than replacing the above medications. There are particular concerns regarding the risks of co-prescribing opioids and benzodiazepines [Babalonis and Walsh, 2015]. Recent guidance by the Centers for Disease Control recommends that providers should prescribe opioids only when benefits outweigh expected risks and that they should avoid prescribing opioids and benzodiazepines concurrently whenever possible [Dowell et al., 2016].

There is theoretical risk and anecdotal description that muscle relaxant

medications and/or too much stretching can exacerbate joint instability and ultimately increase nociceptive pain, but many patients tolerate these modalities well and treatment should be tailored to each individual's response. NSAIDs and COX2 inhibitors may exacerbate gastritis, bleeding and/or bruising, but are often well-tolerated. Chronic high dose NSAID therapy may also increase the risk of coronary artery disease and renal insufficiency; this risk needs to be weighed against the severity of the patient's pain and the patient should be encouraged to make his or her own choice about these risk and benefits. Many of the above pain medications increase serotonin levels, so patients should be monitored for signs and symptoms of serotonin syndrome.

Many patients with hEDS may develop chronic generalized pain which becomes their primary problem. This type of presentation should be considered as a centralized pain state belonging to the spectrum of chronic widespread pain, with additional superimposed musculoskeletal components. Some patients who continue to struggle to cope with their pain may need consideration of a multidisciplinary pain management program [Bathen et al., 2013].

The overall goal should be to maintain adequate control of pain to a tolerable level, not to completely eliminate pain. Such expectation management can help to reduce the overall subjective pain experience, even when objective somatic pain cannot be completely controlled. See "Pain Management in Ehlers–Danlos Syndrome" by Chopra et al., this issue.

Fatigue

Both mental and physical fatigue are as commonly encountered as pain in hEDS [Castori et al., 2011b]. It is often multifactorial. Stimulant medications are often effective for very short periods of time. However, the various contributors of fatigue should be considered such as anemia, nutritional deficiencies, deconditioning, medications, sleep disturbance, dysautonomia, and/or psychological aspects. Screening

questionnaires should be used for diagnosis and ongoing monitoring. Fatigue, much like pain, often responds to treatment such as exercise therapy but only very slowly over time [Edmonds et al., 2004]. See "Chronic Fatigue in Ehlers–Danlos Syndromes" by Hakim et al., this issue.

Orthostatic Intolerance

Non-pharmacologic management includes avoidance of rapid orthostatic change or prolonged upright posture, lower extremity compression garments, and supplementation of water and electrolytes to maximize blood volume. Routine low resistance exercise increases both skeletal muscle and vascular tone, improving venous return to the heart. Beta adrenergic blockade often improves symptoms, perhaps by slowing the heart rate or perhaps by reducing autonomic sympathetic activity. Beta blockade is not strictly contraindicated in patients with low resting blood pressure, but does require close monitoring in such patients. Some additional medication options include midodrine, fludrocortisone, and pyridostigmine [Mathias et al., 2011]. See also "Autonomic Dysregulation in Ehlers–Danlos Syndromes," by Hakim et al., this issue.

Neuropsychiatric

Management starts with validation of the patient's symptoms and efforts to establish rapport and trust with the patient. Psychological counseling should focus on accepting and coping with chronic pain and chronic disease. Cognitive behavioral therapy is particularly beneficial, if the patient is willing to actively engage in the process [Bathen et al., 2013]. Distraction, hypnosis, and judicious use of anti-depressant medication can also help.

Surgery and Anesthesia

In hEDS, surgical risks are generally lower than other EDS variants due to the only minor fragility of skin, vessels, and internal organs. The greatest surgery related issue of hEDS is the possibility of

delay in wound closure and tissue repair. Hence, surgical procedures should be carried out with gentle dissection and use of mild lateral force during incisions, retraction and suturing. Skin closure should be performed in two layers with minimal tension, sufficient amount of sutures, deep stitches, and the support of steri-strips, by using proper distance to the incision in order to avoid sutures cutting through the fragile tissue, and without the use of skin clips. Finally, sutures should be left twice as long as normally recommended in order to avoid wound re-opening [Burcharth and Rosenberg, 2012].

Anesthesia and perioperative management may also deserve special care in hEDS. This is mostly influenced by some primary disease features, including mucosal fragility, propensity to ecchymosis, and the risk of hemorrhage (that are, however, usually limited in hEDS), the risk of orthostatic headache due to spinal anesthesia, but also by several common comorbidities, such as autonomic dysfunction, occipitatlantoaxial joint instability, and spondylosis. A freely downloadable summary of recommendations concerning pre-surgical evaluation, patient monitoring and positioning, airway management, circulatory and bleeding issues, pharmacology, use of tourniquets, central venous catheterization, obstetrical, regional and local anesthesia, and other aspects, is available at the OrphanAnesthesia website (http://www.orphananesthesia.eu/en/rare-diseases/published-guidelines/cat_view/61-rare-diseases/60-published-guidelines/89-ehlers-danlos-syndrome.html) or in the work by Wiesmann et al. [2014]. In both works, recommendations are offered for EDS in general, therefore, specific considerations for hEDS should be carefully extracted by the reader.

FUTURE DIRECTIONS

hEDS is a common clinical entity that affects many disciplines of healthcare. The precise description both in the diagnostic criteria as well as the natural history of hEDS need a great deal of further refinement. Management of this disorder has drawn many parallels to

other disorders as few large-scale studies have been performed in this patient population. The areas of future interest represent a limited partial set but those of higher priority.

hEDS Diagnostic Criteria

The new nosology will have to be applied to all populations and be determined where deficiencies and gaps lie within the criteria. This includes the evaluation of and validation of the modified Beighton scoring system. Formulation of such questions and addressing these concerns will need to be an ongoing mission.

As joint hypermobility is common in many disorders and may be the presenting sign, differentiating hEDS from other HDCTs, especially those with vascular involvement, is important. As hEDS is a clinical diagnosis, refinement of the diagnostic criteria is even more important as is the search for a genetic cause. In a systematic approach to pursuing a molecular diagnosis, Weerakkody et al. [2016] found 28 patients with pathogenic variants including one with suspected hEDS emphasizing the need for a systemic diagnostic approach to EDS that will need to be further refined.

Molecular Basis

hEDS remains the sole EDS major type without a known molecular defect. Such a lack of knowledge is likely due to various complexities. First, although hEDS is inherited as a dominant trait, that is, sex-influenced, this inheritance model may not explain all cases. Locus heterogeneity is very likely which may explain some of the cases with apparent different inheritance patterns. Second, the current diagnostic criteria are generally broad to cover what is suspected to be various phenotypic sub-groups. Therefore, the diagnosis of one individual may be ultimately attributable to a mutation of a particular gene while in another person with a similar or different phenotypic presentation may be due to mutation of another gene altogether. Without recognition and eventual

separation of these sub-groups, efforts to define this group under a diagnosis of hEDS may complicate studies on an exomic or genomic basis. Last, as several factors play into the phenotype presentation such as gender, training, pain threshold, etc. multiple genetic and non-genetic factors may be contributing. It is obvious that there needs to be a broader recognition and recording of the features of hEDS (such as in a database registry) so that phenotypic patterns may emerge that can help the design and interpretation in the pursuit of the genetic etiology(ies).

Dysautonomia

The presence of orthostatic intolerance and POTS or NMH in the hEDS population needs further and large-scale validation. A full descriptive inventory of all of the dysautonomic symptoms also is in need. The link between abdominal symptoms and dysautonomia, possibly via an increased visceral sensitization, still needs additional validation [Farmer et al., 2014].

Bone Density

Due to a few small case reports and series, there is some concern for possible loss of bone density with hEDS. This has been popularized through social media and in the courts as a defense against charges of child abuse in the case of an infant with multiple fractures of unknown etiology. There is no credible studies demonstrating bone fragility fractures in hEDS. Subsequently, hEDS is not considered one of the bone fragility syndromes and the diagnosis of hEDS is far too subjective to rely on in these situations. Those infants with features of a connective tissue disorder and multiple unexplained fractures, should be considered for genetic testing [Byers et al., 2006; Flaherty et al., 2014]. Larger and well-controlled studies of bone density in hEDS are needed at all ages.

Physical Therapy Management

Physical therapy is considered the mainstay of management in hEDS.

