American Journal of Medical Genetics Part C (Seminars in Medical Genetics) 169C:84–96 (2015)

ARTICLE

Connective Tissue, Ehlers–Danlos Syndrome(s), and Head and Cervical Pain

MARCO CASTORI, SILVIA MORLINO, GIULIA GHIBELLINI, CLAUDIA CELLETTI, FILIPPO CAMEROTA, AND PAOLA GRAMMATICO

Ehlers–Danlos syndrome (EDS) is an umbrella term for a growing group of hereditary disorders of the connective tissue mainly manifesting with generalized joint hypermobility, skin hyperextensibility, and vascular and internal organ fragility. In contrast with other well known heritable connective tissue disorders with severe cardiovascular involvement (e.g., Marfan syndrome), most EDS patients share a nearly normal life span, but are severely limited by disabling features, such as pain, fatigue and headache. In this work, pertinent literature is reviewed with focus on prevalence, features and possible pathogenic mechanisms of headache in EDSs. Gathered data are fragmented and generally have a low level of evidence. Headache is reported in no less than 1/3 of the patients. Migraine results the most common type in the hypermobility type of EDS. Other possibly related headache disorders include tension-type headache, new daily persistent headache, headache attributed to spontaneous cerebrospinal fluid leakage, headache secondary to Chiari malformation, cervicogenic headache and neck–tongue syndrome, whose association still lacks of reliable prevalence studies. The underlying pathogenesis seems complex and variably associated with cardiovascular dysautonomia, cervical spine and temporomandibular joint instability/dysfunction, meningeal fragility, poor sleep quality, pain-killer drugs overuse and central sensitization. Particular attention is posed on a presumed subclinical cervical spine dysfunction. Standard treatment is always symptomatic and usually unsuccessful. Assessment and management procedures are discussed in order to put some basis for ameliorating the actual patients' needs and nurturing future research.

KEY WORDS: cervical spine; connective tissue; ligamentous laxity; meninges; occipitoatlantoaxial; POTS; temporomandibular

ABBREVIATIONS: cEDS, classic Ehlers–Danlos syndrome; CSF, cerebrospinal fluid; EDS, Ehlers–Danlos syndrome; EDS-HT, Ehlers–Danlos syndrome hypermobility type; HCTD, heritable connective tissue disorder; gJHM, generalized joint hypermobility; JHS, joint hypermobility syndrome; NDPH, new daily persistent headache; OAAJ, occipitoatlantoaxial joint; TMJ, temporomandibular joint; vEDS, vascular Ehlers–Danlos syndrome.

How to cite this article: Castori M, Morlino S, Ghibellini G, Celletti C, Camerota F, Grammatico P. 2015. Connective tissue, Ehlers–Danlos syndrome(s), and head and cervical pain. Am J Med Genet Part C 169C:84–96.

Marco Castori is a medical geneticist enrolled as senior hospital-based clinician at the San Camillo-Forlanini Hospital in Rome. He obtained his Ph.D. degree with a clinical and management study on Ehlers–Danlos syndrome(s). Major research topics include hereditary connective tissue disorders, genodermatoses, clinical dysmorphology and fetal pathology. He is author and co-author of more than 100 publications in international journals and several book chapters.

Silvia Morlino is a M.D. resident in Medical Genetics at the Sapienza University of Rome. She has a full-time involvement in the clinical and research activity of the Division of Medical Genetics at the San Camillo-Hospital in Rome. Her interests mostly include clinical dysmorphology and hereditary connective tissue disorders.

Giulia Ghibellini has a PhD from UNC, Chapel Hill, School of Pharmacy where she is adjunct faculty and has worked as a clinical research scientist in large and small pharmaceutical companies since 2006. Recently, Giulia has developed a special interest in Ehlers Danlos syndrome, hypermobility type and is pursuing additional training in neurodevelopmental approaches and advocacy for special needs children.

Claudia Celletti is a physiatrist at the Division of Physical Medicine and Rehabilitation of the Umberto I University Hospital. Together with Dr. Filippo Camerota, she is fully involved in the rehabilitation and clinical research of rare diseases, with particular interest on joint hypermobility. She is author of more than 30 papers in international journals, most of them on Ehlers–Danlos syndrome.

Filippo Camerota is a senior physiatrist at the Division of Physical Medicine and Rehabilitation of the Umberto I University Hospital. His special interests include rehabilitative implications of rare diseases, joint hypermobility, neurodegerative disorders and cerebral palsy. He is authors of more than 40 papers in international journals, many of them on Ehlers–Danlos syndrome.

Paola Grammatico is an Associate Professor of Medical Genetics at the Sapienza University and Director of the Division of Medical Genetics at the San Camillo-Forlanini Hospital in Rome. She has various responsibilities in the regional and national Healthcare system with focus on genetic laboratory testing and rare diseases. Her major diagnostic and research interests include cutaneous melanoma, disorders of sex differentiation and fetal pathology. She is author of more than 150 papers in international journals and various book chapters on medical genetics.

*Correspondence to: Marco Castori, M.D., Ph.D., Division of Medical Genetics, San Camillo-Forlanini Hospital, Circonvallazione Gianicolense, 87, I-00152 Rome, Italy. E-mail: m.castori@scf.gov.it

DOI 10.1002/ajmg.c.31426
Article first published online 5 February 2015 in Wiley Online Library (wileyonlinelibrary.com).

INTRODUCTION

Ehlers–Danlos syndrome (EDS) is an umbrella term for an increasing group of heritable connective tissue disorders (HCTDs) sharing the variable triad of (i) generalized joint hypermobility (gJHM) and related osteoarticular complications, (ii) dermal dysplasia extending from minor changes of skin texture to clinically relevant skin fragility and defective scarring and (iii) vascular and internal organ fragility with proneness to traumatic injuries and spontaneous ruptures, dissections and prolapses. The last classification identifies six major variants, including classic (cEDS), hypermobility (EDS-HT), vascular (vEDS), kyphoscoliotic, arthrochalasis and dermatosparaxis subtypes, which are distinguished on the basis of specific diagnostic criteria, i.e., Villefranche criteria [Beighton et al., 1998]. In the clinical practice, adhesion to such criteria help in selecting patients for confirmatory laboratory tests, which are now available for all major EDS subtypes except EDS-HT [Mayer et al., 2013]. As a whole, EDSs have a presumed cumulative frequency of ~1/5,000 [Steinmann et al., 2002], with cEDS and EDS-HT being the most common variants [De Paepe and Malfait, 2012]. The extreme clinical variability of cEDS and EDS-HT [Castori, 2012a; Ritelli et al., 2013], and the lack of a reliable diagnostic test for the EDS-HT [Mayer et al., 2013] underestimate the prevalence of EDSs. Further complexity is added by the clinical overlap between EDS-HT and the joint hypermobility syndrome (JHS), a relatively neglected rheumatologic condition with specific diagnostic criteria [Grahame et al., 2000] and which results unexpectedly common with a presumed frequency of ~1% [Hakim and Sahota, 2006]. An international group of experts now consider these two disorders undistinguishable at the clinical level [Tinkle et al., 2009]. Although this hypothesis still waits molecular confirmation [De Paepe and Malfait, 2012], recent observations support with evidence the concept that EDS-HT and JHS may be indeed one and the same condition (i.e., JHS/EDS-HT) also at the genetic level [Hermanns-Lê et al., 2012].

For decades, practitioners' and researchers' attention was posed at the cutaneous, articular and vascular aspects of EDSs. This generated a perspective distortion that separated cEDS and JHS/EDS-HT, considered relatively benign traits, from vEDS and other variants, which, conversely, reduce lifespan of affected individuals and request close multidisciplinary support. In the last two decades, a growing number of studies pointed out the impact of EDS on quality of life in term of symptom chronification in those patients who skip catastrophic events, and then reach adulthood and the old age. Accordingly, musculoskeletal pain [Voermans et al., 2010a] and chronic fatigue [Voermans et al., 2010b] are highly reported in various forms of EDS and are both important possible determinants of disability in EDS-HT [Voermans and Knoop, 2011]. The long-term management of patients affected by EDS forms with unaffected mortality rate, as well as of long-survivors of potentially life-threatening subtypes, is hampered by the general ineffectiveness of available treatment strategies, as recently reviewed for JHS/EDS-HT [Castori et al., 2012].

