

Re-Writing the Natural History of Pain and Related Symptoms in the Joint Hypermobility Syndrome/Ehlers–Danlos Syndrome, Hypermobility Type

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Joint hypermobility syndrome (JHS) and Ehlers–Danlos syndrome, hypermobility type (EDS-HT) are two clinically overlapping connective tissue disorders characterized by chronic/recurrent pain, joint instability complications, and minor skin changes. Fatigue and headache are also common, although are not yet considered diagnostic criteria. JHS/EDS-HT is a unexpectedly common condition that remains underdiagnosed by most clinicians and pain specialists. This results in interventions limited to symptomatic and non-satisfactory treatments, lacking reasonable pathophysiologic rationale. In this manuscript the fragmented knowledge on pain, fatigue, and headache in JHS/EDS is presented with review of the available published information and a description of the clinical course by symptoms, on the basis of authors' experience. Pathogenic mechanisms are suggested through comparisons with other functional somatic syndromes (e.g., chronic fatigue syndrome, fibromyalgia, and functional gastrointestinal disorders). The re-writing of the natural history of JHS/EDS-HT is aimed to raise awareness among clinical geneticists and specialists treating chronic pain conditions about pain and other complications of JHS/EDS-HT. Symptoms' clustering by disease stage is proposed to investigate both the molecular causes and the symptoms management of JHS/EDS-HT in future studies. © 2013 Wiley Periodicals, Inc.

Key words: disability; EDS; fatigue; headache; hypermobility; JHS; pain; pathogenesis; prevention; treatment

INTRODUCTION

Joint hypermobility syndrome (JHS) and Ehlers–Danlos syndrome (EDS), hypermobility type are two heritable connective tissue disorders (HCTDs) chiefly characterized by generalized joint hypermobility (JHM), complications of joint instability, minor skin changes, and musculoskeletal pain [Castori, 2012, 2013]. Though

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originally considered distinct conditions [Beighton et al., 1997; Grahame et al., 2000], many clinicians and researchers are now interpreting JHS and EDS, hypermobility type (EDS-HT) as the variable expression of the same disorder (i.e., JHS/EDS-HT) [Tinkle et al., 2009]. While the terms JHS and EDS-HT are often used interchangeably for patients' classification, whether such a clinical overlap reflects or not in etiological identity remains to be confirmed at the molecular level [De Paepe and Malfait, 2012]. Intra-familial occurrence of affected members fitting diagnostic criteria

Conflict of interest: none.

Abbreviations: CFS, chronic fatigue syndrome; CLL, capsuloligamentous laxity; EDS, Ehlers–Danlos syndrome; EDS-HT, Ehlers–Danlos syndrome, hypermobility type; HCTD, heritable connective tissue disorder; JHM, joint hypermobility; JHS, joint hypermobility syndrome; OAAJ, occipitoatlantoaxial joint; TMJ, temporomandibular joint.

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of both disorders and sharing the same ultrastructural cutaneous changes supports the former hypothesis [Hermanns-Lê et al., 2012].

The epidemiology of JHS/EDS-HT has not been properly established. Literature defines EDS a rare disease with a cumulative frequency of 1/5,000 [Steinmann et al., 2002], with JHS/EDS-HT, EDS classic, and vascular types being the most common forms of EDS. Nevertheless, clinical practice suggests a much higher prevalence of JHS/EDS-HT with a proposed frequency of 0.75–2% in the general population [Hakim and Sahota, 2006]. Hence, the real prevalence of JHS/EDS-HT is unknown but likely ranges from ~1% to 1/5,000.

Diagnosing JHS/EDS-HT is an elusive task, based on subtle clinical signs originating from various organ systems and unsupported by any confirmatory laboratory or genetic test [Mayer et al., 2013]. For this reason, JHS/EDS-HT is still widely undiagnosed and the potential impact of this condition on patients' quality of life is rarely investigated by clinicians [Grahame and Bird, 2001]. JHS/EDS-HT symptoms often go unrecognized for years and patients are affected not only by being symptomatic but also by being dismissed by practitioners, relatives, and friends [Castori et al., 2010a]. This causes JHS/EDS-HT to be an EDS form with chronic pain, fatigue, and other neurological features likely representing major determinants for disability [Voermans and Knoop, 2011; Celletti et al., 2012a].

The clinical picture attributable to JHS/EDS-HT is evolving. At the time of the establishment of Brighton/JHS [Grahame et al., 2000] and Villefranche/EDS-HT criteria [Beighton et al., 1998], both disorders were considered of nearly exclusive musculoskeletal and cutaneous involvement (Table I). Now, JHS/EDS-HT can be better defined as a widespread disorder tagged with the hallmark of generalized JHM and involvement of the cardiovascular [Mathias et al., 2011], gastrointestinal [Zarate et al., 2010], genitourinary [Castori et al., 2012a], visual [Gharbiya et al., 2012], and neuromuscular [Voermans et al., 2009a; Garcia-Campayo et al., 2011] systems. Remarkably, most visceral manifestations routinely reported in JHS/EDS-HT are indistinguishable from other functional somatic syndromes [Castori et al., 2013]. This suggests an unexpectedly high prevalence of JHS/EDS-HT in the practice of many specialists [Ross and Grahame, 2011], who often do not investigate for an underlying HCTD diagnosis and limit their intervention to symptomatic treatments.

Treating JHS/EDS-HT is frustrating for both patients and practitioners due to the lack of long-term relief. Unfortunately, JHM is still considered by many practitioners a benign trait, possibly important only when planning surgical intervention due to frequent complications [Moriatis et al., 2011]. However, accumulated evidence suggests the importance of increasing awareness on HCTDs and, in particular, EDS-HT, in order to identify preventive, therapeutic, and rehabilitative strategies to preserve function and quality of life in these patients [Castori et al., 2012b]. The first step necessary to increase awareness regarding JHS/EDS-HT is to shift the attention from the overall musculoskeletal/cutaneous clinical picture to the chronology of symptom development, transition and evolution [Grahame, 2009; Castori et al., 2010a, 2011a].

AIM AND METHODS

This work offers insights into the marked *metatropism*¹ of JHS/EDS-HT which underlies some of the most disabling features of the disorder, namely pain, fatigue, and headache. Initially, each feature is presented through a review of the literature via a PubMed search with the MeSH terms “joint laxity/joint instability/Ehlers–Danlos syndrome” and “pain,” “fatigue,” or “headache,” respectively. Only reports on JHS, EDS-HT, or EDS(s) considered as a whole (i.e., without subclassification of results by EDS subtype) were included. A re-interpretation of the literature in light of the multidisciplinary experience of the authors on ~200 patients with a clinical diagnosis of JHS/EDS-HT is offered. Finally, each feature is discussed pathogenically through comparisons with partially overlapping connective tissue disorders and functional somatic syndromes, which have been recently included within the clinical spectrum of JHS/EDS-HT [Castori, 2012, 2013].

The resulting body of evidence and clinical conclusion/speculations are incorporated into an update of the age-related phenotype of JHS/EDS-HT previously proposed by our group [Castori et al., 2010a, 2011a, 2012b] with the purpose of suggesting directions for future research.

MUSCULOSKELETAL AND VISCERAL PAIN

Review

Musculoskeletal pain is extremely common in JHS/EDS-HT [Sacheti et al., 1997]. It is associated with regular analgesic use, JHM, dislocations, corrective surgery, and is strongly related to functional impairment [Voermans et al., 2010a]. Diagnostic relevance of limb pain is demonstrated by its inclusion as major item in the Brighton criteria for JHS [Grahame et al., 2000] and minor feature in the Villefranche criteria for EDS-HT [Beighton et al., 1998]. Such a discrepancy on the relative weight attributed to musculoskeletal pain in diagnosing JHS compared to EDS-HT likely reflects the time-dependence of symptom development (Table I). In fact, arthralgias, back pain and myalgias occur in ~30% of children with JHS/EDS-HT, while their rate increases to >80% among patients over forty [Castori et al., 2011a]. Such a symptomatic evolution is paradoxically coupled with a progressive decrease of the Beighton score which tends to fall below 4/9 at a mean age of 33 years in JHS/EDS-HT even in highly symptomatic subjects [Castori et al., 2011a]. This finding suggests that the Villefranche criteria could have a greater chance of being met in pediatric and young patients who naturally display a greater joint mobility and lower rate of recurrent articular pain, while the Brighton criteria seem to better fit adult patients who often have lost their childhood flexibility but manifest a wide range of musculoskeletal complaints. Therefore, the protean evolution of JHS/EDS-HT should require the use of these diagnostic criteria dynamically, shifting from one set to the other taking into account patient's

¹The term “metatropism” refers to the age-dependent evolution of the phenotype of a disease which may present very differently in distinct life stages. Its etymology, shared with the better known adjective “metatropic”, comes from the ancient greek μετατροπή, which means “change, transformation.”