However, many questions remain including validation of physical therapy in the treatment of EDS. See “The Evidence-Based Rationale for Physical Therapy Treatment of Children, Adolescents and Adults Diagnosed with Joint Hypermobility Syndrome/Hypermobility Ehlers–Danlos Syndrome” by Engelbert et al., this issue.

Craniocervical Junction

As the cervical spine, and most especially the craniocervical junction, comprise a joint(s), it is also believed to be susceptible to the same strain and injuries as seen in other joints in EDS. As these joints protect the central nervous system, it is plausible that neurologic symptoms might also occur. Which symptoms, the proper imaging (and measurements) as well as management are not well-established. Although upright MRI reproduces a more physiologic strain on the craniocervical junction, its routine use has not been recommended [Health Quality Ontario, 2015]. Further studies about the prevalence as well as the symptoms, imaging, and management are needed.

Mast Cell Activation Syndrome

MCAS can complicate management of dysautonomia and may contribute to fatigue and decreased QoL. Further studies of MCAS in the hEDS population are needed to detail the possible comorbidity and its impact on disease manifestation and management.

SUMMARY

hEDS is a heritable connective tissue disorder without a clear etiology. It is common, representing up to 1–3% of the general population. It is multi-systemic with primary musculoskeletal manifestations but various other comorbidities exist such as pain, fatigue, orthostasis, sleep disturbance, anxiety, and a poorer health-related quality of life. Much work in the area of diagnostics, prevalence of hEDS, and the associated comorbidities as well management specific to hEDS is needed.

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REFERENCES

- Abdel Shaheed C, Maher CG, Williams KA, McLachlan AJ. 2017. Efficacy and tolerability of muscle relaxants for low back pain: Systematic review and meta-analysis. *Eur J Pain* 21:228–237.
- Abonia JP, Wen T, Stucke EM, Grotjan T, Griffith MS, Kemme KA, Collins MH, Putnam PE, Franciosi JP, von Tiehl KF, Tinkle BT, Marsolo KA, Martin LJ, Ware SM, Rothenberg ME. 2013. High prevalence of eosinophilic esophagitis in patients with inherited connective tissue disorders. *J Allergy Clin Immunol* 132:378–386.
- Adair SM, Hecht C. 1993. Association of generalized joint hypermobility with history, signs and symptoms of temporomandibular joint dysfunction in children. *Pediatr Dent* 15:323–326.
- Adib N, Davies K, Grahame R, Woo P, Murray KJ. 2005. Joint hypermobility syndrome in childhood. A not so benign multisystem disorder? *Rheumatology (Oxford)* 44:744–750.
- Afrin LB, Butterfield JH, Raithel R, Molderings G. 2016. Often seen, rarely recognized: Mast cell activation disease—A guide to diagnosis and therapeutic options. *Ann Med* 48:190–201.
- Ainsworth SR, Aulicino PL. 1993. A survey of patients with Ehlers–Danlos syndrome. *Clin Orthop Relat Res* 286:250–256.
- Albayrak I, Yilmaz H, Akkurt HE, Salli A, Karaca G. 2015. Is pain the only symptom in patients with benign joint hypermobility syndrome? *Clin Rheumatol* 34:1613–1619.
- Ali Zekry O, Ali Ahmed M, Ali Elsayed Abd Elwahid H. 2013. The impact of fatigue on health related quality of life in adolescents with benign joint hypermobility syndrome. *Egypt Rheumatol* 35:77–85.
- Al-Rawi ZS, Al-Rawi ZT. 1982. Joint hypermobility in women with genital prolapse. *Lancet* 1:1439–1441.
- Arendt-Nielsen L, Kaalund S, Bjerring P, Høgsaa. 1990. Insufficient effect of local analgesics in Ehlers–Danlos type III patients (connective tissue disorder). *Acta Anaesthesiol Scand* 34:358–361.
- Atzinger CL, Meyer RA, Khoury PR, Gao Z, Tinkle BT. 2011. Cross-sectional and longitudinal assessment of aortic root dilation and valvular anomalies in hypermobile and classic Ehlers–Danlos syndrome. *J Pediatr* 158:826–830.
- Aydeniz A, Dikensoy E, Cebesoy B, Altındağ O, Gursoy S, Balat O. 2010. The relation between genitourinary prolapse and joint hypermobility in Turkish women. *Arch Gynecol Obstet* 281:301–304.
- Baeza-Velasco C, Gély-Nargeot MC, Bulbena Vilarrasa A, Bravo JF. 2011. Joint hypermobility syndrome: Problems that require psychological intervention. *Rheumatol Int* 31:1131–1136.
- Babalonis S, Walsh S. 2015. Warnings unheeded: The risks of co-prescribing opioids and benzodiazepines. *Pain Clinical Updates* 23:1–7.
- Barron DF, Cohen BA, Geraghty MT, Violand R, Rowe PC. 2002. Joint hypermobility is more common in children with chronic fatigue syndrome than in healthy controls. *J Pediatr* 141:421–425.
- Bathen T, Hangmann AB, Hoff M, Andersen LO, Rand-Hendriksen S. 2013. Multidisciplinary treatment of disability in Ehlers–Danlos syndrome hypermobility type/hypermobility syndrome: A pilot study using a combination of physical and cognitive-behavioral therapy on 12 women. *Am J Med Genet Part A* 161A:3005–3011.