Among the various contributors of quality of life in EDSs, headache is a further largely unrecognized feature, whose association with these disorders has been only recently outlined [Sacheti et al., 1997]. Although some preliminary studies investigated prevalent patterns of headaches in specific EDSs subtypes [Jacome, 1999; Bendik et al., 2011], practice still suffers for the absence of a structured theoretical backbone for future more evidence-based research. We offered a first and incomplete overview of the clinical contributors to head and cervical pain in JHS/EDS-HT in a recent review further characterizing the natural history of this condition with focus on pain and fatigue [Castori et al., 2013]. Subsequently, another research group presented a good overview of the most common HCTDs presenting headache and speculated on the most likely pathogenic mechanisms in a neurological specialized journal [Martin and Neilson, 2014; Neilson and Martin, 2014]. In the present paper, we will face the same topic from an inverted point of view. The issue of "headache and other head and cervical pains" in HCTDs is discussed as a possible presentation or late complication of a specific multisystem disorder (i.e., EDS) with a protean natural history, in which headache is intermingled with multiple neurologic and non-neurologic dysfunctions in a wider pathogenic process simultaneous spreading most tissues and organs.

METHODS

This review was intended as a PubMed search aimed at investigating the relationships between gJHM/EDSs and headache disorders. As headache is commonly reported by EDS patients, the main effort of this work was to offer a knowledge toll for better classifying and, hopefully, managing patients. The literature review was carried out with the following keywords: [(hypermobility) OR (Ehlers-Danlos syndrome) OR (connective tissue) OR (collagen)] AND [(headache) OR (migraine)]. Results were selected for papers presenting case reports, case series, case-control studies and reviews on headache and/or migraine in patients with various forms of EDS or unclassified gJHM. The reference lists of selected papers were screened for additional works. Most identified works were case reports and case series lacking control groups. After a formal overview of these results, an extended narrative review, guided by authors' clinical and personal expertise (i.e., one of us is indeed affected by EDS), was also performed in order to investigate the possible pathogenic mechanisms underlying headache in EDSs. A section of available management options and recommendations is also presented with proposed adaptations for patients with EDSs.

HEADACHE IN EHLERS–DANLOS SYNDROMES: AN OVERVIEW

Literature review demonstrated that, although practice points out headache as a relatively common finding in EDSs [Grahame, 2009], only a handful of papers investigated this ancillary complaint, which, in turn, has a significant impact in terms of co-morbidity and disability.

In 1997, the work by Sacheti et al. described pain features in 51 individuals with different forms of EDS (including 13 patients with cEDS – nine with type I and four with type II, 28 with EDS-HT, one with JHS, seven with vEDS and two with unclassified type) and showed that neck pain and headache accounted for 30–40% of cases. A subsequent case series reported 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]. Additional works, focused on JHS/EDS-HT, confirmed the high prevalence of headache in this condition without further characterizations [Castori et al., 2010; Rombaut et al., 2010]. 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 with a cumulative frequency of 75% (3/4).

Single case-control studies, case series or case reports pointed out preliminary associations between gJHM/EDS and specific subsets of primary and secondary types of headache, including new daily persistent headache (NDPH) [Rozen et al., 2006], headache attributed to spontaneous (idiopathic) cerebrospinal fluid (CSF) leakage [Schievink et al., 1996, 2004] and headache secondary to Chiari malformation [Castori et al., 2010]. Cervical spine hypermobility/dysfunction is also anecdotally considered a predisposing factor for cervicogenic headache [Hall et al., 2008] and neck–tongue syndrome [Orrell and Marsen, 1994; Sjaastad and Bakketeig, 2006; González de la Aleja Tejera and Porta-Etessam, 2008]. In line with this, Di Palma and Cronin [2005] report a 27-year-old woman with cEDS (type II) with a long-lasting pulsating headache associated with C2 dislocation, while Mathers et al. [2011] point out the utility of looking for occult hypermobility at the craniocervical junction by describing a patient with occipital headache and cervical spine instability. Furthermore, an early report describes two out of three vascular EDS patients with radiologically evident atlantoaxial subluxation [Halko et al., 1995].

Head pain is not limited to headache in EDSs. In a cohort of 31 EDS patients (including 16 with JHS/EDS-HT, nine with cEDS and six with vEDS), 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].

In vEDS, ipsilateral headache may occur together with additional neurologic features, such as ophthalmoplegia and tinnitus, due to vascular accidents, including spontaneous direct cavernous-carotid fistula [Chuman et al., 2002; Tanaka et al., 2014]. Similar presentations may equally be observed in other EDS subtypes with vascular fragility. In fact, intermittent headache due to rupture of an intracranial arterial aneurysm is observed in osteogenesis imperfecta, a well known HCTD with clinical and genetic similarities with EDSs [Havlik and Nashelsky, 2006]. Mutations in *COL1A1* and *COL1A2*, the genes most commonly associated with osteogenesis imperfecta, are also reported in specific EDS subtypes, including the EDS/osteogenesis imperfecta overlap syndrome, EDS with vascular fragility, cardiac-valvular EDS and EDS arthrochalasis type [Marfait and De Paepe, 2012].

Finally, a 36-year-old woman presenting with generalized headache for 8 months and the diagnostic criteria of JHS/EDS-HT has been described [Kurian and Solomon, 2013]. In this patient, headache was subsequently attributed to spontaneous intracranial hypertension (32 cm H_2O). The patient described similarities of the presenting symptom with a previous headache developed following a lumbar pucture after a car accident. The authors also speculated on the pathogenic role of elevated plasma IGF-1 levels they found in this patient.

POSSIBLE MECHANISMS OF HEAD AND CERVICAL PAIN IN EHLERS–DANLOS SYNDROMES

Available data indicate that headache is clinically and pathogenically heterogeneous in EDSs. A discrete number of clinical forms according to the third edition of the International Classification of Headache Disorders (Headache Classification Committee of the International Headache Society, 2013) can be identified in EDS patients with a predominance of migraine in JHS/EDS-HT. Nevertheless, observation suggests marked variability at presentation and possible evolution in mixed chronic headache with multiple patterns affecting the same individual with different timing and chance of superimposition. The level of evidence of available data on headache in association to EDSs and gJHM is generally low.

A wider consultation of the literature offers a fragmented network of distinct pathophysiologic mechanisms of head pain, directly related to a dysfunctional connective tissue composing various non-ossifying structures of the cephalic pole. Four major anatomic fields are identified, namely cardiovascular system, muscles and TMJ, cervical spine and meninges, whose summative or multiplicative anomalies may contribute to the observed phenotypic variability (Fig. 1). Additional contributors to headache manifestations and evolutions include: sleep disturbances, painkiller drugs overuse and central sensitization.