TABLE I. Diagnostic Criteria for Joint Hypermobility Syndrome (JHS) and Ehlers–Danlos Syndrome, Hypermobility Type (EDS-HT)

Brighton criteria (JHS)

Major criteria

- Beighton score $\geq 4/9$
- Arthralgia for >3 months in >4 joints

Minor criteria

- Beighton score of 1–3
- Arthralgia in 1–3 joints
- History of joint dislocations
- Soft tissue lesions >3
- Marfan-like *habitus*
- Skin striae, hyperextensibility, or scarring
- Eye signs, lid laxity
- History of varicose veins, hernias, visceral prolapses

From [Grahame et al., 2000]

The diagnosis of JHS is fixed by the presence of both major, or one major and two minor, or four minor criteria, as well as of two minor criteria plus one or more first-degree affected relative(s). The diagnosis of JHS needs clinical/molecular exclusion of partially overlapping heritable connective tissue disorders

Villefranche criteria (EDS-HT)

Major criteria

- Beighton score $\geq 5/9$
- Skin involvement (hyperextensibility and/or smooth, velvety skin)

Minor criteria

- Recurring joint dislocations
- Chronic joint/limb pain
- Positive family history

From [Beighton et al., 1998]

To date, there is no consensus on the minimum criteria for the diagnosis of EDS-HT. Clinical practice suggests to fix the diagnosis of EDS-HT by the presence of both major criteria (with or without minor criteria) in sporadic cases and to use minor criteria for at-risk relatives not satisfying both major criteria. The exclusion of other heritable connective tissue disorders is indicated also for EDS-HT

age, sex, and clinical history. According to this, we proposed a shifting paradigm which accounts for age and symptoms presentation. In this paradigm we have tentatively defined three phases, distinguished by the relative prevalence of key symptoms, including pain, fatigue, and range of residual joint motion [Castori et al., 2010a, 2011a]. Nevertheless, the applied model should be considered hypothetical as not yet confirmed by rigorous longitudinal studies.

In our clinical experience and in accordance with some reports [McIntosh et al., 1995; Hakim and Grahame, 2004; Castori et al., 2011a, 2012a] a significant increase of visceral and pelvic pain is common in JHS/EDS-HT. In addition to the typical nociceptive pain of musculoskeletal origin, painful sensations often assume neuropathic [Camerota et al., 2013] and dysfunctional features with widespread manifestations originating from all major systems, mainly the gastrointestinal system and pelvis (Table II), as well as headache and various forms of head pain. More investigations are

needed to be able to differentiate between increased rate of visceral/pelvic pain, or accentuation of symptoms for concurrent and pathogenically unrelated disorders due to central sensitization in JHS/EDS-HT.

Manifestations and Evolution

Musculoskeletal pain is not congenital in JHS/EDS-HT and is often influenced by external factors, such as lifestyle, sport activities, traumas, surgery, and various co-morbidities. Many patients report their very first painful sensations acutely, in relation to joint traumas, such as dislocations and sprains, and “growing pain” mostly localized at the knees. These manifestations are indistinguishable from those observed in the general population. Nevertheless, JHS/EDS-HT children and young adults tend to report such symptoms with unexpectedly high rate and intensity [Hakim et al., 2010]. In addition, children with generalized JHM often display a

TABLE II. Forms of Pain in the Joint Hypermobility Syndrome

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

range of neurologic features, including delayed motor development, widespread mild hypotonia, and developmental coordination disorders [Adib et al., 2005; Kirby and Davies, 2007]. The number of patients referring recurrent/chronic musculoskeletal pain increases with age and includes a wider spectrum of musculoskeletal painful sensations [Castori et al., 2011a]. Arthralgias and myalgias are the most common pain presentations in young adult and adult patients. Initially, recurrent arthralgias and myalgias are limited to a few joints and muscles and may have a migratory pattern. Thereafter, they become persistent and assume a more generalized distribution, although asymmetry between the two sides of the body are commonly reported for both intensity of pain and number of painful foci. Muscle cramps and episodic periarticular swelling/inflammation are ancillary findings. Entesopathies are additional forms of localized musculoskeletal pain and include tendinitis, synovitis, bursitis, tenosynovitis, and fasciitis. Recurring or chronic inflammations of soft tissues may lead to thinning and spontaneous ruptures of tendons and ligaments, as well as peripheral nerve entanglement syndromes, such as tarsal and carpal tunnel syndromes [Tinkle, 2010; Granata et al., 2013]. Such complications contribute to the heterogeneity of painful sensations also in patients with preserved quality of life. Once musculoskeletal pain becomes widespread, patients lose the ability to localize the origin of painful sensations. This last form of pain is often described as “cold” and originating directly from bones and deep tissues. Common additional features include burning sensations (dysesthesias), peripheral paresthesias, generalized muscle hyperalgesia (also including fibromyalgia), allodynia, and hypersensitivity to various physical and chemical agents, such as bright light, sounds, and odors. In the most advanced disease stage, analgesic treatments alone are typically not efficacious anymore, while the chronic use of opioids adds side effects to the underlying painful sensations.

The evolution of visceral pain in EDS-HT is less understood. Recurrent abdominal pain is common in JHS/EDS-HT and, as for musculoskeletal pain, its prevalence increases with age [Castori et al., 2011a]. Upper abdominal pain is usually related to heartburns, symptoms of gastroesophageal reflux and post-prandial abdominal discomfort due to bloating, and abdominal distension. Lower abdominal pain presenting as “colonic spasms” appears the most debilitating form of visceral pain and can be associated with defecation rate changes. Fading or reduction of pain intensity after defecation in a background of chronic constipation is common. Women also frequently suffer from various forms of pelvic pain. Intense dysmenorrhea is common and usually persists for the entire fertile age with remissions only in case of oral contraceptive use. Dyspareunia and vulvodinia associate with a higher impact on quality of life in young adult and adult women and still remain without disease-oriented therapies [McIntosh et al., 1995; Castori et al., 2012a].

Pathogenesis of Musculoskeletal Pain

Mechanisms of musculoskeletal pain triggering, distribution, progression, and chronicization appear to be complex in JHS/EDS-HT. This complexity likely stems from various pathophysiologic processes, which progressively interfere with more “archaic” pain mechanisms related to human evolution and survival. Recognizable

forms of peripheral pain attributable to joint instability dominate the early phases of the natural history of JHS/EDS-HT. Pain chronicization and combination with satellite symptoms is typical of advanced stages of these syndromes and may be interpreted as a convergent phenotype (i.e., “central” pain prone phenotype). This concept is shared with other chronic musculoskeletal pain disorders, such as fibromyalgia, rheumatoid arthritis, and osteoarthritis (Fig. 1) [Phillips and Clauw, 2013].