- Beighton P, de Paepe A, Danks D, Finidori G, Gedde-Dahl T, Goodman R, Hall JG, Hollister DW, Horton W, McKusick VA, Opitz JM, Pope FM, Pyeritz RE, Rimoin DL, Silience D, Spranger JW, Thompson E, Tsipouras D, Viljoen D, Winship I, Young I, Reynolds JF. 1988. International Nosology of Heritable Disorders of Connective Tissue, Berlin, 1986. *Am J Med Genet* 29:581–594.
- Beighton P, De Paepe A, Steinmann R, Tsipouras P, Wenstrup RJ. 1998. Ehlers–Danlos syndromes: Revised nosology, Villefranche, 1997. Ehlers–Danlos National Foundation (USA) and Ehlers–Danlos Support Group (UK). *Am J Med Genet* 77:31–37.
- Beighton P, Grahame R, Bird HA. 2012. *Hypermobility of joints*, 4th edition. London, UK: Springer.
- Beiraghdar F, Rostami Z, Panahi Y, Einollahi B, Teimoori M. 2013. Veisocurethral reflux in pediatric with hypermobility syndrome. *Nephrourol Mon* 5:924–927.
- Bendik EM, Tinkle BT, Al-shuik E, Levin L, Martin A, Thaler R, Atzinger CL, Rueger J, Martin VT. 2011. Joint hypermobility syndrome: A common clinical disorder associated with migraine in women. *Cephalalgia* 31:603–613.
- Berglund B, Mattiasson A-C, Randers I. 2010. Dignity not fully upheld when seeking health-care: Experiences expressed by individuals suffering from Ehlers–Danlos syndrome. *Disabil Rehabil* 32:1–7.
- Berglund B, Björck E. 2012. Women with Ehlers–Danlos syndrome experience low oral health-related quality of life. *J Orofacial Pain* 26:307–314.
- Berglund B, Pettersson C, Pigg M, Kristiansson P. 2015. Self-reported quality of life, anxiety and depression in individuals with Ehlers–Danlos syndrome (EDS): A questionnaire study. *BMC Musculoskelet Disord* 16:89.
- Berglund B. 2015. Food hypersensitivity in individuals with EDS: A common problem. *Nord J Nurs Res* 35:10–12.
- Besteiro Gonzalez JL, Suarez Fernandez TV, Arboleya Rodriguez L, Muniz J, Lemos Diraldez S, Alvarez Fernandez A. 2011. Sleep architecture in patients with fibromyalgia. *Psicothema* 23:368–373.
- Bird HA, Tribe CR, Bacon PA. 1978. Joint hypermobility leading to osteoarthritis and chondrocalcinosis. *Ann Rheum Dis* 37:203–211.
- Bovet C, Carison M, Taylor M. 2016. Quality of life, unmet needs, and iatrogenic injuries in rehabilitation of patients with Ehlers–Danlos syndrome hypermobility type/joint hypermobility syndrome. *Am J Med Genet A* 170:2044–2051.
- Boyan BD, Hart DA, Enoka RM, Nicoletta DP, Resnick E, Berkley KJ, Sluka KA, Kwok CK, Tosi LL, O'Connor MI, Coutts RD, Kohrt WM. 2013. Hormonal modulation of connective tissue homeostasis and sex differences in risk for osteoarthritis of the knee. *Biol Sex Diff* 4:3.
- Branson JA, Kozłowska K, Kaczynski KJ, Roesler TA. 2011. Managing chronic pain in a young adolescent girl with Ehlers–Danlos syndrome. *Harv Rev Psychiatry* 19:259–270.
- Briggs J, McCormack M, Hakim AJ, Grahame R. 2009. Injury and joint hypermobility syndrome in ballet dancers—A 5-year follow-up. *Rheumatology* 48:1613–1614.
- Buchsbaum GM, Duecy EE, Kerr LA, Huang LS, Perevich M, Guzik DS. 2006. Pelvic organ prolapse in nulliparous women and their parous sisters. *Obstet Gynecol* 108:1388–1393.
- Buchsbaum GM, Duecy EE. 2008. Incontinence and pelvic organ prolapse in parous/nulliparous pairs of identical twins. *NeuroUrol Urodyn* 27:496–498.
- Burcharth J, Rosenberg J. 2012. Gastrointestinal surgery and related complications in patients with Ehlers–Danlos syndrome: A systematic review. *Dig Surg* 29:349–357.
- Byers PH, Krakow D, Nunes ME, Pepin M. 2006. Genetic evaluation of suspected osteogenesis imperfecta (OI). *Genet Med* 8:383–388.
- Calguneri M, Bird HA, Wright V. 1982. Changes in joint laxity occurring during pregnancy. *Ann Rheum Dis* 41:126–128.
- Camerota F, Castori M, Celletti C, Colotto M, Amato S, Colella A, Curione M, Danese C. 2014. Heart rate, conduction and ultrasound abnormalities in adults with joint hypermobility syndrome/Ehlers–Danlos syndrome, hypermobility type. *Clin Rheumatol* 33:981–987.
- Carbone L, Tyllavsky FA, Bush AJ, Koo W, Orwoll E, Cheng S. 2000. Bone density in Ehlers–Danlos syndrome. *Osteoporos Int* 11:388–392.
- Castori M, Camerota F, Celletti C, Grammatico P, Padua L. 2010a. Ehlers–Danlos syndrome hypermobility type and the excess of affected females: Possible mechanisms and perspectives. *Am J Med Genet Part Part A* 152A:2406–2408.
- Castori M, Camerota F, Celletti C, Danese C, Santilli V, Saraceni VM, Grammatico P. 2010b. Natural history and manifestations of the hypermobility type Ehlers–Danlos syndrome: A pilot study on 21 patients. *Am J Med Genet Part A* 152A:556–564.
- Castori M, Sperduti I, Celletti C, Camerota F, Grammatico P. 2011a. Symptom and joint mobility progression in the joint hypermobility syndrome (Ehlers–Danlos syndrome, hypermobility type). *Clin Exp Rheumatol* 29:998–1005.