Cardiovascular System

Indirect evidence suggests that vascular dysfunction is a major contributor to

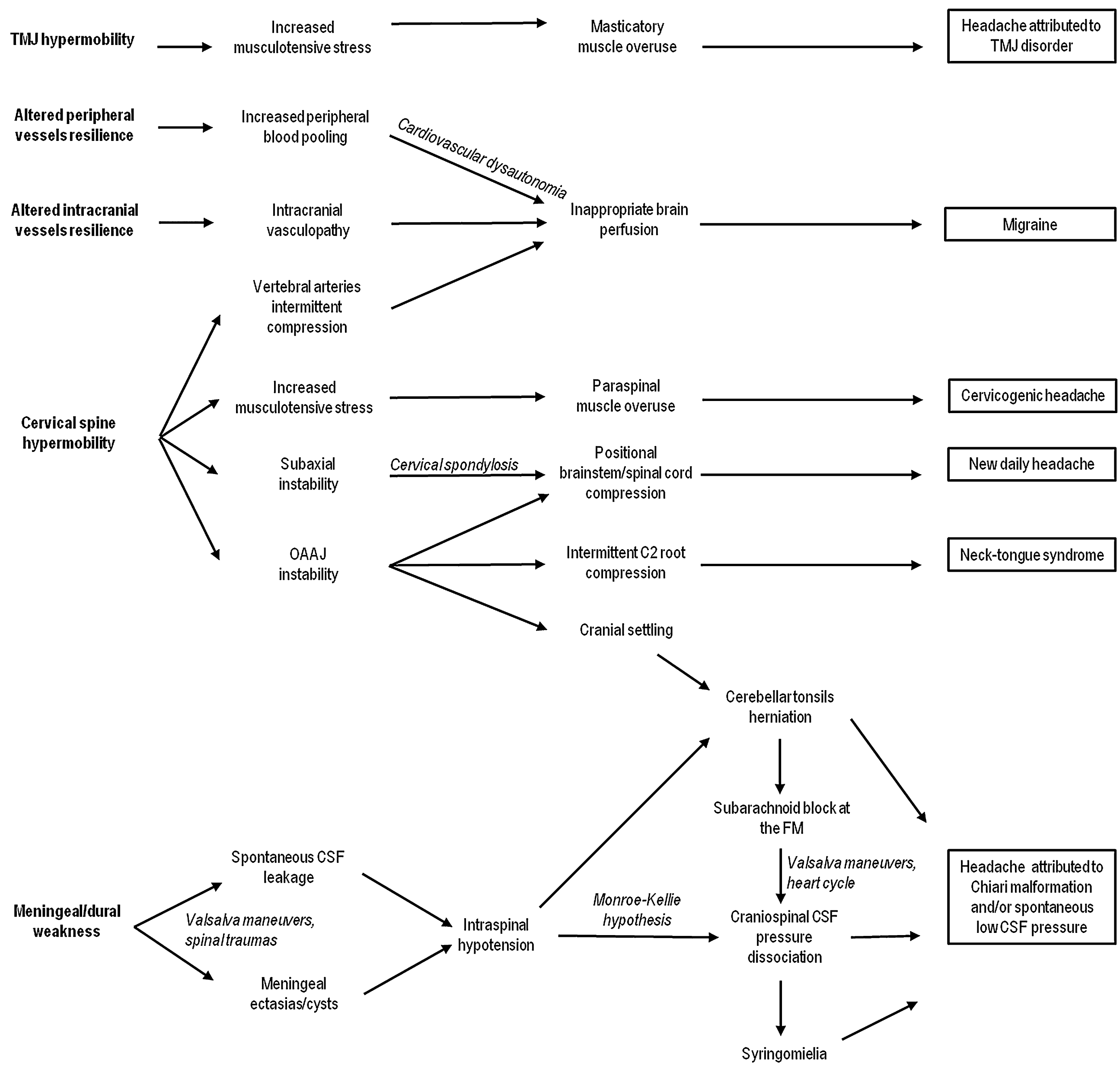

Figure 1. Diagram showing possible relationships between the different functional and anatomical factors contributing to some headache manifestations in EDSs. CSF, cerebrospinal fluid; FM, foramen magnum; OAAJ, occipito-atlanto-axial joint; TMJ, temporomandibular joint.

headache in EDSs. Migraine is, at the moment, considered the most common form of headache in JHS/EDS-HT [Bendik et al., 2011]. In order to explain such an association, it has been speculated that vascular dysfunction may be a trigger of head pain due to either an underlying arteriopathy or cardiovascular dysautonomia. The former is indirectly supported by the evidence of reduced aortic stiffness in patients with mitral valve prolapse and JHS/EDS-HT [Yazici et al., 2004]. Accordingly, increased intracranial vascular compliance may affect central nervous system homeostasis and, thus, causes headache. The latter refers to the high rate of orthostatic hypotension in EDS compared to healthy controls [Gazit et al., 2003]. A better definition of the underlying dysautonomia in EDSs identifies the most common neuromediated cardiovascular dysfunction in postural orthostatic tachycardia syndrome [Mathias et al., 2011]. Then, a direct link between headache and cardiovascular dysautonomia can be postulated, as headache is a main symptom of chronic orthostatic intolerance in both pediatric and adults patients [Mack et al., 2010; Mathias et al., 2011]. Inappropriate neuromediated cardiovascular adaptation to rapid postural changes may be triggered by increased venous pooling due to reduced peripheral vessels resilience [Bohora, 2010]. In particular, by studying 37 patients with EDS-HT, De Wandele et al. [2014] collected Head-up Tilt-test data suggestive for a common neurogenic dysfunction of the cardiovascular system. Whether this finding is a primary (pleiotropy) or secondary/remote feature of the underlying connective tissue defect needs further investigations.

Repeated evidence underlies an increased rate of vertebral artery hypoplasia among migraineurs compared to healthy subjects. Although a causal relationship between such an anatomical variant and migraine remains unclear [Chuang et al., 2008], this broadens the spectrum of possible cardiovascular connections between headache and EDSs. In fact, vertebral arteries are branches of the subclavian arteries, which get through to a stiff, anelastic passage constituted by the transverse foramen of the cervical vertebrae, before fusing intracranially in the basilar artery. Neck rotation may stress vertebral arteries between the transverse foramina of C1 and C2, where rotational injury of the vertebral artery usually occurs. One could speculate that, in EDSs, the combination of increased cervical spine mobility and reduced resilience of the vertebral artery wall due to a constitutionally deficient connective tissue may functionally mimic vertebral artery hypoplasia and, then, contribute to migraine development.

Finally, EDS forms with marked vascular fragility may present with sudden/thunderclap headache due to intracranial or epiaortic vascular ruptures. Recognition of vascular accident and prompt treatment may be delayed in patients affected by these EDS subtypes and suffering of chronic/recurrent background headache due to one or more of the other mechanisms here described.

Muscles and Temporomandibular Joint

It is well known that TMJ and cervical spine instability associate with an increased rate of temporal [Pasinato et al., 2011] and neck/occipital [Sahin et al., 2008] myofascial pain. This may result from increased pericranial musculotensive stress due to excessive range of motion of the affected joints during daily activities, thus causing repetitive masticatory and paravertebral muscle damage. Some environmental factors, such as whiplash injuries or non-ergonomic postures at work and school, may facilitate myogenous pain in a hypermobile individual. In the general population, myogenous headache is usually unilateral/monofocal and may present with the additional features of focal point of tenderness of the involved muscle(s), induration of the adjacent muscle, restricted range of motion, presence of myofascial trigger point(s), as well as dizziness, tinnitus and poor balance in case of paravertebral muscles involvement [Bennett, 2007]. In the presence of gJHM, simultaneous and possibly symmetric involvement of multiple muscles is also possible.

Headache attributed to TMJ dysfunction may manifest as (bi-)temporal myogenous pain with variable features of tension-type headache and/or migraine [Glaros et al., 2007]. Whether TMJ dysfunction correlates or not with gJHM/EDS is still a matter of debate. An early literature review of 14 previous works concluded that a clear association between gJHM and TMJ disorder cannot be delineated and further studies are needed [Dijkstra et al., 2002]. Conversely, their correlation appears consistent in specific populations, including children [Adair and Hecht, 1993] and young/young-adult women [Pasinato et al., 2011]. Additionally, features of TMJ dysfunction can be observed in more than 2/3 of EDS patients [De Coster et al., 2005]. A likely explanation of such a discrepancy is the inverse correlation between joint-related symptoms and residual gJHM, that typically characterizes the natural history of HCTDs, especially JHS/EDS-HT [Castori et al., 2011]. In other words, it is possible that symptomatic TMJ dysfunction is commoner among patients that have lost their gJHM and, then, resulted negative at standard Beighton score screening. Clear positive associations emerge only in studies focused on symptomatic subpopulations that are inherently more "double-jointed", such as women and children. Therefore, the correlation between gJHM and TMJ dysfunction is expected to be stronger than generally thought, and a link with myogenous head pain is its direct consequence.

Cervical Spine

Cervicogenic headache is a common form of head pain, distinguishable from migraine and tension-type headache by restricted neck movements, pain exacerbation by neck mobilization or external pressure over the upper cervical and occipital region, ipsilateral shoulder and/or arm pain and confirmatory evidence by diagnostic anesthetic block [Sjaastad et al., 1998]. Although its pathophysiology remains largely unknown, upper (C1-C3) cervical spine dysfunction is considered a possible underlying mechanism [Hall et al., 2008]. The direct connection between the rectus capitis posterior minor and the dura mater, termed "myodural bridge", is evoked as a possible pathogenic factor in cervicogenic headache [Kahkeshani and Ward, 2012]. The myodural bridge is essentially constituted of connective tissue and its structural abnormality may facilitate cervicogenic headache in EDSs.