During early disease stages, limb pain presents as nociceptive and is commonly limited to large and small joints. Joint instability (i.e., excessive motion of articular surfaces along non-physiologic directions) due to congenital capsuloligamentous laxity (CLL) predisposes toddlers and children to soft-tissue traumas [Hudson et al., 1998] and dislocations [Voermans et al., 2010a]. In addition, the occurrence of acute/recurrent articular pain secondary to microtraumas (i.e., repetitive subclinical damage) is often unrelated to anamnestic joint trauma(s), and is likely facilitated by CLL. Occasional and recurrent entesopathies and myalgias are further presentations of acute musculoskeletal pain in JHS/EDS-HT. Indeed, abnormal range of motion at a hypermobile joint can increase tensile stress on adjacent muscles and tendons with consequent elicitation of nociceptive afferents. Recently, an increased rate of upper limb nerve (sub)luxations was demonstrated in JHS/EDS-HT and this may contribute to some peripheral neuropathic features of pain, such as paresthesias [Granata et al., 2013]. Additional contributors to peripheral/nociceptive pain in JHS/EDS-HT could include lower bone mass [Dolan et al., 1998; Nijs et al., 2000; Gulbahar et al., 2006] and precocious osteoarthritis [Jónsson et al., 2009]. These symptoms could be interpreted as degenerative consequences of mechanical stress on articular surfaces due to congenital CLL. Nevertheless, the impact of osteoarthritis [Dolan et al., 2003] and, perhaps, of lower bone mass on the overall clinical picture of symptomatic JHM is still a matter of debate.

Congenital CLL, though necessary, does not appear sufficient for causing generalized joint instability in JHS/EDS-HT, as indirectly evidenced by the well-consolidated concept that only ~10% of individuals with generalized JHM will become symptomatic [Hakim and Sahota, 2006]. For this reason, while variability within the same genetic trait (i.e., connective tissue laxity) may play a role, other factors, including lack of proprioception and muscle hypotonia, should be considered in the pathogenesis of chronic joint traumatism in JHS/EDS-HT. Impaired proprioception with poor joint kinesthesia and spatial awareness has been demonstrated in hypermobile subjects [Mallik et al., 1994; Hall et al., 1995; Fatoye et al., 2009; Rombaut et al., 2010a; Celletti et al., 2011]. Muscle weakness, likely related to hypotonia, has been recently pointed out as a mild, though consistent ancillary feature of many EDS forms, including EDS-HT [Voermans et al., 2009b, 2011b]. Nevertheless, etiopathogenic relationships between congenital CLL, muscle hypotonia, and impaired proprioception in JHS/EDS-HT remain poorly investigated and rarely reported.

Pain thresholds and painful sensation transmission are complex phenomena influenced by both peripheral and central factors. Therefore, it is likely that in JHS/EDS-HT contributors to joint traumas interact with independent genetic determinants of variability in pain sensitivity. Preliminary studies investigating pain thresholds in healthy individuals highlight a prominent role for

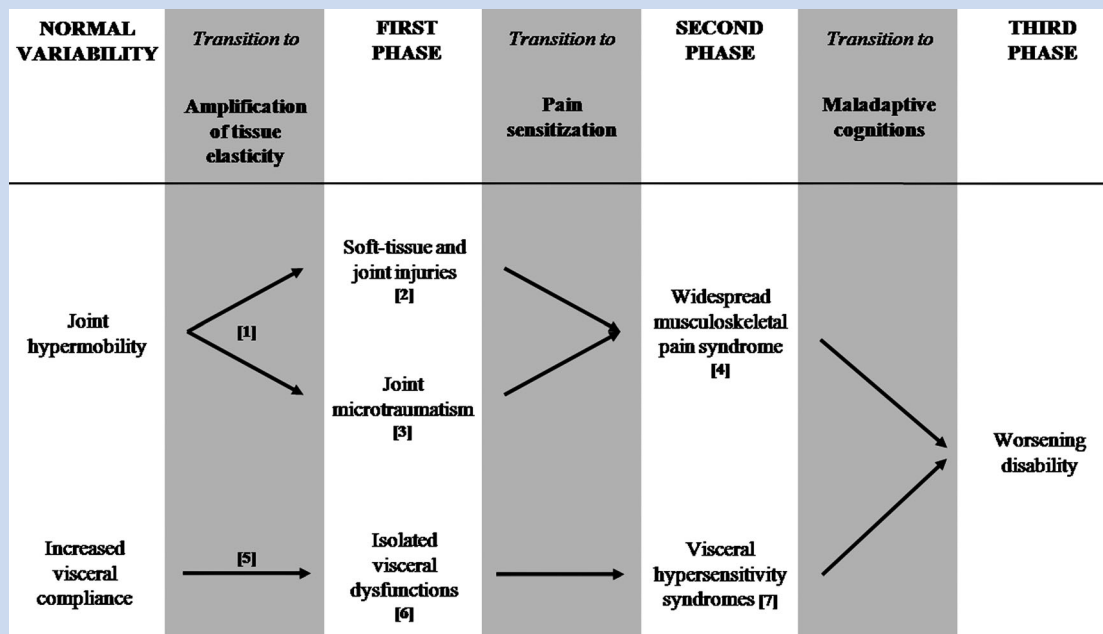


FIG. 1. Schematization of disease evolution in four distinct phases. Joint hypermobility and increased compliance of (hollow) viscera are relatively common in general population and are often asymptomatic. The first disease phase is dominated by dysfunctional symptoms which result from the interactions/summations between the underlying genetic variability and other apparently unrelated factors, converging in an excessive amplification of tissue laxity/elasticity. Recurrent/chronic musculoskeletal with or without visceral pain with augmented sensitization to a wide range of physical and chemical stimuli is the hallmark of the second disease phase. The third disease phase is characterized by full-blown “central sensitization” manifestations and worsening disability with many patients living a very restricted life, which is the result of long-lasting maladaptive cognitions. [1] Factors influencing joint stability mainly include the degree of ligamentous laxity (primary genetic defects?), muscle tone, and proprioception. [2] Manifesting as occasional painful sensations secondary to sprains, strains, and joint dislocations. [3] Joint microtraumatism is usually asymptomatic, although may associate with precocious osteoarthritis and lower bone mass. [4] With or without features of fibromyalgia. [5] Factors influencing visceral elasticity mainly include the degree of “tissue laxity” at the visceral wall and ligaments (primary genetic defect?), visceral muscle tone and mechanoreception. [6] Such as chronic constipation, esophageal and gastric motor dysfunction, and underactive bladder. [7] Such as irritative bowel syndrome, interstitial cystitis, and chronic pelvic pain syndrome.

common genetic variations in proteins, such as catechol-*o*-methyltransferase [Zubieta et al., 2003], involved in various aspects of pain neurotransmission. The contribution of other gender-influenced factors in modulating pain and, consequently, in meeting the Brighton and Villefranche criteria may also explain the markedly skewed gender bias observed in JHS/EDS-HT, with females being the most affected [Castori et al., 2010b; Tinkle, 2010]. This implies that the lower pain thresholds, normally observed in women, might facilitate elicitation of recurrent painful sensations and disease progression. In the intermediate phase of the disease, pain symptoms are not persistent, often remain localized, and are rarely associated with deterioration of quality of life.

In the most advanced stage, patients lose the ability to localize pain. This is characterized by moderate to intense painful background interrupted by excruciating exacerbations triggered by trivial stimuli, which are often not easily identified by the affected individual. It is likely that central sensitization determines the transition from a “common” rheumatologic affliction with recurrent peripheral pain, to a centralized form of widespread pain with a

range of neurological symptoms, as proposed for other classic rheumatologic diseases, such as rheumatoid arthritis and *lupus erythematosus systemicus* [Phillips and Clauw, 2013]. Mechanisms underlying such a phenomenon are still under investigation and more details can be found elsewhere [Yunus, 2007a,b]. It appears that central nervous system neuronal plasticity has a prominent role in this centralization of pain, as recently suggested by the evidence of greater amygdale volumes in reportedly hypermobile patients compared with non-hypermobile subjects. Additional findings included decreased volume of anterior cingulate and parietal lobe [Eccles et al., 2012]. Similar findings are reported in other functional somatic syndromes, such as fibromyalgia, with features of central sensitization [Lutz et al., 2008].