- Castori M, Celletti C, Camerota F, Grammatico P. 2011b. Chronic fatigue syndrome is commonly diagnosed in patients with Ehlers-Danlos syndrome hypermobility type/joint hypermobility syndrome. *Clin Exp Rheumatol* 29:597–598.
- Castori M. 2012. Ehlers-Danlos syndrome, hypermobility type: An underdiagnosed hereditary connective tissue disorder with mucocutaneous, articular, and systemic manifestations. *ISRN Dermatol* 2012:751–768.
- Castori M, Morlino S, Celletti C, Celli M, Morrone A, Colombi M, Camerota F, Grammatico P. 2012a. 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. *Am J Med Genet Part A* 158A:2055–2070.
- Castori M, Morlino S, Dordoni C, Celletti C, Camerota F, Ritelli M, Morrone A, Venturini M, Grammatico P, Colombi M. 2012b. Gynecologic and obstetric implications of the joint hypermobility syndrome (a.k.a. Ehlers-Danlos syndrome hypermobility type) in 82 Italian patients. *Am J Med Genet Part A* 158A:2176–2182.
- Castori M, Morlino S, Dordoni C, Celletti C, Camerota F, Ritelli M, Morrone A, Venturini M, Grammatico P, Colombi M. 2012c. Gynecologic and obstetric implications of the joint hypermobility syndrome (a.k.a. Ehlers-Danlos syndrome hypermobility type) in 82 Italian patients. *Am J Med Genet Part A* 158A:2176–2182.
- Castori M, Morlino S, Celletti C, Ghibellini G, Bruschini M, Grammatico P, Blundo C, Camerota F. 2013. Re-writing the natural history of pain and related symptoms in the joint hypermobility syndrome/Ehlers-Danlos syndrome, hypermobility type. *Am J Med Genet Part A* 161A:2989–3004.
- Castori M, Dordoni C, Valiante M, Sperduti I, Ritelli M, Morlino S, Chiarelli N, Celletti C, Venturini M, Camerota F, Calzavara-Pinton P, Grammatico P, Colombi M. 2014. Nosology and inheritance pattern(s) of joint hypermobility syndrome and Ehlers-Danlos syndrome, hypermobility type: A study of intrafamilial and interfamilial variability in 23 Italian pedigrees. *Am J Med Genet Part A* 164A:3010–3020.
- Castori M. 2015. Ehlers-Danlos syndrome(s) mimicking child abuse: Is there an impact on clinical practice? *Am J Med Genet* 169:289–292.
- Castori M, Colombi M. 2015. Generalized joint hypermobility, joint hypermobility syndrome and Ehlers-Danlos syndrome, hypermobility type. *Am J Med Genet Part C* 169C:1–5.
- Castori M, Morlino S, Pascolini G, Blundo C, Grammatico P. 2015a. Gastrointestinal and nutritional issues in joint hypermobility syndrome/Ehlers-Danlos syndrome, hypermobility type. *Am J Med Genet Part C* 169C:54–75.
- Castori M, Dordoni C, Morlino S, Sperduti I, Ritelli M, Valiante M, Chiarelli N, Zanca A, Celletti C, Venturini M, Camerota F, Calzavara-Pinton P, Grammatico P, Colombi M. 2015b. Spectrum of mucocutaneous manifestations in 277 patients with joint hypermobility syndrome/Ehlers-Danlos syndrome, hypermobility type. *Am J Med Genet Part C* 169C:43–53.
- Castori M, Morlino S, Ghibellini G, Celletti C, Camerota F, Grammatico P. 2015c. Connective tissue, Ehlers-Danlos syndrome(s), and head and cervical pain. *Am J Med Genet Part C* 169C:1–14.
- Cazzato D, Castori M, Lombardi R, Caravello F, Bella ED, Petrucci A, Grammatico P, Dordoni C, Colombi M, Lauria G. 2016. Small fiber neuropathy is a common feature of Ehlers-Danlos syndromes. *Neurology* 87:155–159.
- Celletti C, Galli M, Cimolin V, Castori M, Albertini G, Camerota F. 2012. Relationship between fatigue and gait abnormality in joint hypermobility syndrome/Ehlers-Danlos syndrome hypermobility type. *Res Develop Disabil* 33:1914–1918.
- Celletti C, Castori M, La Torre G, Camerota F. 2013. Evaluation of kinesiophobia and its correlations with pain and fatigue in joint hypermobility syndrome/Ehlers-Danlos syndrome hypermobility type. *BioMed Res Intl* 2013:580460.
- Chen CW, Jao SW. 2007. Images in clinical medicine. Ehlers-Danlos syndrome. *N Engl J Med* 357:e12.
- Chou R, Deyo R, Friedly J, Skelly A, Hashimoto R, Weimer M, Fu R, Dana T, Kraegel P, Griffin J, Grusing S, Brodt E. 2016. Noninvasive treatments for low back pain [Internet]. *AHRQ Comparative Effectiveness Reviews*, Report 16-EHC004-EF. Rockville (MD): Agency for Healthcare Research and Quality (US). PMID: 26985522.
- Coelho PC, Santos RA, Gomes JA. 1994. Osteoporosis and Ehlers-Danlos syndrome. *Ann Rheum Dis* 53:212–213.
- Czaprowski D. 2014. Generalised joint hypermobility in Caucasian girls with idiopathic scoliosis: Relation with age, curve size, and curve pattern. *Scientific World Journal* 2014:370134.
- Danese C, Castori M, Celletti C, Amato S, Lo Russo C, Grammatico P, Camerota F. 2011. Screening for celiac disease in the joint hypermobility syndrome/Ehlers-Danlos syndrome hypermobility type. *Am J Med Genet Part A* 155A:2314–2316.
- Dauvilliers Y, Touchon J. 2001. Sleep in fibromyalgia: A review of clinical and polysomnographic data. *Neurophysiol Clin* 31:18–33.
- Day H, Koutedakis Y, Wyon MA. 2011. Hypermobility and dance: A review. *Int J Sports Med* 32:485–489.
- De Coster PJ, Martens LC, De Paepe A. 2005. Oral health in prevalent types of Ehlers-Danlos syndromes. *J Oral Pathol Med* 34:298–307.
- Defuentes G, Damiano J, Moulin O, Hervouet M, Zing E, Berets O. 2004. Colite diverticulaire droite révélatrice d'un syndrome d'Ehlers-Danlos. *Presse Med* 33:1591–1592.
- De Kort LM, Verhulst JA, Engelbert RH, Uiterwaal CS, de Jong TP. 2003. Lower urinary tract dysfunction in children with generalized hypermobility of joints. *J Urol* 170:1971–1974.
- Delling FN, Vasan RS. 2014. Epidemiology and pathophysiology of mitral valve prolapse: New insights into disease progression, genetics, and molecular basis. *Circulation* 129:2158–2170.
- Deodhar AA, Woolf AD. 1994. Ehlers Danlos syndrome and osteoporosis. *Ann Rheum Dis* 53:841–842.
- Derpapas A, Cartwright R, Upadhyaya P, Bhide AA, Digesu AG, Khullar V. 2015. Lack of association of joint hypermobility with urinary incontinence subtypes and pelvic prolapse. *BJU Int* 115:639–643.
- De Wandele I, Rombaut L, Malfait F, De Backer T, De Paepe A, Calders P. 2013. Clinical heterogeneity in patients with the hypermobility type of Ehlers-Danlos syndrome. *Res Dev Disabil* 34:873–881.
- De Wandele I, Calders P, Peersman W, Rimbaut S, De Paepe A, Malfait F, De Paepe A, Rombaut L. 2014a. Autonomic symptom burden in the hypermobility type of Ehlers-Danlos syndrome: A comparative study with two other EDS types, fibromyalgia, and healthy controls. *Semin Arthritis Rheum* 44:353–361.
- De Wandele I, Rombaut L, Leybaert L, Van de Borne P, De Backer T, Malfait F, De Paepe A, Calders P. 2014b. Dysautonomia and its underlying mechanisms in the hypermobility type of Ehlers-Danlos syndrome. *Semin Arthritis Rheum* 44:93–100.
- Dickin DC, Doan JB. 2008. Postural stability in altered and unaltered sensory environments following fatiguing exercise of lower extremity joints. *Scand J Med Sci Sports* 18:765–772.
- Di Stefano G, Celletti C, Baron R, Castori M, Di Franco M, La Cesa S, Leone C, Pepe A, Cruccu G, Truini A, Camerota F. 2016. Central sensitization as the mechanism underlying pain in joint hypermobility syndrome/Ehlers-Danlos syndrome, hypermobility type. *Eur J Pain* 20:1319–1325.
- Dolan AL, Mishra MB, Chambers JB, Grahame R. 1997. Clinical and echocardiographic survey of the Ehlers-Danlos syndrome. *Br J Rheumatol* 36:459–462.
- Dolan AL, Arden NK, Grahame R, Spector TD. 1998. Assessment of bone in Ehlers Danlos syndrome by ultrasound and densitometry. *Ann Rheum Dis* 57:630–633.
- Dolan AL, Hart DJ, Doyle DV, Grahame R, Spector TD. 2003. The relationship of joint hypermobility, bone mineral density, and osteoarthritis in the general population: The Chingford Study. *J Rheumatol* 30:799–803.
- Dordoni C, Ritelli M, Venturini M, Chiarelli N, Pezzani L, Vascellaro A, Calzavara-Pinton P, Colombi M. 2013. Recurring and generalized viscerotaxis in Ehlers-Danlos syndrome hypermobility type. *Am J Med Genet Part A* 161A:1143–1147.
- Douglas BS, Douglas HM. 1973. Rectal prolapse in the Ehlers-Danlos syndrome. *Aust Paediatr J* 9:109–110.
- Dowell D, Haegerich TM, Chou R. 2016. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *JAMA* 315:1624–1645.
- Easton V, Bale P, Bacon H, Jerman E, Armon K, Macgregor AJ. 2014. A89: The relationship between benign joint hypermobility syndrome and developmental coordination disorders in children. *Arthritis Rheumatol* 66:S124[poster].