Upper cervical spine (C0-C2) hypermobility may generate head pain also via direct, intermittent compression of nerve roots, usually in association with specific neck movements, such as lateral flexion and rotation. This is the case of "neck-tongue syndrome", a peculiar and apparently rare form of headache dominated by sudden occipital stab associated with (homolateral) tongue numbness [Sjaastad and Bakketeig, 2006]. In many patients, pathology of C0-C1 and/or C1-C2, also comprising fractures, may be demonstrated [Orrell and Marsden, 1994], with instability of the odontoid process pressing on the C2 nerve roots at lateral flexion/rotation as a possible explanation [Bogduk, 1981]. Temporary abnormal subluxation of the lateral atlantoaxial joint, which strains the joint capsule, was proposed as the likely mechanism for pain in neck-tongue syndrome. This phenomenon is expected to occur more frequently in subjects with congenitally lax joints. Non-casual concurrence of cervicogenic headache and neck-tongue syndrome has been reported in two cases, also showing features of cervical instability [Sjaastad and Bakketeig, 2006]. It is, therefore, expected that future studies will investigate the prevalence of cervicogenic headache and neck-tongue syndrome in patients with gJHM and EDSs.

NDPH is characterized by bilateral (occipital) head pain with common migranous features, absence of pain-free time, moderate-to-severe intensity and female preponderance [Rozen, 2011]. A preliminary study by Rozen et al. [2006] on 12 patients with NDPH finds positive Beighton score in 10 subjects and clinical findings indicative of cervical instability in eleven. The relationship between cervical spine hypermobility and head pain has been explained by the authors as the consequence of an influence on the trigeminal and cervical afferents to the trigeminal nucleus caudalis by a hypermobile spine [Rozen et al., 2006]. In other words, an instable cervical spine may cause functional brainstem compression possibly influenced by neck movements and damaging the sensory fibers entering the nucleus caudalis. In line with this, a recent study demonstrated positional cervical spinal cord compression in fibromyalgia [Holman, 2008], a frequent co-morbility in gJHM [Gedalia et al., 1993; Ofluoglu et al., 2006; Sendur et al., 2007] with possible pathophysiologic links with EDSs.

Most features related to NDPH are probably linked to occipitoatlantoaxial joint (OAAJ) instability. However, also subaxial instability may have a role in the development of neck and head pain in JHS/EDS-HT. Generally speaking, it is still debated whether gJHM predisposes to or rather protects from precocious osteoarthritis [Dolan et al., 2003]. In contrast to limb joints for which causal correlation between gJHM and precocious degenerative changes is unclear, spondylosis of the cervical spine is usually observed at C5–6, which are the most mobile segments of the cervical spine. Therefore, it is likely that constitutional gJHM may accelerate this process and determine degenerative disc disease with consequent (persistent — in contrast to intermittent compressions inherently related to a hypermobile spine) spinal cord/nerve roots compression at an early age. In addition to bony compressions of cranial nerves and brachial plexus nerves due to an instable cervical spine, by studying peripheral nerves, Granata et al. [2013] suggest an increased rate of spontaneous nerve subluxations, which may contribute to neuropathic pain in EDS, also possibly comprising head and neck pain.

The mechanism by which OAAJ instability contributes to headache may be more complex than expected. Milhorat et al. [2007] report clinical and neuroradiological features of a large group of patients with failure of surgery for Chiari malformation type 1. Approximately 13% of them have unspecific features of HCTD and present more severe and common satellite symptoms, such as nausea, dysphagia, sleep apnea, double vision and cardiovascular dysautonomia. Neuroradiologically, these patients display OAAJ hypermobility and cranial settling (i.e., reduced distance between basion and odontoid), in addition to cerebellar tonsillar descent. The authors suggest that cranial settling and consequent herniation of the cerebellar tonsils are secondary to the increased motion of the OAAJ, in turn attributed to congenital laxity of C0-C2 ligaments. In these patients, brainstem symptoms, as well as headache, may be secondary to brainstem compression as a result of OAAJ instability combined with the consequences of cerebellar tonsillar descent. On a pathogenic perspective, OAAJ instability and "functional" Chiari malformation may have further long-term consequences, including an incomplete and/or intermittent arachnoid block at the foramen magnum level with consequent dissociation of the CSF pressure facilitated by Valsalva's maneuvers and heart cycle [Williams, 1981]. This phenomenon may determine structural features, including syringomyelia [Levine, 2004] which likely go underdiagnosed in EDSs, and may contribute to the understanding of the associated symptoms.

Hypothesis: Remote Implications of Cervical Spine Pathology in Ehlers–Danlos Syndrome(s)

Previous considerations magnify the role of cervical spine instability in headache manifestations of EDS. Consequences of an instable cervical spine due to constitutionally lax ligaments may extend much beyond head and neck pain. Lessons come from rheumatoid arthritis (RA), a rheumatologic condition, which is commonly complicated by an acquired form of cervical instability. This phenomenon arises from the typical destructive synovitis, which causes bone erosions and ligamentous laxity, the latter eventually leading to instability of the cervical spine variably presenting with atlantoaxial subluxation, cranial settling and subaxial subluxation [Wasserman et al., 2011]. Involvement of the cervical spine is common in RA, with craniocervical complications observed in 30–50% of the patients who have had RA more than 7 years, and atlantoaxial subluxation with cervical myelopathy in 2.5% of those with RA for more than 14 years [Moskovich et al., 1996]. Neck pain with occipital headache is the most common associated complaint [Rawlins et al., 1998]. Further forms of head pain include occipital neuralgia, facial pain and ear pain secondary to compression of C1 and C2 nerve roots. Patients who develop cervical myelopathy may also manifest a plethora of additional features, such as increased fatigue and/or musculoskeletal pain, balance, gait control, coordination and proprioception deficiency, contractures, paresthesias, tinnitus, vertigo, diplopia, visual deficits, dysphagia, bladder and bowel dysfunction [Wasserman et al., 2011].

Table I summarizes a spectrum of ancillary neurological findings, which are not included in the available diagnostic

TABLE I. EDSs and JHS Ancillary Features Which May Be Influenced by an Underlying Cervical Spine Pathology

Feature
Dizziness/vertigo
Numbness (i.e., peripheral hypo/anesthesias)
Dysesthesias (e.g., allodynia, hyperalgesia, burning sensations, etc.)
Paresthesias
Tremulousness
Limb muscle weakness
Lack of balance and coordination
Abnormal movements (e.g., fasciculations, periodic limb movements, dystonias)
Bladder dysfunction
Unexplained ocular/visual and auditory disturbances (e.g., tinnitus, diplopia)
Minor memory and concentration disturbances
Hand interosseous muscles hypotrophy

criteria of EDSs and JHS, but may be not rarely encountered in the daily activity of specialized clinics, especially in patients with JHS/EDS-HT. Similarly to RA, in EDS, these features, which often represent major burdens for affected individuals but still remain pathogenically unexplained, may be easily traced back to repeated compressive damage on brainstem and spinal cord by an instable cervical spine. In EDS, a stable compressive process, such as fixed vertebral subluxation or posterior annulus bulging, can be demonstrated rarely. In presence of cervical spine hypermobility, brainstem/spinal cord compression is strictly influenced by neck movements and postural changes. Consequently, in EDS patients with disabling symptoms purportedly linked to an occult cervical spine pathology, standard cervical spine X-rays in static position and MRI in clinostatism, performed as baseline investigations in patients with chronic neck/head pain, usually fail to demonstrate significant changes. This implies a general underestimation of cervical spine pathology in EDS and may explain the actual lack of knowledge on the cause of many reported symptoms. Eventually, this causes further worsening of the disease state due to patients' perception of being not fully upheld in healthcare environment. Investigating the "positional cervical spinal cord compression" may be a possible field of future research in EDS, as demonstrated in fibromyalgia patients with a MRI protocol, including acquisitions in flexion and extension of the cervical spine [Holman, 2008].

Cerebrospinal Fluid and Meninges

Meninges are further structures surrounding the central nervous system, which display a high content in connective tissue and its various fibrillar components. Meningeal involvement is a well consolidated concept in various HCTDs, including Marfan, Loeys–Dietz and EDSs [Loeys et al., 2010], as well as the rarer and prototypic lateral meningocele syndrome [Gripp et al., 1997]. In line with this, gJHM and Marfanoid habitus is observed in a significant proportion of patients suffering from headache attributed to idiopathic intraspinal hypotension [Schrijver et al., 2002; Schievink et al., 2004]. Complementarily, spontaneous intraspinal hypotension is repeatedly described in Marfan syndrome, osteogenesis imperfecta and EDSs [Eddeine et al., 2009; Voermans et al., 2009; Grosveld et al., 2011; Reinstein et al., 2013].