Maladaptive cognitions represent the behavioral counterpart to neuronal plastic changes during central sensitization and are likely to have a role in JHS/EDS-HT. Pain catastrophizing, fear of pain, and kinesiophobia are among the most known maladaptive cognitions in many chronic pain conditions [Borkum, 2010]. Accordingly, Rombaut et al. [2011] commonly encountered fear of falling

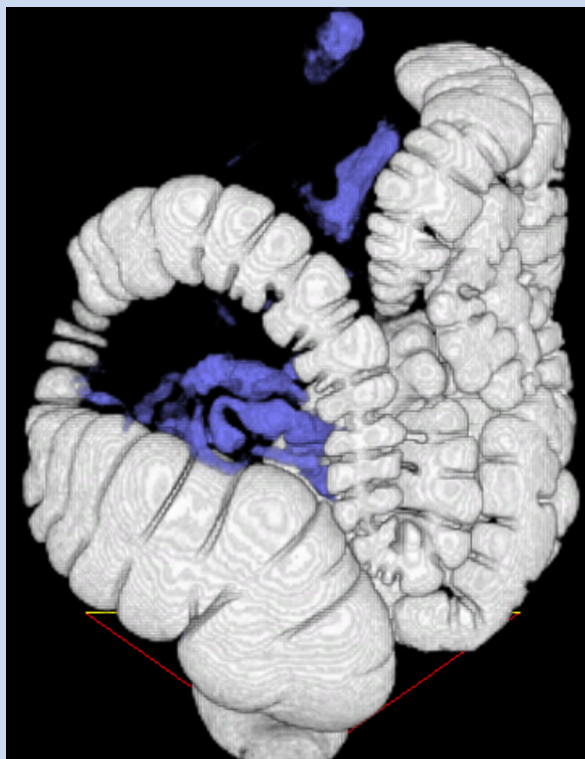


FIG. 2. Virtual colonoscopy in a 42-year-old woman with JHS/EDS-HT and severe gastrointestinal involvement. Image shows marked ptosis of the transverse colon with an apparently increased colonic length (dolichocolon). Note medialized and dilated cecum.

among women with JHS/EDS-HT. In addition, Grahame [2009] proposed kinesiophobia as a major prognostic determinant in JHS/EDS-HT. The mechanisms by which maladaptive cognitions operate in worsening the disease state are largely obscure. It is possible that maladaptive cognitions are developed after a painful event and instauration of fear of pain as an “avoidance” coping strategy, as opposed to the “confrontation” strategy which naturally leads to reduction or elimination of the fear [Lethem et al., 1983]. This “avoidance” strategy, acting at both the cognitive and behavioral levels, contributes to a vicious cycle and paradoxically leads to increased pain and disability [Somers et al., 2009]. Kinesiophobia causes to stop/reduce physical activities thought to generate pain, and this progressively limits the mobility of affected individuals. The consequent disuse and muscle deconditioning generate further loss of muscle strength, flexibility and aerobic capacity, which may explain the worsening disability characterizing the most severe phase of JHS/EDS-HT. Avoidance strategies are likely not the only cognitions interfering with pain modulation and disease progression in JHS/EDS-HT. Other emotional and cognitive mechanisms, such as hypervigilance, may play a role, as observed in other chronic pain conditions, such as irritable bowel disease [Azpiroz et al., 2007].

Genetic and animal model studies are expanding our knowledge on the biochemical basis of pain in humans. For example, recent works identified a major genetic locus on 5p15.2 linked to chronic widespread pain in humans [Peters et al., 2013] and demonstrate that inhibition of TGF- β signaling may attenuate osteoarthritis changes in a knock-out mouse model [Zhen et al., 2013]. As JHS/EDS-HT patients may represent a significant proportion of cases with apparently unspecific widespread chronic pain, it is reasonable to expect that future research will investigate the presence/absence of JHM/JHS/EDS-HT/HCTD as a relevant clinical marker for phenotypic variability and, hopefully, treatment outcomes in chronic pain.

Pathogenesis of Visceral Pain

The processes leading to visceral pain in JHS/EDS-HT are not well understood and the relationship between this form of pain and JHS/EDS-HT still needs appropriate investigations. Fragmented knowledge indicates that visceral and pelvic prolapses are a common, though likely underreported finding in JHS/EDS-HT [Reinstein et al., 2012; Castori et al., 2012a; Dordoni et al., 2013]. Dolichocolon may be an additional common finding in JHS/EDS-HT [Castori et al., 2013], but more systematic studies regarding abdominal anatomy are warranted. In women, dysmenorrhea is common and occasionally associated with polycystic ovaries, endometrial cysts, uterine leiomyomas, endometrial hypertrophy, and endometriosis, but remains “functional” in origin in most cases [Castori et al., 2012a]. In conclusion, available data do not permit to identify a consistent anatomic milieu and, then, trace a reasonable pathogenesis for visceral pain in JHS/EDS-HT.

Speculatively, increased compliance of hollow viscera may parallel congenital CLL in the earliest phases of disease progression and pain generation in JHS/EDS-HT. This speculation might be substantiated by a recent study highlighting that colonic compliance is responsible for up to 25% in variation of gas and pain sensation in healthy subjects [Iturrino et al., 2012]. Therefore, the excessive “laxity” of the colonic wall could serve as a trigger for visceral hypersensitivity in JHS/EDS-HT. In functional gastrointestinal disorders, the altered adaptive response to intestinal stimuli involves both branches of the sensorimotor reflex, the mechanoreceptor afferences and the visceral muscle activity [Azpiroz et al., 2007]; it could be, therefore, hypothesized that, in JHS/EDS-HT, an exaggerated reaction to visceral stimuli results from lower pain thresholds due to increased visceral compliance, and this would be translated into a painful sensation by an abnormal sensorimotor reflex. A recent retrospective study on 17 adult JHS patients with dysphagia demonstrated esophageal dysmotility or hypomotility in all patients [Fikree et al., 2011]. Although this study is very preliminary and focused on a biased sample, it points out abnormal esophageal motility as a common primary mechanism leading to upper gastrointestinal complaints in JHS/EDS-HT, compared and/or superimposed to acquired esophageal anomalies, such as esophagitis due to gastroesophageal reflux. Visceral ptosis, elongation, and dilatation may represent the anatomic counterpart of this functional derangement, linking the genetic defect to the resulting painful sensation.

Further progression of visceral sensitization requires the involvement of the central nervous system with mechanisms partially

overlapping with those proposed for musculoskeletal pain [Anand et al., 2007]. Therefore, central sensitization and maladaptive cognitions are convergent mechanisms of pain amplification for both musculoskeletal and visceral involvement in JHS/EDS-HT. The resulting downward spiral affects the entire body leading to an inexorable worsening of physical disability, as experienced by many adults in the most advanced stage of the disease.

FATIGUE

Review

For decades, fatigue has been a neglected feature of JHS/EDS-HT. Conversely, a recent seminal paper highlighted that 84% of JHS/EDS-HT patients (mostly, females) are severely fatigued [Voermans et al., 2010b]. Similar results were obtained by other research groups [Rombaut et al., 2010b; Castori et al., 2011a]. In JHS/EDS-HT, the impact of fatigue on daily life is often equal or more dramatic than the impact of pain [Voermans et al., 2010b], underscoring the importance of this feature for both assessment and treatment planning of these patients. Some probable contributors to fatigue-related disability have been investigated and include sleep disturbances, concentration problems, social functioning, self-efficacy concerning fatigue, and pain severity [Voermans et al., 2010b]. A few experimental studies demonstrate that fatigue associates with muscle weakness [Voermans et al., 2011b; Gerrits et al., 2013], worsens with exercise [Rombaut et al., 2012], and affects gait pattern [Celletti et al., 2012b]. Nevertheless, severely fatigued JHS/EDS-HT patients often display a wider spectrum of fatigue-related symptoms, which often meet the chronic fatigue syndrome (CFS) criteria [Castori et al., 2011b] and are hardly explained by only muscular origin.