- Eccles JA, Owens AP, Mathias CJ, Umeda S, Critchley HD. 2015. Neurovisceral phenotypes in the expression of psychiatric symptoms. *Front Neurosci* 9:4.
- Edmonds M, McGuire H, Price J. 2004. Exercise therapy for chronic fatigue syndrome. *Cochrane Database Syst Rev* 3:CD003200.
- el-Shahaly HA, el-Sherif AK. 1991. Is the benign joint hypermobility syndrome benign? *Clin Rheumatol* 10:302–307.
- Engelbert RH, Bank RA, Sakkars RJ, Helders PJ, Beemer FA, Uiterwaal CS. 2003. Pediatric generalized joint hypermobility with and without musculoskeletal complaints: A localized or systemic disorder? *Pediatrics* 111:e248–e254.
- Farmer AD, Fikree A, Aziz Q. 2014. Addressing the confounding role of joint hypermobility syndrome and gastrointestinal involvement in postural orthostatic tachycardia syndrome. *Clin Auton Res* 24:157–158.
- Feldman K, Smith WG. 2007. Idiopathic striae atrophicae of puberty. *Can Med Assoc J* 176:930–931.
- Fikree A, Grahame R, Aktar R, Farmer AD, Hakim AJ, Morris JK, Knowles CH, Aziz Q. 2015. A prospective evaluation of undiagnosed joint hypermobility syndrome in patients with gastrointestinal symptoms. *Clin Gastroenterol Hepatol* 27:569–579.
- Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, Gilron I, Haanpää M, Hansson P, Jensen TS, Kamerman PR, Lund K, Moore A, Raja SN, Rice ASC, Rowbotham M, Sena M, Siddall P, Smith BH, Wallace M. 2015. Pharmacotherapy for neuropathic pain in adults: A systematic review and meta-analysis. *Lancet Neurol* 14:162–173.
- Flaherty EG, Perez-Rossello JM, Levine MA, Hennrikus WL, American Academy of Pediatrics Committee on Child Abuse and Neglect; Section on Radiology, American Academy of Pediatrics; Section on Endocrinology, American Academy of Pediatrics; Section on Orthopaedics, American Academy of Pediatrics; Society for Pediatric Radiology. 2014. Evaluating children with fractures for child physical abuse. *Pediatrics* 133:e477–e489.
- Fogel S. 2013. Surgical failures: Is it the surgeon or the patient? The all too often missed diagnosis of Ehlers-Danlos syndrome. *Am Surg* 79:608–613.
- Fossey M, Libman E, Bailes S, Blatzan M, Schondorf R, Ansel R, Fichten CS. 2004. Sleep quality and psychological adjustment in chronic fatigue syndrome. *J Behav Med* 27:581–605.
- Gamble JG, Mochizuki C, Rinsky LA. 1989. Trapeziometacarpal abnormalities in Ehlers-Danlos syndrome. *J Hand Surg* 14A:89–94.
- Gazit Y, Nahir AM, Grahame R, Jacob G. 2003. Dysautonomia in the joint hypermobility syndrome. *Am J Med* 115:33–40.
- Gedalia A, Press J, Buskila D. 1996. Diffuse musculoskeletal pain syndromes in pediatric practice. *J Clin Rheumatol* 2:325–330.
- Grahame R. 1989. How often, when and how does joint hypermobility lead to osteoarthritis. *Br J Rheumatol* 28:320.
- Grahame R, Bird HA, Child A. 2000. The revised (Brighton 1998) criteria for the diagnosis of benign joint hypermobility syndrome (BJHS). *J Rheumatol* 27:1777–1779.
- Granata G, Padua L, Celletti C, Castori M, Saraceni VM, Camerota F. 2013. Entrapment neuropathies and polyneuropathies in joint hypermobility syndrome/Ehlers-Danlos syndrome. *Clin Neurophysiol* 124:1689–1694.
- Guilleminault C, Primeau M, Chiu H, Yuen KM, Leger D, Metlaine A. 2013. Sleep-disordered-breathing in Ehlers-Danlos syndrome (a genetic model of obstructive sleep apnea). *Chest* 144:1503–1511.
- Gulbahar S, Sahin E, Baydar M, Bircan C, Kizil R, Manisali M, Akalin E, Peker O. 2006. Hypermobility syndrome increases the risk for low bone mass. *Clin Rheumatol* 25:511–514.
- Gürer G, Bozbas GT, Tuncer T, Unobol AI, Ucar UG, Memetoglu OI. 2016. Frequency of joint hypermobility in Turkish patients with knee osteoarthritis: A cross sectional multi-center study. *Int J Rheum Dis* July 27 [ePub ahead of print].
- Hagberg C, Berglund B, Korpe L, Andersson-Norinder J. 2004. Ehlers-Danlos Syndrome (EDS) focusing on oral symptoms: A questionnaire study. *Orthod Craniofac Res* 7:178–185.
- Hakim AJ, Grahame R. 2004. Non-musculoskeletal symptoms in joint hypermobility syndrome. Indirect evidence for autonomic dysfunction? *Rheumatology (Oxford)* 43:1194–1195.
- Hakim AJ, Cherkas LF, Grahame R, Spector TD, MacGregor AJ. 2004. The genetic epidemiology of joint hypermobility. A population study of female twins. *Arthritis Rheumat* 50:2640–2644.
- Hakim AJ, Grahame R, Norris P, Hopper C. 2005. Local anaesthetic failure in joint hypermobility syndrome. *J Royal Society Med* 98:84–85.
- Hakim AJ, Sahota A. 2006. Joint hypermobility and skin elasticity: The hereditary disorders of connective tissue. *Clin Dermatol* 24:521–533.
- Hallock JL, Handa VL. 2016. The epidemiology of pelvic floor disorders and childbirth: An update. *Obstet Gynecol Clin North Am* 43:1–13.
- Hamonet C, Gompel A, Mazaltarine G, Brock I, Baeza-Velasco C, Zeitoun JD, Bienvenu B. 2015. Ehlers-Danlos syndrome or disease? *J Syndrome* 2:5.
- Harrison B, Sannic K, Janis JE. 2016. Collagenopathies-implications for abdominal wall reconstruction: A systematic review. *Plast Reconstr Surg Glob Open* 24:e1036.
- Health Quality Ontario. 2015. Positional magnetic resonance imaging for people with Ehlers-Danlos syndrome or suspected craniovertebral or cervical spine abnormalities: An evidence-based analysis. *Ont Health Technol Assess Ser* 15:1–24.
- Hermanns-Lê T, Reginster MA, Piérard-Franchimont C, Delvenne P, Piérard GE, Manicourt D. 2012. Dermal ultrastructure in low Beighton score members of 17 families with hypermobile-type Ehlers-Danlos syndrome. *J Biomed Biotechnol* 2012:878107.
- Hershenfeld SA, Wasim S, McNiven V, Parikh M, Majewski P, Faghfoury H, So J. 2016. Psychiatric disorders in Ehlers-Danlos syndrome are frequent, diverse and strongly associated with pain. *Rheumatol Int* 36:341–348.
- Herzka A, Sponseller PD, Pyeritz RE. 2000. Atlantoaxial rotatory subluxation in patients with Marfan syndrome. A report of three cases. *Spine* 25:524–526.
- Hugon-Rodin J, Lebegue G, Becourt S, Hamonet C, Gompel A. 2016. Gynecologic symptoms and the influence on reproductive life in 386 women with hypermobility type of Ehlers-Danlos syndrome: A cohort study. *Orphan J Rare Dis* 11:124.
- Hunter A, Morgan AW, Bird HA. 1998. A survey of Ehlers-Danlos syndrome: Hearing, voice, speech and swallowing difficulties. Is there an underlying relationship? *Br J Rheumatol* 37:803–804.
- Hurst BS, Lange SS, Kullstam SM, Usadi RS, Matthews ML, Marshburn PB, Templin MA, Merriam KS. 2014. Obstetric and gynecologic challenges in women with Ehlers-Danlos syndrome. *Obstet Gynecol* 123:506–513.
- Jacks SK, Zirwas MJ. 2016. Abnormal wound healing related to high-dose systemic corticosteroid therapy in a patient with Ehlers-Danlos syndrome benign hypermobility type. *Cutis* 98:E20–E23.
- Jacome DE. 1999. Headache in Ehlers-Danlos syndrome. *Cephalalgia* 19:791–796.
- Jonsson H, Valtysdottir ST. 1995. Hypermobility features in patients with hand osteoarthritis. *Osteoarthritis Cartilage* 3:1–5.
- Johannessen EC, Reiten HS, Lovaas H, Maeland S, Juul-Kristensen B. 2016. Shoulder dysfunction, pain and health related quality of life in adults with joint hypermobility syndrome/Ehlers-Danlos syndrome-hypermobility type. *Disabil Rehabil* 38:1382–1390.
- Kajbafzadeh AM, Sharifi-Rad L, Seyedian SS, Mozafarpour S, Paydary K. 2014. Generalized joint hypermobility and voiding dysfunction in children: Is there any relationship? *Eur J Pediatr* 173:197–201.
- Kanjwal K, Saeed B, Karabin, Kanjwal Y, Grubb BP. 2010. Comparative clinical profile of postural orthostatic tachycardia patients with and without joint hypermobility syndrome. *Indian Pacing Electrophysiol J* 10:173–178.
- Kapferer-Seebacher I, Pepin M, Werner R, Aitman TJ, Nordgren A, Stoiber H, Thielens N, Gaboriaud C, Amberger A, Schossig A, Gruber R, Giunta C, Bamshad M, Björck E, Chen C, Chitayat D, Dorschner M, Schmitt-Egenolf M, Hale CJ, Hanna D, Hennies HC, Heiss-Kisielewsky I, Lindstrand A, Lundberg P, Mitchell AL, Nickerson DA, Reinstein E, Rohrbach M, Romani N, Schmuth M, Silver R, Taylan F, Vandersteen A, Vandrovcova J, Weerakkody R, Yang M, Pope FM; Molecular Basis of Periodontal EDS Consortium. 2016. Periodontal Ehlers-Danlos syndrome is caused by mutations in C1R and C1S, which encode subcomponents C1r and C1a of complement. *Am J Hum Genet* 99:1005–1014.
- Kim HJ, Yeom JS, Lee DB, Kang KT, Chang BS, Lee CK. 2013. Association of benign joint hypermobility with spinal segment motion and its implication in active young males. *Spine* 38:e1013–e1019.