CSF leakage is thought to occur via the excessive distension and/or rupture of spontaneous dilatations (e.g., cysts and ectasias), as well as microscopic, multiple fenestrations of the meninges [Schievink, 2006]. Neuroradiological studies identify a series of imaging features, which also comprise downward displacement of the brain with flattening of the pons against the clivus and Chiari malformation-like changes [Fishman and Dillon, 1993]. Therefore, it is likely that at least some symptoms linked to idiopathic intraspinal hypotension are due to an incomplete arachnoid block at the level of the foramen magnum, thus magnifying, by a downward spiral, the dissociation of CSF pressure. Accordingly, EDSs may be considered an exceptional condition in which two apparently distinct mechanisms of head pain (i.e., OAAJ instability and spontaneous CSF leakage) converge on the same pathogenic mechanism (i.e., dissociation of the CSF pressure at the foramen magnum characterized by intraspinal hypotension and raising of the intracranial CSF pressure) with multiplicative deleterious effects on symptom development and treatment outcome. This hypothesis is partly supported by the repeated observation of intraspinal hypotension due to idiopathic CSF leakage associated with Chiari malformation and syringomyelia, the latter being considered a long-term anatomic consequence of incomplete arachnoid block at the brainstem/spinal cord [Mamelak et al., 1996; Johnston et al., 1998; Pratiparnawatr et al., 2000; Sharma et al., 2001; Owler et al., 2004]. Intriguingly and in partial support of the plausibility of Monroe–Kellie hypothesis in EDS, there is a 36-year-old woman with JHS/EDS-HT and generalized headache due to idiopathic intracranial hypertension [Kurian and Solomon, 2013]. Therefore, in EDSs, the searching for OAAJ instability and abnormal CSF drainage should not be mutually exclusive, as both may concur in symptom development and need specific care.

Additional Contributors

It is well known that, in the general population, "headache, particularly morning headache and chronic headache may be consequent to, or aggravated by, a sleep disorder, and management of the sleep disorder may improve or resolve the headache" [Rains and Poceta, 2006]. Quality of sleep is generally poor in EDSs

[Verbraecken et al., 2001; Tinkle, 2010; Voermans et al., 2010b] and possible causes include periodic limb movements and nocturnal musculoskeletal pain [Verbraecken et al., 2001; Voermans et al., 2010a]. True sleep apnea seems relatively rare in EDSs [Verbraecken et al., 2001]. However, a higher rate of nocturnal incomplete airway obstruction, including primary snoring and upper airway resistance syndrome [Rains and Poceta, 2006], due to oropharyngeal hypotonia and soft tissue laxity, may be present. Accordingly, a recent paper reporting results of polysomnography in 34 EDS patients demonstrates flow limitation, apneas and hypopneas with a decrease in flow limitation and an increase of apnea and hypopnea events with age. Rhinomanometry also shows increased nasal resistance [Guilleminault et al., 2013].

The third edition of the International Classification of Headache Disorders recognizes medication-overuse headache with specific entries for simple analgesic, opioid and combined analgesic overuse headaches, as well as for opioid-withdrawal headache. Given the high rate of recurrent/chronic musculoskeletal pain in various forms of EDS [Voermans et al., 2010a] and its usual refractoriness to standard treatments [Castori et al., 2012], pain-killer drugs overuse may be frequently reported in these patients. This possibility in EDS and, particularly, JHS/EDS-HT has been recently emphasized [Martin and Neilson, 2014], and accurate gathering of the drug medical use for headache and other painful manifestations is crucial for avoiding amplification of side effects related to drugs.

The natural history of headache in JHS/EDS-HT tells us an evolving phenotype with progressive chronification and mixture of different clinical forms of headache in the same individual [Castori et al., 2013]. A contributor to such a transformation may be the neuronal plasticity leading to pain sensitization. Its existence in JHS/EDS-HT has been first postulated in 2009 by Grahame by describing kinesiophobia as a major prognostic determinant in JHS/EDS-HT. This hypothesis was subsequently supported by more objective data [Rombaut et al., 2011]. Kinesiophobia is a maladaptive cognition considered one cognitive counterpart of central sensitization. Rombaut et al. [2014] demonstrated primary and secondary hyperalgesia in JHS/EDS-HT, a preliminary but encouraging proof for central sensitization in EDS. On a practical point of view, chronification, loss of pain localization, somatic hyperalgesia and allodynia are anamnestic features suggestive for the instauration of central sensitization in an EDS headache patient.

ASSESSMENT CONSIDERATIONS

Assessing and managing headache disorders in EDSs is a frustrating task. Such a complexity is two-fold. First, practitioners not previously experienced in HCTDs have difficulties in suspecting and, then, promptly diagnosing EDS. Second, even when a patient is recognized as affected by a specific EDS variant, the clinical approach to the referring symptom (e.g., headache) lacks of any systemized body of evidence supporting the practitioner's work. Among the various forms of EDS, special attention should be posed at variants with increased vascular fragility, namely vEDS, kyphoscoliotic and cEDS with arterial rupture [De Paepe and Malfait, 2012]. In these subtypes, rapid diagnosis may be crucial for more accurately tailoring dangerous interventions, such as catheterization [Malfait and De Paepe, 2009] for angio-TC and MRI with gadolinium enhancement, and prudently evaluating symptoms, particularly in case of thunderclap or unusually painful headaches. Especially in these circumstances, formal confirmation of the EDS subtype by reliable laboratory tests according to Mayer et al. [2013] should be encouraged.

Outside the emergence of excruciating headache in a patient with suspected/confirmed EDS subtype with increased vascular risk, the patient should be carefully assessed by investigating all the potential contributors to head pain as previously illustrated (Table II). Recorded symptoms may guide specific instrumental investigations with the aim of identifying and, possibly, quantifying the contribution of the various possible triggers pleiotropically related to the underlying connective tissue dysplasia (Table III). The assessment phase should be carried our carefully following specific "red flags", whose adherence may be useful

TABLE II. Checklist for Assessing the Headache Patient with Ehlers–Danlos Syndrome

Item
Full neurological assessment (history and examination)
Assessing temporomandibular joint
Assessing cervical spine mobility/instability (also including postural intraoral/perioral/retroauricular paresthesias)
Checking for pericranial muscle hyperalgesia/tenderness
Checking for postural intolerance and influences on headache triggering/modulation
Checking for sleep quality by appropriate scales/questionnaires (e.g., Epworth sleepiness scale)
Checking for pain-killer drugs chronic use/overuse

TABLE III. Possibly Useful Investigations for Headache in Ehlers–Danlos Syndromes

Investigation	In case of	Features to search
Brain angio-MRI	Thunderclap or unusually painful headache	Intracranial vascular accident
Tilt-test	Orthostatic intolerance	Postural orthostatic tachycardia or other dysautonomic profiles.
Polysomnography	Morning headache	Sleep fragmentation, arousals and nocturnal apneas.
Static and dynamic cervical spine radiograph at standard projection	Occipital headache with features of cervical spine instability	Fixed vertebrae subluxations, spondylosis, loss of the physiological curvature, measurement of the anterior and posterior atlantodental intervals, radiographic signs of cranial settling (McGregor's line, Ranawat index, etc.), antero- and postero-listhesis at flexion and hyperextension, changes in length of the anterior and posterior atlantodental intervals, posterior tilting of the dens of C2 at flexion.
Static and dynamic cervical spine radiograph at open mouth/odontoid projection	Neck–tongue syndrome	Lateral deviation of the odontoid process; lateral listhesis of C1–C2.
Brain MRI without gadolinium	Migraine, occipital headache, orthostatic headache	White matter lesions, cerebellar tonsillar herniation, engorgement of venous structures, pituitary hyperemia, sagging of the brain, subdural fluid collections.
Cervical spine MRI without gadolinium	Occipital headache, symptoms of myelopathy	Cervical spondylosis, cervical compression of the brainstem/spinal cord.
Total spine MRI without gadolinium	Orthostatic headache, symptoms of myelopathy	Dilatations/ectasias/diverticula of the meninges, dilated dural veins, extrathecal cerebrospinal fluid collections, syringomyelia.
Brain/spine MRI with gadolinium	Orthostatic headache with negative/inconsistent results at MRI without gadolinium	Enhancement of the pachymeninges.

for subsequent treatment planning (Table IV).