Manifestations and Evolution

Prevalence of chronic fatigue in JHS/EDS-HT is directly related to age with a minimum (28%) in the first decade of life and a peak (90%) among adults over 40 years [Castori et al., 2011a]. Fatigue often displays with a “muscular” onset manifesting with easy fatigability, exercise intolerance, and subjective muscle weakness. In this phase, patients usually feel healthy in the morning but complain of reduced “energy” in performing daily and sport activities. They often need extra pauses and fragmenting complex tasks into multiple simpler tasks. Patients with less severe phenotypes, or patients who were involved in athletic activities since early in life, tend to delay or skip this phase of the disease progression. Delayed recovery from physical exertion progressively worsens and eventually becomes a background sensation of daily fatigue. While muscle fatigue is commonly noticed since childhood, morning fatigue, joint stiffness, and post-exertional malaise are more typical of adult patients. These are often combined with poor sleep quality and overt visceral involvement (e.g., symptomatic cardiovascular dysautonomia), and are associated with a more restricted life style [Voermans et al., 2010b; Castori et al., 2011a].

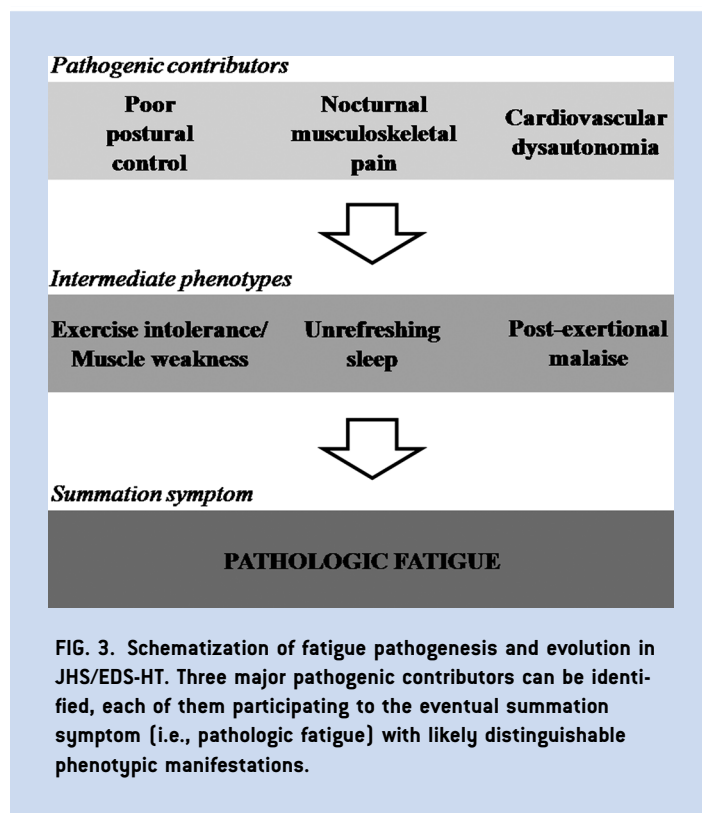
Pathogenesis

The natural history of fatigue and associated symptoms are likely related to a complex underlying pathogenesis, whose mechanisms

are mostly unknown. Nevertheless, some speculations may be put forward in light of previously published data and observations collected clinically.

A careful re-interpretation of patients’ history seems to point to muscle weakness, sleep disturbances, and postural changes intolerance as the three major contributors to fatigue in JHS/EDS-HT (Fig. 3). These, in turn, result from discrete pathogenic processes which need to be unraveled. Muscle weakness and hypotonia, which are commonly reported in JHM clinic, associate with mild, unspecific, and inconstant changes at electromyography and muscle biopsy [Voermans et al., 2009a]. A pilot study demonstrated ineffective postural control strategies in stand position for JHS/EDS-HT adult patients with more pronounced fluctuations of the centre of pressure compared to controls [Rigoldi et al., 2013]. Poor postural control may be easily interpreted as a consequence of muscle hypotonia and lack of proprioception, which is a well-known feature of JHS/EDS-HT [Mallik et al., 1994; Hall et al., 1995; Fatoye et al., 2009; Rombaut et al., 2010a; Celletti et al., 2011]. Therefore, it could be hypothesized that hypermobile subjects lack of postural control and, therefore, need to increase muscle activation to avoid falls and movement failures. Over time, such a pathologic process might lead to persistent structural changes of the muscles, which give inconstant changes at investigations. A possible explanation is a secondary decrease in mitochondrial content (or function), as recently detected in CFS [Smits et al., 2011], with resulting amplification of muscle symptoms, including exercise intolerance and easy fatigability.

As discussed, muscle weakness due to postural control muscle overactivation is probably the earliest pathologic process contributing to chronic fatigue. However, the full-blown CFS phenotype



reported by many JHS/EDS-HT patients needs progressive superimposition of additional mechanisms affecting general homeostasis and contributing to fatigue features. Unrefreshing sleep is commonly reported in JHS/EDS-HT adults [Verbraecken et al., 2001] and may be easily linked to nocturnal musculoskeletal pain [Voermans et al., 2010a] which is a common cause of sleep fragmentation and difficulties in falling asleep. In his monograph on JHS/EDS-HT, Dr. Tinkle [2010] describes periodic limb movements and restless leg syndrome as further contributors to unrefreshing sleep. Nocturnal upper airway obstruction may be a third cause of unrefreshing sleep in JHS/EDS-HT. Although true sleep apnea is not significantly reported in EDS [Verbraecken et al., 2001], hypotonia and laxity of the pharynx could predispose to periodic nocturnal obstruction with snoring and arousals from sleep in form of upper airway resistance syndrome [Rains and Poceta, 2006]. Gastroesophageal reflux, so commonly reported in JHS/EDS-HT [Castori et al., 2011a], may contribute to nocturnal upper airways irritation and consequent arousals. Possible co-morbidities, such as celiac disease [Danese et al., 2011] and respiratory insufficiency [Morgan et al., 2007] may aggravate fatigue, especially in the pediatric patient. Finally, the link between chronic pain and fatigue is complex and a role of the former in central exhaustion is plausible.

Orthostatic intolerance [Rowe et al., 1999], as well as other symptoms related to dysautonomia [Hakim and Grahame, 2004] are extremely common in JHS/EDS-HT. Recent evidence highlights postural orthostatic tachycardia syndrome as the typical presentation of cardiovascular dysfunction in JHS/EDS-HT [Mathias et al., 2011]. As fatigue, shortness of breath, and lethargy are common among individuals suffering from postural orthostatic tachycardia syndrome [Mathias et al., 2011], it is likely that cardiovascular dysfunction has a role in fatigue-related disability seen in JHS/EDS-HT.

HEADACHE

Review

In the work by Sacheti et al. [1997], describing pain features in 51 individuals with different forms of EDS (including 28 patients with JHS/EDS-HT, formerly EDS type III), neck pain and headache accounted for 30–40% of cases. Shortly after, another study described nine EDS patients presenting with various forms of headache, including (i) migraine with aura, (ii) migraine without aura, (iii) tension-type headache, (iv) a combination of tension-type headache and migraine, and (v) post-traumatic headache [Jacome, 1999]. Subsequent works confirmed these findings without further characterizations [Castori et al., 2010a; Rombaut et al., 2010a]. More recently, Bendik et al. [2011] showed that migraine (with or without aura) is approximately three times more common among JHS/EDS-HT women compared to controls. Single studies/observations confirmed an increased rate of JHM/JHS in specific subsets of primary and secondary types of headache, including new daily persistent headache [Rozen et al., 2006], headache attributed to spontaneous (idiopathic) cerebrospinal fluid leakage [Schievink et al., 2004], and headache secondary to Chiari malformation [Castori et al., 2010a]. Cervical spine hypermobility/dysfunction is also considered a predisposing factor for cervicogenic headache [Hall et al., 2008] and neck-tongue syndrome (Table III) [Orrell and Marsden, 1994; Sjaastad and Baketeig, 2006]. In line with this, Di Palma and Cronin [2005] reported a

27-year-old woman with EDS classic type (type II) with a long-lasting pulsating headache associated with C2 dislocation.