- Kirby A, Davies R, Bryant A. 2005. Hypermobility syndrome and developmental coordination disorder: Similarities and features. *Int J Ther Rehabil* 12:431–436.
- Kirk JA, Ansell BM, Bywaters EGL. 1967. The hypermobility syndrome. Musculoskeletal complaints associated with generalized joint hypermobility. *Ann Rheum Dis* 26:419–425.
- Kizilbash SJ, Ahrens SP, Bruce BK, Chelimsky G, Driscoll SW, Harbeck-Weber C, Lloyd RM, Mack KJ, Nelson DE, Ninis N, Pianosi PT, Stewart JM, Weiss KE, Fischer PR. 2014. Adolescent fatigue, POTS, and recovery: A guide for clinicians. *Curr Probl Pediatr Adolesc Health Care* 44:108–133.
- Klemp P. 1997. Hypermobility. *Ann Rheum Dis* 56:573–575.
- Knoepf LR, McDermott KC, Munoz A, Blomquist JL, Handa VL. 2013. Joint hypermobility, obstetrical outcomes, and pelvic floor disorders. *Int Urogynecol* 24:735–740.
- Konopinski M, Graham I, Johnson MI, Jones G. 2015. The effect of hypermobility on the incidence of injury in professional football: A multi-site cohort study. *Phys Ther Sport* 21:7–13.
- Kovacic K, Chelimsky TC, Sood MR, Simpson P, Nugent M, Chelimsky G. 2014. Joint hypermobility: A common association with complex functional gastrointestinal disorders. *J Pediatr* 165:973–978.
- Kozanoglu E, Coskun Benlidayi I, Eker Akilli R, Tasal A. 2016. Is there any link between joint hypermobility and mitral valve prolapse in patients with fibromyalgia syndrome? *Clin Rheumatol* 35:1041–1044.
- Lammers K, Lince SL, Spath MA, van Kempen LC, Hendriks JC, Vierhout ME, Kluivers KB. 2012. Pelvic organ prolapse and collagen-associated disorders. *Int Urogynecol J* 23:313–319.
- Laszkowska M, Roy A, Lebowl B, Green PH, Sundelin HE, Ludvigsson JF. 2016. Nationwide population-based cohort study of celiac disease and risk of Ehlers-Danlos syndrome and joint hypermobility syndrome. *Dig Liver Dis* 48:1030–1034.
- Lind J, Wallenburg HC. 2002. Pregnancy and the Ehlers-Danlos syndrome: A retrospective study in a Dutch population. *Acta Obstet Gynecol Scand* 81:293–300.
- Liu FC, Fuh JL, Wang YF, Wang SJ. 2011. Connective tissue disorders in patients with spontaneous intracranial hypotension. *Cephalalgia* 31:691–695.
- Lumley MA, Jordan M, Rubenstein R, Tsiouras P, Evans MI. 1994. Psychosocial functioning in the Ehlers-Danlos syndrome. *Am J Med Genet* 53:149–152.
- Lyons JJ, Sun G, Stone KD, Nelson C, Wisch L, O'Brien M, Jones N, Lindsley A, Komarow HD, Bai Y, Scott LM, Cantave D, Maric I, Abonia JP, Rothenberg ME, Schwartz LB, Milner JD, Wilson TM. 2014. Mendelian inheritance of elevated serum tryptase associated with atopy and connective tissue abnormalities. *J Allergy Clin Immunol* 133:1471–1474.
- Lyons JJ, Yu X, Hughes JD, Le QT, Jamil A, Bai Y, Ho N, Zhao M, Liu Y, O'Connell MP, Trivedi NN, Nelson C, DiMaggio T, Jones N, Matthews H, Lewis KL, Oler AJ, Carlson RJ, Arkwright PD, Hong C, Agama S, Wilson TM, Tucker S, Zhang Y, McElwee JJ, Pao M, Glover SC, Rothenberg ME, Hohman RJ, Stone KD, Caughey GH, Heller T, Metcalfe DD, Biesecker LG, Schwartz LB, Milner JD. 2016. Elevated basal serum tryptase identifies a multisystem disorder associated with increased TPSAB1 copy number. *Nat Genet* 48:1564–1569.
- Machet L, Huttenberger B, Georgesco G, Dore C, Jamet F, Bonnin-Goga B, Giraudea B, Maruani A, Laure B, Vaillant L. 2010. Absence of inferior labial and lingual frenula in Ehlers-Danlos syndrome: A minor diagnostic criterion in French patients. *Am J Clin Dermatol* 11:269–273.
- Maeland S, Assmus J, Berglund B. 2011. Subjective health complaints in individuals with Ehlers-Danlos syndrome: A questionnaire study. *Int J Nurs Stud* 48:720–724.
- Mallorqui-Bagué N, Bulbena A, Roé-Vellvé N, Hoekzema E, Carmona S, Barba-Müller E, Fauquet J, Paillet G, Vilarroya O. 2015. Emotion processing in joint hypermobility: A potential link to the neural bases of anxiety and related somatic symptoms in collagen anomalies. *Eur Psychiatry* 30:454–458.
- Mandelbaum DE, de la Monte SM. 2017. Adverse structural and functional effects of marijuana on the brain: Evidence reviewed. *Pediatr Neurol* 66:12–20.
- Manning J, Korda A, Bennes C, Solomon M. 2003. The association of obstructive defecation, lower urinary tract dysfunction and the benign joint hypermobility syndrome: A case-control study. *Int Urogynecol J Pelvic Floor Dysfunct* 14:128–132.
- Mastoroudes H, Giarenis I, Cardozo L, Srikrishna S, Vella M, Robinson D, Kazkaz H, Grahame R. 2013a. Lower urinary tract symptoms in women with benign joint hypermobility syndrome: A case-control study. *Int Urogynecol* 24:1553–1558.
- Mastoroudes H, Giarenis I, Cardozo L, Srikrishna S, Vella M, Robinson D, Kazkaz H, Grahame R. 2013b. Prolapse and sexual function in women with benign joint hypermobility syndrome. *BJOG* 120:187–192.
- Mathias CJ, Low DA, Iodice V, Owens AP, Kirbis M, Grahame R. 2011. Postural tachycardia syndrome—current experience and concepts. *Nat Rev Neurol* 8:22–34.
- Mazziotti G, Dordoni C, Doga M, Galderisi F, Venturini M, Calzavara-Pinton P, Maroldi R, Giustina A, Colombi M. 2016. High prevalence of radiologic vertebral fractures in adult patients with Ehlers-Danlos syndrome. *Bone* 18:88–92.
- McDonnell NB, Gorman BL, Mandel KW, Schurman SH, Assanah-Carroll A, Mayer SA, Najjar SS, Francomano CA. 2006. Echocardiographic findings in classical and hypermobile Ehlers-Danlos syndromes. *Am J Med Genet Part A* 140A:129–136.
- McIntosh LJ, Mallett VT, Frahm JD, Richardson DA, Evans MI. 1995. Gynecologic disorders in women with Ehlers-Danlos syndrome. *J Soc Gynecol Invest* 2:559–564.
- McIntosh LJ, Stanitski DF, Mallett VT, Frahm JD, Richardson DA, Evans MI. 1996. Ehlers-Danlos syndrome: Relationship between joint hypermobility, urinary incontinence, and pelvic floor prolapse. *Gynecol Obstet Invest* 41:135–139.
- Meeus M, Nijs J, Merleir KD. 2007. Chronic musculoskeletal pain in patients with chronic fatigue syndrome: A systematic review. *Eur J Pain* 11:377–386.
- Merke DP, Chen W, Morissette R, Xu Z, Van Ryzin C, Sachdev V, Hannouh H, Shanbhag SM, Acevedo AT, Nishitani M, Arai AE, McDonnell NB. 2013. Tenascin-X haploinsufficiency associated with Ehlers-Danlos syndrome in patients with congenital adrenal hyperplasia. *Eur J Med Genet* 54:112–117.
- Milhorat TH, Bolognese PA, Nishikawa M, McDonnell NB, Francomano CA. 2007. Syndrome of occipitoatlantoaxial hypermobility, cranial settling, and Chiari malformation type I in patients with hereditary disorders of connective tissue. *J Neurosurg Spine* 7:601–609.
- Morissette R, Chen W, Perritt AF, Dreiling JL, Arai AE, Sachdev V, Hannouh H, Mallappa A, Xu Z, McDonnell NB, Quezado M, Merke DP. 2015. Broadening the spectrum of Ehlers Danlos syndrome in patients with congenital adrenal hyperplasia. *J Clin Endocrinol Metab* 100:E1143–E1152.
- Morris SL, O'Sullivan PB, Murray KJ, Baer N, Hands B, Smith AJ. 2016. Hypermobility and musculoskeletal pain in adolescents. *J Pediatr* 163:31044–31047.
- Mulvey MR, Macfarlane GJ, Beasley M, Symmons DP, Lovell K, Keeley P, Woby S, McBeth J. 2013. Modest association of joint hypermobility with disabling and limiting musculoskeletal pain: Results from a large-scale general population-based survey. *Arthritis Care Res (Hoboken)* 65:1325–1333.
- Murray B, Yashar BM, Uhlmann WR, Clauw DJ, Petty EM. 2013. Ehlers-Danlos syndrome, hypermobility type: A characterization of the patients' lived experience. *Am J Med Genet Part A* 161A:2981–2988.
- Murray KJ, Woo P. 2001. Benign joint hypermobility in childhood. *Rheumatology* 40:489–491.
- Narcisi P, Richards AJ, Ferguson SD, Pope FM. 1994. A family with Ehlers-Danlos syndrome type III/articular hypermobility syndrome has a glycine 637 to serine substitution in type III collagen. *Hum Mol Genet* 3:1617–1620.
- National Guideline Clearinghouse (NGC). 2013. Guideline summary: Assessment and management of chronic pain. In: National Guideline Clearinghouse (NGC) [Web site]. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ). [cited 2017 Jan 21]. Available: <https://www.guideline.gov>
- Nazem M, Mottaghi P, Hoseini A, Khodadadi H. 2013. Benign joint hypermobility syndrome among children with inguinal hernia. *J Res Med Sci* 18:904–905.
- Nef W, Gerber NJ. 1998. Hypermobility syndrome. When too much activity causes pain. *Schweiz Med Wochenschr* 128:302–310.
- Neilson D, Martin VT. 2014. Joint hypermobility and headache: Understanding the glue that binds the two together—Part 1. *Headache* 54:1393–1402.
- Nelson AD, Mouchli MA, Valentin N, Deyle D, Pichurin P, Acosta A, Camilleri M. 2015. Ehlers Danlos syndrome and gastrointestinal manifestations: A 20-year experience at Mayo Clinic. *Neurogastroenterol Motil* 27:1657–1666.