MANAGEMENT CONSIDERATIONS

Data on treatment outcomes of headache in EDSs are still missing in the literature. Unpublished experience suggests that in the most common forms of EDSs, headache disorders rarely have spontaneous resolution and are usually linked to degenerative processes of collagen-rich non-ossified tissues. Disease progression is unpredictable. Nevertheless, an onset in the form of episodic/recurrent single-type headache and slow progression in a chronic, mixed and highly disabling headache is frequently observed, at least, in the JHS/EDS-HT [Castori et al., 2013]. Single treatment unsuccessfulness is common and the planning of more integrated approaches suffers of the likely simultaneousness of multiple pathophysiological processes. Therefore, at the moment, prevention strategies appear the most effective approach for symptom control in the a-/oligo-symptomatic patient. General lifestyle recommendations for the congenitally hypermobile patient and the headache patient with orthostatic intolerance may be found in Castori et al. [2012] and Mack et al. [2010] and are summarized in Table V.

Standardized pharmacologic treatments for most primary headache disorders, mainly including migraine, are available [Bendtsen et al., 2012]. Any adjustment specifically addressed for EDS has not yet been published. In light of some empiric considerations of disease characteristics and anecdotal observations, specific drugs, including acetylsalicylic acid, myorelaxants, corticosteroids (chronic treatments), opioids and anti-epileptics, should be handled with care due an increased risk of side effects, at least, in JHS/EDS-HT [Castori et al., 2012]. Expert opinion on drug therapy in EDS is reported in the review by Martin and Nelson [2014] with annotations by type of headache. Among the various psychological approaches, behavioral treatments,

TABLE IV. Red Flags in Treating Headache in the Ehlers-Danlos Syndromes

Red flag
Classify accurately (co-) existent headache disorder(s)
Support symptomatic classification by searching organic triggers, as proposed in Table II
Promote an integrated approach by using simultaneously multiple therapeutic resources
Postpone the use of drugs with presumed higher rate of side effects in Ehlers–Danlos syndrome[a]
Consider first physical therapy and conservative approaches
Promote adhesion to general lifestyle recommendations, as proposed in Table V

[a]Including acetilsalycilic acid, myorelaxants, corticosteroids (chronic treatments), opioids and anti-epileptics.

including relaxation, biofeedback and cognitive-behavioral therapy, are the most promising for various forms of headache [Nicholson et al., 2011]. In light of the prominent role of maladaptive cognitions in pain chronicization in JHS/EDS-HT, a potentially high impact has been recently envisaged for cognitive behavioral therapy [Grahame, 2009].

Physical therapy for head/neck pain is usually focused on treating TMJ, upper spine and limbs. No specific guidelines are available for the hypermobile patient; however, some practical considerations emerge from available literature. In particular, TMJ dysfunction/instability may be conservatively managed by orofacial myofunctional therapy [de Felício et al., 2010]. Neck pain is successfully treated with therapeutic exercises [Pangarkar and Lee, 2011], spinal manipulation with better results than mobilization [Vernon and Humphreys, 2008] and traction. Although, any trial is not available investigating the effects of traction by an evidenced-based approach, isolated observations suggest effective applications of this technique for treating syringomyelia and basilar invagination [Joseph and Rajshekhar, 2003]. While basilar invagination seems rare in EDS except in forms with markedly reduced bone mass (e.g., EDS kyphoscoliotic, EDS/osteogenesis imperfecta overlap), neck traction may be considered an adjuvant pre-treatment and/or post-treatment in case of undeferred surgical intervention [Simsek et al., 2006; Botelho et al., 2007; Peng et al., 2011], as previously demonstrated in other genetic disorders with OAAJ instability, such as Down syndrome [Taggard et al., 1999]. Chiropractic management has been reported successfully in two adult EDS patients with headache [Colloca and Polkinghorn, 2003]. Hence, chiropractic may be considered an alternative therapeutic resource in EDS, although its use should be performed with a gentle touch considering softness of tissues. Acupuncture is a further non-traditional treatment reportedly successful in selected cases of EDS patients with headache [Martin and Nelson, 2014].

TABLE V. Lifestyle Recommendations and Prevention Strategies for the Ehlers-Danlos Syndrome Patient with Focus on Headache

Recommendations
Promote regular, aerobic fitness
Promote postural and ergonomic hygiene of the spine and upper limbs
Promote daily relaxation activities
Promote early treatment of malocclusion
Avoid hard foods intake and excessive jaw movements (ice, gums, etc.)
Avoid high-impact sports/activities
Avoid excessive weight lifting/carrying
In case of orthostatic intolerance (or documented cardiovascular dysautonomia):
Promote assumption of generous isotonic liquid intake (2–2.5 L/day)
Promote assumption of high salt intake (avoided in case of arterial hypertension)
Promote use of elastic stocks (and/or abdominal binders)
Promote sleeping on a sloping surface (10–15 degree grade)
Avoid large meals (especially of refined carbohydrate)
Avoid prolonged sitting positions and prolonged recumbency
Avoid sudden head-up postural changes
Illustrate counter-maneuvers to apply in case of exacerbation of symptoms

Consolidated evidence indicates improvement of symptoms by orthosis applications in various forms of headache possibly related to gJHM. In particular, neuromuscular orthosis may be considered in NDPH [Didier et al., 2011] and headache attributed to TMJ dysfunction/instability [Cooper and Kleinberg, 2009], while palatal non-occluding splint may be successfully used for improving quality of life of migraineurs [Shevel, 2005]. Moreover, application of cervical collar results effective in >50% pediatric patients with atlantoaxial rotatory subluxation [Beier et al., 2012], a possible complication of gJHM.

Formally, surgery has a very limited application for the treatment of headache in EDS. Occasionally, headache may be associated with Chiari malformation, which is reasonably treated with surgery. Nevertheless, recent evidence indicates a very low efficacy for standard surgery of Chiari malformation in patients with hereditary connective tissue disorders due to the high risk of recurrence [Milhorat et al., 2007]. The advent of innovative techniques and accurate patients' stratification could identify, in the future, discrete applications for invasive approaches in highly selected subjects. Injections of autologous blood are a well consolidated treatment option for persistent spinal CSF leakage [Schievink, 2006]. Prolotherapy with 10% dextrose or autologous blood is a further promising approach for symptomatic TMJ instability [Refai et al., 2011; Triantafillidou et al., 2012]. Comparably with other conditions (e.g., RA and Down syndrome) with cervical spine instability due to ligamentous laxity, canonical surgery could be considered in presence of marked instability and unresponsiveness to conservative treatments. The surgical repertoire includes various approaches, comprising occipitovertebral fusion [Garrido and Sasso, 2012], C1-C2 posterior fixation (Jacobson et al., 2012) and subaxial cervical fixation [Pelton et al., 2012]. Possible applications of these or, perhaps, novel techniques could be considered in the future, after accurate neuroimaging study and repeated evidence of failure of other approaches.

Finally, in all EDS patients, spinal anesthesia should be performed with care in order to avoid the risk of postdural puncture headache [Turnbull and Shepherd, 2003], in consideration of a presumed meningeal fragility. More in general, any surgical procedure should be performed after accurate planning and considering the peculiarities of and the risks related to the underlying disorder, in order to avoid preventable complications also including headache [Burcharth and Rosenberg, 2012; Castori, 2012b].

CONCLUSIONS

The present review outlined a very fragmented picture of headache in EDSs. While practice and literature indicate a high prevalence of this feature in EDS, available data do not mirror with evidence such a clinical need. At the moment, we have a too small knowledge of the spectrum of headache disorders linked to gJHM/EDS and, consequently, of the underlying pathophysiologic mechanisms, as well as potentially efficacious treatments. Except of a limited number of preventive interventions relating to patients' lifestyle and practitioners' choices, management of headache in EDS still relies on personal experience rather than shared information. We hope that the dissection of the clinical and pathological basis of headache in EDS will become a field of future research, whose outcomes could extend beyond the group of patients with generalized HCTDs but also to individuals manifesting limited/regional features of a hereditary or acquired connective tissue dysplasia.

ACKNOWLEDGMENTS

No funding was active on this project. All authors declare that there is no conflict of interest concerning this work.

REFERENCES

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.