Head pain is not limited to headache in EDS. In a cohort of 31 EDS patients (including 16 with JHS/EDS-HT), De Coster et al. [2005] demonstrated temporomandibular joint (TMJ) dysfunction in 100% of the cases, unilateral myofascial pain (i.e., temple headache) in 83%, and unilateral and bilateral TMJ arthralgia in 28% and 51% of the patients, respectively. Although details on the occurrence of myogenous headache (i.e., headache secondary to TMJ dysfunction) in this cohort were not presented, an increased frequency of this type of headache can be extrapolated on the basis of the higher rate of TMJ dysfunction in tension-type headache [Ballegaard et al., 2008].

Manifestations and Evolution

Contrarily to musculoskeletal pain and fatigue, prevalence data by decade of life are lacking for headache. Evidence indicates that 3/4 of women with JHS/EDS-HT suffer of migraine with or without aura [Bendik et al., 2011]. Clinical experience refines this observation, as JHS/EDS-HT adults usually refer symptoms of additional headaches and different head pain patterns which are often recognized on a background of migraine. Accordingly, during medical history collection for JHS/EDS-HT patients many features are often noted such as: temple headache, occipital headache with reduced neck motion and local muscle hyperalgesia, amplification of pain intensity or symptom onset at the transition to orthostatism, as well as peri/intraoral and/or occipital paresthesias/numbness associated with neck stab at neck flexion and/or rotation. Additionally, a few patients describe a severe form of headache, characterized by restless and untreatable head pain which starts early in very early hours of the day or during sleep, and persists until bedtime with dizziness, blurred vision, myodesopsiae, reduced hearing, photophobia, phonophobia, and intolerance to smells. In these subjects, convergence of multiple pathogenic pathways of head pain lead to a mixed chronic headache with marked disability.

Pathogenesis

On a pathogenic perspective, predominance of migraine indicates a common vascular compromise in the development and/or progression of head pain in JHS/EDS-HT. Various mechanisms have been suspected, including intracranial vasculopathy [Yazici et al., 2004; Bendik et al., 2011] and postural orthostatic tachycardia as a form of cardiovascular dysfunction [Gazit et al., 2003; Khurana and Eisenberg, 2011]. In our experience, the apparently non-causal association of JHS/EDS-HT and subcortical white matter lesions in adults with a history of thunderclap headache could identify in the spasm of the cerebral middle arteries a possible specific manifestation of intracranial vasculopathy. These lesions may represent relatively rare remnants of a reversible cerebral vasoconstriction [Ducros, 2012]. Painkiller drugs overuse is an additional major contributor to headache in JHS/EDS-HT patients suffering from recurrent/chronic musculoskeletal pain [Voermans et al., 2010a]. Although vascular pathology and chronic medication side-effects may explain a proportion of headache in JHS/EDS-HT, additional mechanisms should exist, especially in patients not displaying drug overuse and migraine.

TABLE III. Headache Disorders and Joint Hypermobility

Type of headache	Type of study	Evidence	Possible underlying mechanism(s) of head pain	Reference
Migraine	Case-control study	This headache is reported in ~3/4 women with JHS/EDS-HT and associates with disability	Cardiovascular dysautonomia Intracranial arteriopathy	Bendik et al. [2011]
Cervicogenic headache	Multiple case-control studies	Upper cervical spine dysfunction is considered a feature of this headache	Amplification of pericranial musculotensive stress due to upper cervical spine dysfunction	Hall et al. [2008]
Neck-tongue syndrome	Multiple case series	Various C0-C2 pathologies predispose to/associate with this headache	Intermittent C2 compressions due to upper cervical spine instability	Orrell and Marsden [1994]
Headache secondary to TMJ dysfunction	Case series	This headache is common in EDS patients	Amplification of pericranial musculotensive stress due to TMJ dysfunction	De Coster et al. [2005]
Headache secondary to spontaneous CSF leakage	Case series	JHM/EDS is observed in ~1/3 patients with this headache	Meningeal fragility Proneness to meningeal protrusions	Schievink et al. [2004]
New daily persistent headache	Case series	JHM ± cervical spine instability has been reported in 10/12 patients with this headache	Brainstem intermittent compression due to upper cervical spine instability	Rozen et al. [2006]
Headache secondary to Chiari malformation	Case reports	Chiari malformation has been reported in single patients with EDS	Chiari malformation may occur as a remote consequence of cervical spine instability ¹	Castori et al. [2010a]
Post-traumatic headache	Case report	This headache has been reported in single EDS patients	Proneness to musculoskeletal traumas Delayed post-traumatic recovery	Jacome [1999]
Tension-type headache	Case report	This headache has been reported in single EDS patients	Increased pericranial musculotensive stress	Jacome [1999]

EDS, Ehlers-Danlos syndrome; EDS-HT, Ehlers-Danlos syndrome hypermobility type; JHM, joint hypermobility; JHS, joint hypermobility syndrome; TMJ, temporomandibular joint.

¹As commented by Milhorat et al. [2007].

Occipito-atlanto-axial joint (OAAJ) dysfunction could represent an additional pathogenic node for head pain in JHS/EDS-HT. A preliminary association among positive Beighton score, cervical spine hypermobility, and new daily persistent headache was suggested by Rozen et al. [2006] in 12 subjects. Although similar results have not yet replicated, clinical practice points out the utility of looking for occult OAAJ in patients with occipital headache [Mathers et al., 2011]. Recurrence of cerebellar tonsils herniation and brainstem symptoms in patients operated for Chiari malformation clusters with neuroradiologic features of OAAJ instability, and is related to an underlying generalized HCTD [Milhorat et al., 2007]. As JHS/EDS-HT is likely the most common HCTD, subclinical OAAJ may have a role in specific subsets of headache patients through various mechanisms including increased pericranial musculotensive stress, intermittent compression of the cervical roots and subtle chronic myelopathy (Fig. 4A-C). Craniofacial JHM also manifests at the TMJ level by increasing masticatory muscles tensile stress, which, in turn, leads to monolateral or bilateral temple pain.

Tarlov cysts and dural ectasias at the lumbosacral and, more rarely, thoracic metameres are neuroradiologic features which may be encountered in JHS/EDS-HT (Fig. 4D). Although prevalence rates of lateral extensions of the spinal meninges are still unavailable in JHS/EDS-HT, an increased frequency due to weakness of the meninges may be hypothesized. Recently, it has been emphasized the existence of HCTDs, other than Marfan syndrome and related disorders, that display an increased rate of dural ectasias [Sheikhzadeh et al., 2011]. While these lesions are often considered benign in the general population, their presence in JHS/EDS-HT patients with orthostatic headache should be properly investigated. Headaches due to cerebrospinal fluid leakage through a spontaneous rupture of the meninges has been reported in Marfan syndrome and EDS classic/unclassified types [Voermans et al., 2009c; Grosveld et al., 2011; Reinstein et al., 2013]. The concurrent mechanisms of head pain related to OAAJ instability and intraspinal hypotension secondary to increased compliance of the meninges (with or without cerebrospinal fluid leakage) may converge in a remittent incomplete arachnoid block at the brainstem/spinal cord. This may