- Nijs J, Meeus M, De Meirleir K. 2006. Chronic musculoskeletal pain in chronic fatigue syndrome: Recent developments and therapeutic implications. *Man Ther* 11:187–191.
- Norton PA, Baker JE, Sharp HC, Warenski JC. 1995. Genitourinary prolapse and joint hypermobility in women. *Obstet Gynecol* 85:225–228.
- Nosouhian S, Haghghat A, Mohammadi I, Shadmehr E, Davoudi A, Badrian H. 2015. Temporomandibular joint hypermobility manifestation based on clinical observations. *J Intl Oral Health* 7:1–4.
- Ofluoglu D, Gunduz OH, Kul-Panza E, Guven Z. 2006. Hypermobility in women with fibromyalgia syndrome. *Clin Rheumatol* 25:291–293.
- Owens J. 2014. Insufficient sleep in adolescents and young adults: An update on causes and consequences. *Pediatr* 134:e921.
- Pacey V, Tofts L, Adams RD, Munns CF, Nicholson LL. 2013. Exercise in children with joint hypermobility syndrome and knee pain: A randomized controlled trial comparing exercise into hypermobile versus neutral knee extension. *Pediatr Rheumatol Online* 11:30.
- Pacey V, Adams RD, Tofts L, Munns CF, Nicholson LL. 2015a. Joint hypermobility syndrome subclassification in paediatrics: A factor analytic approach. *Arch Dis Child* 100:8–13.
- Pacey V, Tofts L, Adams RD, Munns CF, Nicholson LL. 2015b. Quality of life prediction in children with joint hypermobility syndrome. *J Paediatr Child Health* 51:689–695.
- Palmer S, Bailey S, Barker L, Barney L, Elliot A. 2014. The effectiveness of therapeutic exercise for joint hypermobility syndrome: A systematic review. *Physiotherapy* 100:220–227.
- Plackett TP, Kwon E, Gagliano RA Jr., Oh RC. 2014. Ehlers-Danlos syndrome-hypermobility type and hemorrhoids. *Case Rep Surg* 2014:171–180.
- Puledda F, Vigano A, Celletti C, Petolicchio B, Toscano M, Vicenzini E, Castori M, Laudani G, Valente D, Camerota F, Di Piero V. 2015. A study of migraine characteristics in joint hypermobility syndrome a.k.a. Ehlers-Danlos syndrome, hypermobility type. *Neuro Sci* 36:1417–1424.
- Quatman CE, Ford KR, Myer GD, Paterno MV, Hewett TE. 2008. The effects of gender and pubertal status on generalized joint laxity in young athletes. *J Sci Med Sport* 11:257–263.
- Rahman N, Dunstan M, Teare MD, Hanks S, Douglas J, Coleman K, Bottomly WE, Campbell M, Berglund B, Nordenskjöld M, Forssell B, Burrows N, Lunt P, Young I, Williams N, Bignell GR, Futreal A, Pope FM. 2003. Ehlers-Danlos syndrome with severe early-onset periodontal disease (EDS-VIII) is a distinct, heterogeneous disorder with one predisposition gene at chromosome 12p13. *Am J Hum Genet* 73:198–203.
- Reinstein E, Pimentel M, Pariani M, Nemes S, Sokol T, Rimoin DL. 2012. Visceroptosis of the bowel in the hypermobility type of Ehlers-Danlos syndrome: Presentation of a rare manifestation and review of the literature. *Eur J Med Genet* 55:548–551.
- Reinstein E, Pariani M, Bannykh S, Rimoin DL, Schievink WI. 2013. Connective tissue spectrum abnormalities associated with spontaneous cerebrospinal fluid leaks: A prospective study. *Eur J Hum Genet* 21:386–390.
- Rodrigues VJ, Elsayed S, Loeys BL, Dietz HC, Yousem DM. 2009. Neuroradiologic manifestations of Loeys-Dietz syndrome type 1. *AJNR Am J Neuroradiol* 30:1614–1619.
- Rombaut L, Malfait F, Cools A, De Paepe A, Calders P. 2010. Musculoskeletal complaints, physical activity and health-related quality of life among patients with the Ehlers-Danlos syndrome hypermobility type. *Disabil Rehabil* 32:1339–1345.
- Rombaut L, Malfait F, De Paepe A, Rombaut S, Verbruggen G, De Wandele I, Calders P. 2011a. Impairment and impact of pain in female patients with Ehlers-Danlos syndrome: A comparative study with fibromyalgia and rheumatoid arthritis. *Arthritis Rheum* 63:1979–1987.
- Rombaut L, Malfait F, De Wandele I, Cools A, Thijs Y, De Paepe A, Calders P. 2011b. Medication, surgery, and physiotherapy among patients with the hypermobility type of Ehlers-Danlos syndrome. *Arch Phys Med Rehabil* 92:1106–1112.
- Rombaut L, Malfait F, De Wandele I, Taes Y, Thijs Y, De Paepe A, Calders P. 2012. Muscle mass, muscle strength, functional performance, and physical impairment in women with the hypermobility type of Ehlers-Danlos syndrome. *Arthritis Care Res (Hoboken)* 64:1584–1592.
- Rombaut L, Schepers M, De Wandele I, De Vries J, Meeus M, Malfait F, Englebert R, Calders P. 2015. Chronic pain in patients with the hypermobility type of Ehlers-Danlos syndrome: Evidence for hyperalgesia. *Clin Rheumatol* 34:1121–1129.
- Rowe PC, Barron DF, Calkins H, Maumenee IH, Tong PY, Geraghty MT. 1999. Orthostatic intolerance and chronic fatigue syndrome associated with Ehlers-Danlos syndrome. *J Pediatr* 135:494–499.
- Rozen TD, Roth JM, Denenberg N. 2006. Cervical spine hypermobility as a predisposing factor for the development of new daily persistent headache. *Headache* 45:828–829.
- Sacheti A, Szemere J, Bernstein B, Tafas T, Schechter N, Tsiouras P. 1997. Chronic pain is a manifestation of the Ehlers-Danlos syndrome. *J Pain Symptom Manage* 14:88–93.
- Sardeli C, Axelsen SM, Bek KM. 2005. Use of porcine small intestinal submucosa in the surgical treatment of recurrent rectocele in a patient with Ehlers-Danlos syndrome type III. *Int Urogynecol J Pelvic Floor Dysfunct* 16:504–505.
- Scheper MC, de Vries JE, de Vos R, Verbunt J, Nollet F, Engelbert RHH. 2013. Generalized joint hypermobility in professional dancers: A sign of talent or vulnerability? *Rheumatol* 52:651–665.
- Scheper MC, de Vries JE, Verbunt J, Engelbert RHH. 2015. Chronic pain in hypermobility syndrome and Ehlers-Danlos syndrome (hypermobility type): It is a challenge. *J Pain Res* 20:591–601.
- Scheper MC, Pacey V, Rombaut L, Adams RD, Tofts L, Calders P, Nicholson LL, Engelbert RHH. 2016a. Generalized hyperalgesia in children and adults diagnosed with hypermobility syndrome and Ehlers-Danlos syndrome hypermobility type: A discriminative analysis. *Arthritis Care Res Aug 2* [Epub ahead of print].
- Scheper MC, Juul-Kristensen B, Rombaut L, Rameekers EZ, Verbunt J, Engelbert RHH. 2016b. Disability in adolescents and adults diagnosed with hypermobility-related disorders: A meta-analysis. *Arch Phys Med Rehab* 97:2174–2187.
- Scott D, Bird H, Wright V. 1979. Joint laxity leading to osteoarthritis. *Rheumatol Rehabil* 18:167–169.
- Shultz SJ, Wideman L, Montgomery MM, Beasley KN, Nindl BC. 2012. Changes in serum collagen markers, IGF-I, and knee joint laxity across the menstrual cycle. *J Orthop Res* 30:1405–1412.
- Simmonds JV, Keer RJ. 2007. Hypermobility and the hypermobility syndrome. *Man Ther* 12:298–309.
- Sinibaldi L, Ursini G, Castori M. 2015. Psychopathological manifestations of joint hypermobility and joint hypermobility syndrome/Ehlers-Danlos syndrome, hypermobility type: The link between connective tissue and psychological distress revised. *Am J Med Genet C Semin Med Genet* 169C:97–106.
- Sipilä K, Suominen AL, Alanen P, Heliövaara M, Tittanen P, Kõnönen M. 2011. Association of clinical findings of temporomandibular disorders (TMD) with self-reported musculoskeletal pains. *Eur J Pain* 15:1061–1067.
- Skinner HB, Wyatt MP, Stone ML, Hodgdon JA, Barrack RL. 1986. Exercise-related knee joint laxity. *Am J Sport Med* 14:30–34.
- Sleep Working Group and Committee on Adolescence, and Council on School Health. 2014. American Academy of Pediatrics Policy Statement: School start times for adolescents. *Pediatrics* 134:642–649.
- Smith MT, Edwards RR, McCann UD, Haythornwaite JA. 2007. The effects of sleep deprivation on pain inhibition and spontaneous pain in women. *Sleep* 30:494–505.
- Sorokin Y, Johnson MP, Rogowski N, Richardson DA, Evans MI. 1994. Obstetric and gynecologic dysfunction in the Ehlers-Danlos syndrome. *J Reprod Med* 39:281–284.
- Sparto PJ, Parnianpour M, Reinsel TE, Simon S. 1997. The effect of fatigue on multijoint kinematics, coordination, and postural stability during a repetitive lifting test. *J Orthopaedic Sport Phys Therap* 25:3–12.
- Stanitski DF, Nadjarian R, Stanitski CL, Bawle E, Tsiouras P. 2000. Orthopaedic manifestations of Ehlers-Danlos syndrome. *Clin Orthop Relat Res* 376:213–221.
- Steinmann B, Royce PM, Superti-Furga A. 2002. The Ehlers-Danlos syndrome. In: Royce PM, Steinmann B, editors. *Connective tissue and its heritable disorders*, 2nd edition. New York (US): Wiley-Liss, pp 431–524.
- Stern CM, Pepin MJ, Stoler JM, Kramer DE, Spencer SA, Stein CJ. 2016. Musculoskeletal conditions in a pediatric population with Ehlers-Danlos syndrome. *J Pediatr* 347:31212–31214.
- Sundelin HE, Stephansson O, Johansson K, Ludvigsson JE. 2017. Pregnancy outcome in joint hypermobility syndrome and