Ballegaard V, Thede-Schmidt-Hansen P, Svensson P, Jensen R. 2008. Are headache and temporomandibular disorders related. A blinded study. Cephalalgia 28:832–841.

Beier AD, Vachhrajani S, Bayerl SH, Aguilar CY, Lamberti-Pasculli M, Drake JM. 2012. Rotatory subluxation: Experience from the hospital for sick children. J Neurosurg Pediatr 9:144–148.

Beighton P, De Paepe A, Steinmann B, 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.

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.

Bendtsen L, Birk S, Kasch H, Aegidius K, Sørensen PS, Thomsen LL, Poulsen L, Rasmussen MJ, Kruuse C, Jensen R. 2012. Reference programme: Diagnosis and treatment of headache disorders and facial pain. Danish Headache Society, 2nd Edition. J Headache Pain 13:S1–S29.

Bennett R. 2007. Myofascial pain syndromes and their evaluation. Best Pract Res Clin Rheumatol 21:427–445.

Bogduk N. 1981. An anatomical basis for the neck-tongue syndrome. J Neurol Neurosurg Psychiatry 44:202–208.

Bohora S. 2010. Joint hypermobility syndrome and dysautonomia: Expanding spectrum of disease presentation and manifestation. Indian Pacing Electrophysiol J 10:158–161.

Botelho RV, Neto EB, Patriota GC, Daniel JW, Dumont PA, Rotta JM. 2007. Basilar invagination: Craniocervical instability treated with cervical traction and occipitocervical fixation. Case report. J Neurosurg Spine 7:444–449.

Burcharth J, Rosenberg J. 2012. Gastrointestinal surgery and related complications in patients with Ehlers-Danlos syndrome: A systematic review. Dig Surg 29:349–357.

Castori M, Camerota F, Celletti C, Danese C, Santilli V, Saraceni VM, Grammatico P. 2010. Natural history and manifestations of the hypermobility type Ehlers-Danlos syndrome: A pilot study on 21 patients. Am J Med Genet A 152A:556–564.

Castori M, Morlino S, Celletti C, Celli M, Morrone A, Colombi M, Camerota F, Grammatico P. 2012. 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 A 158A: 1:2055–2070.

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 A 161A: 1:2989–3004.

Castori M, Sperduti I, Celletti C, Camerota F, Grammatico P. 2011. Symptom and joint mobility progression in the joint hypermobility syndrome (Ehlers-Danlos syndrome, hypermobility type). Clin Exp Rheumatol 29:998–1005.

Castori M. 2012a. Ehlers-Danlos syndrome, hypermobility type: An underdiagnosed hereditary connective tissue disorder with mucocutaneous, articular, and systemic manifestations. ISRN Dermatol 2012: 751768.

Castori M. 2012b. Surgical recommendations in Ehlers-Danlos syndrome(s) need patient classification: The example of Ehlers-Danlos syndrome hypermobility type (a.k.a. joint hypermobility syndrome). Dig Surg 29: 453–455.

Chuang YM, Hwang YC, Lin CP, Liu CY. 2008. Toward a further elucidation: Role of vertebral artery hypoplasia in migraine with aura. Eur Neurol 59:148–151.

Chuman H, Trobe JD, Petty EM, Schwarze U, Pepin M, Byers PH, Deveikis JP. 2002. Spontaneous direct carotid-cavernous fistula in Ehlers-Danlos syndrome type IV: Two case reports and a review of the literature. J Neuroophthalmol 22:75–81.

Colloca CJ, Polkinghorn BS. 2003. Chiropractic management of Ehlers-Danlos syndrome: A report of two cases. J Manipulative Physiol Ther 26:448–459.

Cooper BC, Kleinberg I. 2009. Relationship of temporomandibular disorders to muscle tension-type headaches and a neuromuscular orthosis approach to treatment. Cranio 27:101–108.

De Coster PJ, Van den Berghe LI, Martens LC. 2005. Generalized joint hypermobility and temporomandibular disorders: Inherited connective tissue disease as a model with maximum expression. J Orofac Pain 19:47–57.

de Felício CM, de Oliveira MM, da Silva MA. 2010. Effects of orofacial myofunctional therapy on temporomandibular disorders. Cranio 28:249–259.

De Paepe A, Malfait F. 2012. The Ehlers-Danlos syndrome, a disorder with many faces. Clin Genet 82:1–11.

De Wandele I, Rombaut L, Leybaert L, Van de Borne P, De Backer T, Malfait F, De Paepe A, Calders P. 2014. Dysautonomia and its underlying mechanisms in the hypermobility type of Ehlers-Danlos syndrome. Semin Arthritis Rheum 44:93–100.

Di Palma F, Cronin AH. 2005. Ehlers-Danlos syndrome: Correlation with headache disorders in a young woman. J Headache Pain 6:474–475.

Didier H, Marchetti C, Borromeo G, Tullo V, D'amico D, Bussone G, Santoro F. 2011. Chronic daily headache: Suggestion for the neuromuscular oral therapy. Neurol Sci 32: ():S161–S164.

Dijkstra PU, Kropmans TJ, Stegenga B. 2002. The association between generalized joint hypermobility and temporomandibular joint disorders: A systematic review. J Dent Res 81:158–163.

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.

Eddeine HS, Dafer RM, Schneck MJ, Biller J. 2009. Bilateral subdural hematomas in an adult with osteogenesis imperfecta. J Stroke Cerebrovasc Dis 18:313–315.

Fishman RA, Dillon WP. 1993. Dural enhancement and cerebral displacement secondary to intracranial hypotension. Neurology 43:609–611.

Garrido BJ, Sasso RC. 2012. Occipitocervical fusion. Orthop Clin North Am 43:1–9.

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, Klein M, Buskila D. 1993. Joint hypermobility and fibromyalgia in schoolchildren. Ann Rheum Dis 52:494–496.

Glaros AG, Urban D, Locke J. 2007. Headache and temporomandibular disorders: Evidence for diagnostic and behavioural overlap. Cephalalgia 27:542–549.

González de la Aleja Tejera J, Porta-Etessam J. 2008. [Neck-tongue syndrome. Possible joint hypermobility as an aetiopathogenic process]. An Pediatr (Barc) 69:484–485.

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.

Grahame R. 2009. Joint hypermobility syndrome pain. Curr Pain Headache Rep 13:427–433.

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.

Gripp KW, Scott CI, Jr, Hughes HE, Wallerstein R, Nicholson L, States L, Bason LD, Kaplan P, Zderic SA, Duhaime AC, Miller F, Magnusson MR, Zackai EH. 1997. Lateral meningocele syndrome: three new patients and review of the literature. Am J Med Genet 70:229–239.

Grosveld WJ, Gilhuis HJ, Voermans NC. 2011. Spontaneous intracranial hypotension in a patient with classical type Ehlers-Danlos syndrome. Neurol India 59:633–634.

Guilleminault C, Primeau M, Chiu HY, Yuen KM, Leger D, Metlaine A. 2013. Sleep-disordered breathing in Ehlers-Danlos syndrome: A genetic model of OSA. Chest 144:1503–1511.

Hakim AJ, Sahota A. 2006. Joint hypermobility and skin elasticity: The hereditary disorders of connective tissue. Clin Dermatol 24: 521–533.

Halko GJ, Cobb R, Abeles M. 1995. Patients with type IV Ehlers-Danlos syndrome may be predisposed to atlantoaxial subluxation. J Rheumatol 22:2152–2155.

Hall T, Briffa K, Hopper D. 2008. Clinical evaluation of cervicogenic headache: A clinical perspective. J Man Manip Ther 16:73–80.

Havlik DM, Nashelsky MB. 2006. Ruptured cerebral artery aneurysm and bacterial meningitis in a man with osteogenesis imperfecta. Am J Forensic Med Pathol 27:117–120.

Headache Classification Committee of the International Headache Society. 2013. The International Classification of Headache Disorders (beta version). Classification Committee of the International Headache Society (IHS) 33:629–808.

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.

Holman AJ. 2008. Positional cervical spinal cord compression and fibromyalgia: A novel comorbidity with important diagnostic and treatment implications. J Pain 9:613–622.

Holman AJ. 2008. Positional cervical spinal cord compression and fibromyalgia: A novel comorbidity with important diagnostic and treatment implications. J Pain 9:613–622.

Jacobson ME, Khan SN, An HS. 2012. C1-C2 posterior fixation: indications, technique, and results. Orthop Clin North Am 43:11–18.