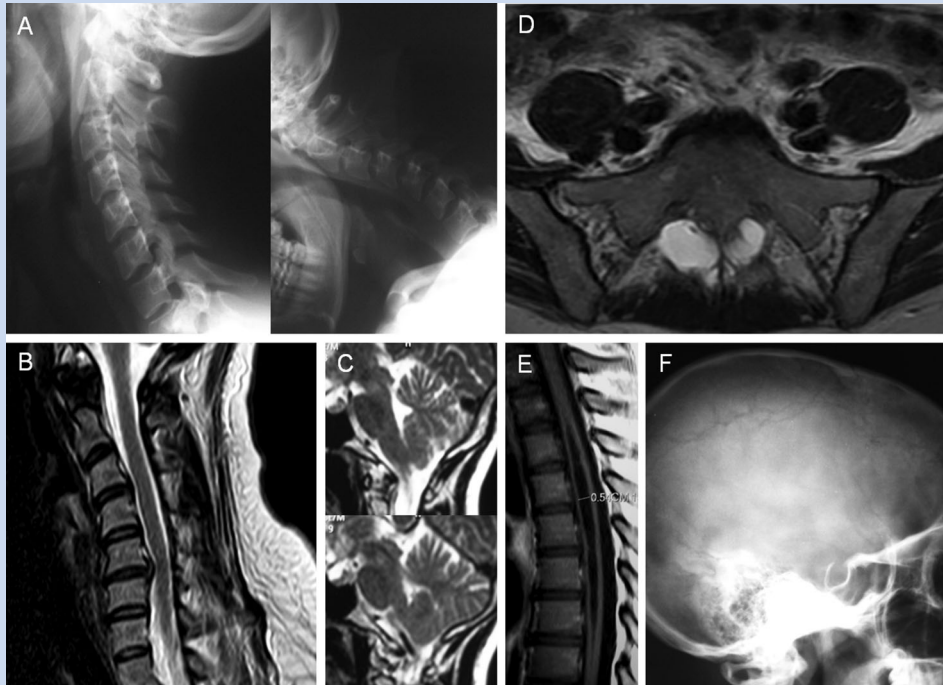


FIG. 4. Neuroimaging in JHS/EDS-HT. A: Non-traumatic cervical spine instability in a 19-year-old man. B: Spinal cord compression due to median intervertebral protrusion in a 35-year-old woman. C: Mild cerebellar tonsil herniations in the occipital hole combined with cervical spine instability [Chiari malformation type "0"] in a 11-year-old boy. D: Bilateral sacral Tarlov cysts in a 43-year-old woman. E: Thoracic syringomyelia in a 35-year-old woman. F: Copper-beaten aspect of the calvarial internal table and thinning of the *dorsum sellae*.

also lead to long terms consequences of an intermittent valve mechanism at the OAAJ level. Indirect evidence of such a phenomenon may include the possible increased rate of syringomyelia and subtle signs of intracranial hypertension in JHS/EDS-HT patients (Fig. 4E,F).

REVISING THE NATURAL HISTORY

This review indicates that pain, fatigue, and headache can be interpreted as summation symptoms resulting from functional derangements of a variety of systems, interacting in a chronologically hierarchical model and should be routinely investigated in JHS/EDS-HT. We propose an age-related phenotype characterized by a series of discrete phases linked to the onset of specific symptoms affecting multiple systems. Along with JHM, which is congenital and tends to reduce/disappear with age [Castori et al., 2011a], a prototypic disease progression was outlined (Table IV). This new vision of the development of symptoms in JHS/EDS-HT is more complete than what we previously proposed [Castori et al., 2010a] and adds complexity to the classic pathophysiologic model described by others [Grahame, 2009].

This research is still in its infancy and is based on the experience of a single research group, lacking longitudinal and prospective studies. Therefore, some caution should be used in applying the proposed schematic to routine clinical practice. The subclassifica-

tion of features by phase and systems is affected by a degree of uncertainty, as at the moment it is unknown whether phenotype evolution proceeds always homogeneously within the various systems. For example, there is no evidence that children with delayed motor development and dyspraxias cannot develop recurrent myalgias before attaining the puberal stage. Therefore, Table IV could be used by clinicians as a helpful tool during the evaluation of patients with symptomatic JHM for tracking the protean manifestations of JHS/EDS-HT. The need for more focus on the pediatric manifestations of JHS/EDS-HT is evident to our group and to others [Adib et al., 2005; Kirby and Davies, 2007]. In our experience, overt clinical manifestations of pediatric onset remain unrecognized until the onset, delayed of decades, of widespread pain. This has a deleterious effect on the ability to diagnose JHS/EDS-HT by pain specialists often unaware of the effects of JHS/EDS-HT on pain and fatigue.

Management and prevention of symptoms in JHS/EDS-HT is currently hampered by the lack of evidence-based studies objectively demonstrating effectiveness of specific intervention programs [Castori et al., 2012b]. As a consequence, all published recommendations, including those presented here, are solely based on the clinical opinion of experts. This underlines the need of large collaborative programs and experimental studies aimed at improving specific symptoms, in the light of a better understood pathogenesis. It is the authors' belief that patients' stratification by disease

TABLE IV. Features by Type and Disease Phase in the Joint Hypermobility Syndrome.

Disease "phase"	First	Second	Third
Common age at onset	First decade	Second-third decade	Third-fourth decade
Osteoarticular features	Sprains	Recurrent arthralgias	Chronic arthralgias
	Dislocations	Recurrent back pain	Chronic back pain
	Joint "cracks"	Tenosinovitis	Tendon/ligament degenerations
	Growing pain	Radiographic osteoarthritis/spondylosis	Widespread rigidity
	Occasional back/joint pain	Osteopenia	Osteoporosis
Muscular features	(Post)exertional myalgias/cramps	Recurrent myalgias	Chronic myalgias
	Mild hypotonia	Focal muscle hyperalgesia	Fibromyalgia
			Overt muscle weakness
Sensorimotor features	Delayed motor attainment	Recurrent falls	Allodynia
	Lack of coordination	Dysphagia	Dysesthesias
		Dysphonia	Abnormal reactions to multiple physical stimuli (e.g., bright light, noises)
Headache	Occasional/recurrent single-type headache	Paresthesias	Chronic headache(s)
		Recurrent multi-type headache	
		Mild symptoms of cervical spine pathology	Chronic symptoms of cervical spine pathology
Fatigue	Easy fatigability	Poor sleep quality	Post-exertional malaise
		Post-exertional dyspnea	Disabling morning fatigue
			Pelvic prolapses/stress incontinence
Visceral features	Constipation (or/and diarrhea)	Menses irregularities	Multiple visceral prolapses
	Bronchial hyper-reactivity	Dysmenorrhea	Chronic pulmonary insufficiency
	Sensitivity to various foods (e.g., gluten, milk proteins)	Dyspareunia/vulvodinia	
	Under/hyperactive bladder	Gastrointestinal functional disorder(s)	
			Interstitial cystitis

phase may also help in designing more efficient and cost-effective preventive strategies slowing disease progression (Fig. 5). Early diagnosis followed by a phase-specific prevention program should be considered as a powerful strategy to contrasting patients' disability and reducing costs to the healthcare system. Adapted exercise, general lifestyle recommendations [Castori et al., 2012b], physical therapy [Keer and Simmonds, 2011] and cognitive-behavioral therapy [Grahame, 2009], are already prescribed and known to mitigate JHS/EDS-HT consequences in many cases. However, at the present time, these interventions are employed to treat already developed symptoms. Figure 5 is a proposed schematic of their application as preventive measures. Prospective studies will be necessary to support the value of this proposal both under a quality of life and a cost of care point of view. In the

meanwhile, some multi-modal recommendations can be outlined for the management of both pain and fatigue in Tables V and VI [Hakim et al., 2010; Tinkle, 2010; Castori et al., 2012b; Martino, 2013].

FUTURE PERSPECTIVES

This work summarizes the authors' clinical experience and previous literature on JHS/EDS-HT in order to offer insights on the evolution of the three major disability determinants in JHS/EDS-HT, namely pain, fatigue, and headache. JHS/EDS-HT is a complex disorder in which the underlying heritable defects, responsible for congenital laxity of the connective tissue, interacts with a series of intrinsic and extrinsic factors contributing to the various disease

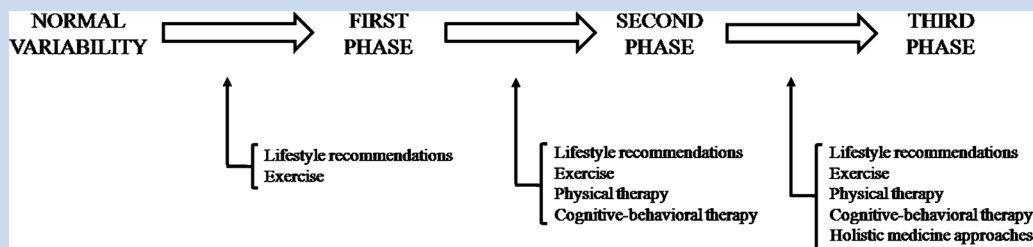


FIG. 5. Stratification of prevention strategies in JHS/EDS-HT in relation to the various transitions among disease phases.