- Ehlers-Danlos syndrome. *Acta Obstet Gynecol Scand* 96:114–119.
- Syx D, Symoens S, Steyaert W, De Paepe A, Coucke PJ, Malfait F. 2015. Ehlers-Danlos syndrome, hypermobility type, is linked to chromosome 8p22–8p21.1 in an extended Belgian family. *Dis Mark* 2015:828970.
- Ting TV, Hashkes PJ, Schikler K, Desai AM, Spalding S, Kashikar-Zuck S. 2012. The role of benign joint hypermobility in the pain experience in juvenile fibromyalgia: An observational study. *Pediatr Rheumatol Online J* 10:16.
- Tinkle BT, Bird HA, Grahame R, Lavalley M, Levy HP, Sillence D. 2009. The lack of clinical distinction between the hypermobility type of Ehlers-Danlos syndrome and the joint hypermobility syndrome (a.k.a. hypermobility syndrome). *Am J Med Genet Part A* 149A:2368–2370.
- Tobias JH, Deere K, Palmer S, Clark EM, Clinch J. 2013. Joint hypermobility is a risk factor for musculoskeletal pain during adolescence. Findings of a prospective cohort study. *Arthritis Rheumat* 65:1107–1115.
- Tofts LJ, Elliot EJ, Munns C, Pacey V, Sillence DO. 2009. The differential diagnosis of children with joint hypermobility: A review of the literature. *Pediatr Rheumatol Online J* 7:1.
- van der Esch M, Steultjens M, Knol DL, Dinant H, Dekker J. 2006. Joint laxity and the relationship between muscle strength and functional ability in patients with osteoarthritis of the knee. *Arthritis Rheum* 55:953–959.
- Veit-Rubin N, Cartwright R, Singh AU, Digesu GA, Fernando R, Khullar V. 2016. Association between joint hypermobility and pelvic organ prolapse in women: A systemic review and meta-analysis. *Int Urogynecol J* 27:491–493.
- Verbraecken J, Declerck A, Van de Heyning P, De Backer W, Wouters EF. 2001. Evaluation for sleep apnea in patients with Ehlers-Danlos syndrome and Marfan: A questionnaire study. *Clin Genet* 60:360–365.
- Voermans NC, Knoop H, van de Kamp N, Hamel BC, Bleijenberg G, van Engelen BG. 2010a. Fatigue is a frequent and clinically relevant problem in Ehlers-Danlos syndrome. *Semin Arthritis Rheum* 40:267–274.
- Voermans NC, Knoop H, Bleijenberg G, van Engelen BG. 2010b. Pain in Ehlers-Danlos syndrome is common, severe, and associated with functional impairment. *J Pain Symptom Manag* 40:370–378.
- Voermans NC, Knoop H, Bleijenberg G, van Engelen BG. 2011. Fatigue is associated with muscle weakness in Ehlers-Danlos syndrome: An explorative study. *Physiotherapy* 97:170–174.
- Weerakkody RA, Vandrovicova J, Kanonidou C, Mueller M, Gampawar P, Ibrahim Y, Norsworthy P, Biggs J, Abdullah A, Ross D, Black HA, Ferguson D, Cheshire NJ, Kazkaz H, Grahame R, Ghali N, Vandersteen A, Pope FM, Aitman TJ. 2016. Targeted next-generation sequencing makes new molecular diagnoses and expands genotype-phenotype relationship in Ehlers-Danlos syndrome. *Genet Med* 18:1119–1127.
- Wenstrup RJ, Meyer RA, Lyle JS, Hoechstetter L, Rose PS, Levy HP, Francomano CA. 2002. Prevalence of aortic root dilation in the Ehlers-Danlos syndrome. *Genet Med* 4:112–117.
- Werker CL, Nijhof SL, van de Putte EM. 2013. Clinical practice. Chronic fatigue syndrome. *Eur J Pediatr* 172:1293–1298.
- Westling L. 1992. Temporomandibular joint dysfunction and systemic joint laxity. *Swed Dent J Suppl* 81:1–79.
- Wiesmann T, Castori M, Malfait F, Wulf H. 2014. Recommendations for anesthesia and perioperative management in patients with Ehlers-Danlos syndrome(s). *Orphanet J Rare Dis* 9:109.
- Wijnhoven HA, de Vet HC, Picavet HS. 2006. Explaining sex differences in chronic musculoskeletal pain in a general population. *Pain* 124:158–166.
- Wolf JM. 2009. Influence of ligamentous laxity and gender: Implications for hand surgeon. *J Hand Surg* 34A:161–163.
- Wright Clayton E. 2015. Beyond myalgic encephalomyelitis/chronic fatigue syndrome. An IOM report on redefining an illness. *JAMA* 313:1101–1102.
- Yancey JR, Thomas SM. 2012. Chronic fatigue syndrome: Diagnosis and management. *Am Fam Physician* 86:741–746.
- Zarate N, Farmer AD, Grahame R, Mohammed SD, Knowles CH, Scott SM, Aziz Q. 2010. Unexplained gastrointestinal symptoms and joint hypermobility: Is connective tissue the missing link? *Neurogastroenterol Motil* 22:252–e78.
- Zeitoun JD, Lefevre JH, de Parades V, Sejourne C, Sobhani I, Coffin B, Hamonet C. 2013. Functional digestive symptoms and quality of life in patients with Ehlers-Danlos syndromes: Results of a national cohort study on 134 patients. *PLoS ONE* 8:e80321.
- Zweers MC, Bristow J, Steijlen PM, Dean WB, Hamel BC, Otero M, Kucharekova M, Boezeman, Schalkwijk J. 2003. Haploinsufficiency of TNXB is associated with hypermobility type of Ehlers-Danlos syndrome. *Am J Hum Genet* 73:214–217.