TABLE V. Principles of Management of Musculoskeletal Pain in the Joint Hypermobility Syndrome

Recommendation

- (1) Preventing acute joint and muscle injury/pain
 - Regular physical activity comprising gentle stretching and exercises aimed at improving proprioception and muscle tone, but avoiding joint overuse/traumas (e.g., cycling/swimming/walking and pilates/yoga/etc.)
 - Avoid smoking and over/underweight
 - Stabilize excessively loose joints with soft bracing and/or taping
 - Improve ergonomics at home, school, and workplace
 - Prevent osteopenia with vitamin D supplementation (200 IU/day for adults, 400 IU/day for children), if needed
 - (2) Treating acute/recurrent joint and muscle pain
 - Active rest
 - Cold/heat pack application
 - Joint stabilization avoiding complete immobilization
 - Physical therapy application (e.g., passive therapy, massage) contrasting muscle spasm
 - NSAIDs/paracetamol and/or minor opioids at full dosage
 - (3) Preventing chronicization of pain
 - Optimize treatment of acute/recurrent musculoskeletal pain
 - Personalized, long-term physical therapy program based on both passive and active exercises, aimed at reducing diffuse muscle spasms (also comprising fibromyalgia), and improving proprioception and muscle tone/strength
 - Maintain autonomy/regular physical activity by pacing after periods of immobilization/re-acutezation of pain and with the support of an occupational therapist
 - Regularly perform activities focused on stress management
 - Improve sleep quality
 - Request specialized psychological support for improving coping strategies (i.e., cognitive-behavioral therapy)
 - Prevent osteoporosis with vitamin D (usually 880 IU/day for adults) and calcium (usually 1,000 mg/day for adults), or treat it by standard protocols
 - (4) Treating chronic pain
 - As above and:
 - Personalized painkiller drug schedule, including NSAIDs and/or opioids, as well as other pain modulators (e.g., Cox-2 inhibitors, tricyclic antidepressants, serotonin/norepinephrine receptor inhibitors) in presence of specific pain phenotypes, such as neuropathic pain and precocious osteoarthritis
 - Consider an integrative (multi-modal) approach including non-traditional medicine resources, such as acupuncture and mind-body medicine
 - (5) Options to consider with caution
 - Most orthopedic surgical interventions aimed at stabilizing joints, such as arthroscopic debridement, tendon relocations, capsulorrhaphy and arthroplasty, and reducing annulus hernias (e.g., high risk for recurrence, abnormal wound healing, adhesion formation, and pain amplification); surgery should be postponed to more conservative approaches
 - Generous prescription of periods of inactivity and abstention from regular sport activity (i.e., muscle deconditioning of rapid onset)
 - Use of myorelaxants (i.e. amplification of joint instability with multiple dislocations with consequent exacerbation of pain and fatigue)
 - Chronic local and systemic use of steroids (i.e., steroid-induced connective tissue damage on soft tissues and bone)
 - Use of antiplatelet drugs, for example, as acetylsalicylic acid (i.e., increased tendency to mucosal hemorrhages and ecchymoses)
 - Use of antiepileptic drugs (i.e., exacerbation of dysautonomic symptoms)
- All recommendations presented in this table MUST be considered low-level treatments for JHS/EDS-HT
- Some patients refer some improving of acute/recurrent musculoskeletal pain by the use of non-traditional resources, such as gentle chiropractic, ultrasound, deep heat, TENS, and epsom/magnesium salt baths (two cups in warm water for ~15 min). Although most of these integrative resources have a few or no major side effects, their use should be considered with caution

manifestations (Table VII). The classic “inverse genetics” approach repeatedly failed to identify the molecular cause of JHS/EDS-HT [Malfait et al., 2006]. Reasons for this may be the likely underlying locus heterogeneity and the lack of studies investigating the relationships between inter-individual variability and the inherited genetic defects in generating the clinical phenotype. Such studies will be important to identify the causative/predisposing traits and long-lasting effective therapies. Future molecular studies should consider a much complex inheritance pattern than the largely accepted autosomal dominant for JHS/EDS-HT [Castori et al., 2011a]. Extended family clinical history, in our experience, indicates that the trait co-segregates with objective (i.e., positive

Beighton score) or historical generalized JHM rather than Brighton and/or Villefranche criteria. The range of presenting phenotypes even within the same pedigree appears extremely variable including but not limited to JHS and EDS-HT diagnostic criteria. This observation would explain, for example, why a toddler with generalized JHM born to a mother with an unclassified chronic pain syndrome is followed for a developmental coordination disorder in a child neurology setting. Difficulties in diagnosis are expected if the transmitting parent is an asymptomatic father, who has lost his congenital hypermobility after puberty, unless a careful medical history of the father’s family is carried out in the context of JHS/EDS-HT emerging features. Therefore, although, for clinical pur-

TABLE VI. Principles of Management of Fatigue in the Joint Hypermobility Syndrome

Recommendation

- (1) General
 - Optimal sleep hygiene [consultable at yoursleep.aasmnet.org/Hygiene.aspx]
 - Regular physical exercise
 - Weight control (avoid over- and underweight)
 - Avoid smoking and alcohol
 - (2) Unrefreshing sleep
 - Bedtime intake of melatonin (3–5 mg for adults) in case of insomnia
 - Bedtime intake of painkillers (e.g., ibuprofen) in case of nocturnal pain
 - Pharmacologic and non-pharmacologic treatment of gastroesophageal reflux in case of nocturnal events
 - Sleep clinic evaluation in case of persistent poor sleep quality
 - (3) Muscle weakness
 - Carnitin (250 mg for adults) and coenzyme Q10 (100 mg for adults) daily intake at appropriate dosage
 - (4) Orthostatic intolerance
 - Generous liquid intake preferring isotonic drinks (2–2.5 lts/day)
 - Adequate food salting (to avoid in case of systemic hypertension)
 - Fragmented meals avoiding refined carbohydrates
 - Elastic stockings (and abdominal binders)
 - Head-up tilt at night
 - Physical counter-maneuvers
 - Consider drug use in case of persistence of symptoms and positive autonomic investigations
 - (5) Respiratory complaints
 - Consider pharmacologic treatment/prevention of pulmonary obstructive disease
 - (6) Food intolerances/malabsorption
 - Consider appropriate food restrictions in case of confirmed intolerance(s)
- All recommendations presented in this table MUST be considered low-level treatments for JHS/EDS-HT

poses, an updated consensus on JHS/EDS-HT diagnostic criteria is needed [Remvig et al., 2011], future molecular studies should not lay on such phenotypic restrictions, but should select families using more “lax” criteria within a truly holistic approach.

TABLE VII. Selected Factors Influencing Phenotype in the Joint Hypermobility Syndrome

Factor

- (1) Sex hormones and sexual dimorphism
- (2) Variability in motor control (e.g., proprioception and muscle tone)
- (3) Variability in pain modulation
- (4) Adaptive/coping strategies (e.g., avoidance versus confrontation strategies, hypervigilance)
- (5) Weight (both overweight/obesity and underweight)
- (6) Diet (e.g., vitamin deficits, diet restrictions)
- (7) Physical activity (e.g., sedentariness, abrupt interruption of regular sport activity)
- (8) Traumas and surgery (e.g., deconditioning, delayed wound repair, biomechanical reverberations)

In this perspective, clinical studies and molecular research will represent two sides of the same coin and advances in both fields will be necessarily intermingled to improve our understanding of this disorder and help symptoms management and disability prevention. The authors realize that many points discussed in this work are very speculative and are limited by lack of actual clinical and experimental resources. Nevertheless, we believe that management of JHS/EDS-HT in a more efficient way and wider awareness among medical professionals, will not only help JHS/EDS-HT patients, but also those affected by rarer HCTDs affecting soft-tissues, of which JHS/EDS-HT likely represents a biopathological model.

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