Jacome DE. 1999. Headache in Ehlers-Danlos syndrome. Cephalalgia 19:791–796.

Johnston I, Jacobson E, Besser M. 1998. The acquired Chiari malformation and syringomyelia following spinal CSF drainage: A study of incidence and management. Acta Neurochir (Wien) 140:417–427.

Joseph V, Rajshekhar V. 2003. Resolution of syringomyelia and basilar invagination after traction. Case illustration. 298.

Kahkeshani K, Ward PJ. 2012. Connection between the spinal dura mater and suboccipital musculature: evidence for the myodural bridge and a route for its dissection–A review. Clin Anat 25:415–422.

Kurian M, Solomon GD. 2013. Can elevated IGF-1 levels among patients with Ehlers-Danlos syndrome cause idiopathic intracranial hypertension. Headache 53:1666–1669.

Levine DN. 2004. The pathogenesis of syringomyelia associated with lesions at the foramen magnum: A critical review of existing theories and proposal of a new hypothesis. J Neurol Sci 220:3–21.

Loeys BL, Dietz HC, Braverman AC, Callewaert BL, De Backer J, Devereux RB, Hilhorst-Hofstee Y, Jondeau G, Faivre L, Milewicz DM, Pyeritz RE, Sponseller PD, Wordsworth P, De Paepe AM. 2010. The revised Ghent nosology for the Marfan syndrome. J Med Genet 47:476–485.

Mack KJ, Johnson JN, Rowe PC. 2010. Orthostatic intolerance and the headache patient. Semin Pediatr Neurol 17:109–116.

Malfait F, De Paepe A. 2009. Bleeding in the heritable connective tissue disorders: Mechanisms, diagnosis and treatment. Blood Rev 23:191–197.

Mamelak AN, Fishman RA, Dillon WP, Wilson CB. 1996. Spontaneous intracranial hypotension. J Neurosurg 85:192–193.

Martin VT, Neilson D. 2014. Joint hypermobility and headache: The glue that binds the two together – Part 2. Headache 54:1403–1411.

Mathers KS, Schneider M, Timko M. 2011. Occult hypermobility of the craniocervical junction: A case report and review. J Orthop Sports Phys Ther 41:444–457.

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.

Mayer K, Kennerknecht I, Steinmann B. 2013. Clinical utility gene card for: Ehlers-Danlos syndrome types I-VII and variants – update. Eur J Hum 21:doi:10.1038/ejhg.2012.162

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.

Moskovich R, Shott S, Zhang ZH. 1996. Does the cervical canal to body ratio predict spinal stenosis. Bull Hosp Jt Dis 55:61–71.

Neilson D, Martin VT. 2014. Joint Hypermobility and Headache: Understanding the Glue That Binds the Two Together - Part 1. Headache 54:1393–1402.

Nicholson RA, Buse DC, Andrasik F, Lipton RB. 2011. Nonpharmacologic treatments for migraine and tension-type headache: How to choose and when to use. Curr Treat Options Neurol 13:28–40.

Ofluoglu D, Gunduz OH, Kul-Panza E, Guven Z. 2006. Hypermobility in women with fibromyalgia syndrome. Clin Rheumatol 25:291–293.

Orrell RW, Marsden CD. 1994. The neck-tongue syndrome. J Neurol Neurosurg Psychiatry 57:348–352.

Owler BK, Halmagyi GM, Brennan J, Besser M. 2004. Syringomyelia with Chiari malformation; 3 unusual cases with implications for pathogenesis. Acta Neurochir (Wien) 146:1137–1143.

Pangarkar S, Lee PC. 2011. Conservative treatment for neck pain: Medications, physical therapy, and exercise. Phys Med Rehabil Clin N Am 22:503–520.

Pasinato F, Souza JA, Corrêa EC, Silva AM. 2011. Temporomandibular disorder and generalized joint hypermobility: Application of diagnostic criteria. Braz J Otorhinolaryngol 77:418–425.

Pelton MA, Schwartz J, Singh K. 2012. Subaxial cervical and cervicothoracic fixation techniques–indications, techniques, and outcomes. Orthop Clin North Am 43:19–28.

Peng X, Chen L, Wan Y, Zou X. 2011. Treatment of primary basilar invagination by cervical traction and posterior instrumented reduction together with occipitocervical fusion. Spine (Phila Pa 1976) 36:1528–1531.

Pratiparnawatr P, Tiamkao S, Tanapaisal C, Kanpittaya J, Jitpimolmard S. 2000. Downbeating nystagmus and postural hypotension due to basilar invagination. J Med Assoc Thai 83:1530–1534.

Rains JC, Poceta JS. 2006. Headache and sleep disorders: Review and clinical implications for headache management. Headache 46:1344–1363.

Rawlins BA, Girardi FP, Boachie-Adjei O. 1998. Rheumatoid arthritis of the cervical spine. Rheum Dis Clin North Am 24:55–65.

Refai H, Altahhan O, Elsharkawy R. 2011. The efficacy of dextrose prolotherapy for temporomandibular joint hypermobility: A preliminary prospective, randomized, double-blind, placebo-controlled clinical trial. J Oral Maxillofac Surg 69: 2962–2970.

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.

Ritelli M, Dordoni C, Venturini M, Chiarelli N, Quinzani S, Traversa M, Zoppi N, Vascellaro A, Wischmeijer A, Manfredini E, Garavelli L, Calzavara-Pinton P, Colombi M. 2013. Clinical and molecular characterization of 40 patients with classic Ehlers-Danlos syndrome: identification of 18 COL5A1 and 2 COL5A2 novel mutations. Orphanet J Rare Dis 8:58.

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 Wandele I, Thijs Y, Palmans T, De Paepe A, Calders P. 2011. Balance, gait, falls, and fear of falling in women with the hypermobility type of Ehlers-Danlos syndrome. Arthritis Care Res (Hoboken) 63:1432–1439.

Rombaut L, Scheper M, De Wandele I, De Vries J, Meeus M, Malfait F, Engelbert R, Calders P. 2014. Chronic pain in patients with the hypermobility type of Ehlers-Danlos syndrome: Evidence for generalized hyperalgesia. Clin Rheumatol (in press) .

Rozen TD, Roth JM, Denenberg N. 2006. Cervical spine joint hypermobility: A possible predisposing factor for new daily persistent headache. Cephalalgia 26:1182–1185.

Rozen TD. 2011. New daily persistent headache: Clinical perspective. Headache. 51: 641–649.

Sacheti A, Szemere J, Bernstein B, Tafas T, Schechter N, Tsipouras P. 1997. Chronic pain is a manifestation of the Ehlers-Danlos syndrome. J Pain Symptom Manage 14: 88–93.

Sahin N, Karata□ O, Ozkaya M, Cakmak A, Berker E. 2008. Demographics features, clinical findings and functional status in a group of subjects with cervical myofascial pain syndrome. Agri 20:14–19.

Schievink WI, Gordon OK, Tourje J. 2004. Connective tissue disorders with spontaneous spinal cerebrospinal fluid leaks and intracranial hypotension: A prospective study. Neurosurgery 54:65–70.

Schievink WI, Meyer FB, Atkinson JL, Mokri B. 1996. Spontaneous spinal cerebrospinal fluid leaks and intracranial hypotension. J Neurosurg 84:598–605.

Schrijver I, Schievink WI, Godfrey M, Meyer FB, Francke U. 2002. Spontaneous spinal cerebrospinal fluid leaks and minor skeletal features of Marfan syndrome: A microfibrillopathy. J Neurosurg 96:483–489.

Sendur OF, Gurer G, Bozbas GT. 2007. The frequency of hypermobility and its relationship with clinical findings of fibromyalgia patients. Clin Rheumatol 26:485–487.

Sharma P, Sharma A, Chacko AG. 2001. Syringomyelia in spontaneous intracranial hypotension. Case report. J Neurosurg 95:905–908.

Shevel E. 2005. Craniomandibular muscles, intraoral orthoses and migraine. Expert Rev Neurother 5:371–377.

Simsek S, Yigitkanli K, Belen D, Bavbek M. 2006. Halo traction in basilar invagination: Technical case report. Surg Neurol 66:311–314.

Sjaastad O, Bakketeig LS. 2006. Neck-tongue syndrome and related (?) conditions. Cephalalgia 26:233–240.

Sjaastad O, Fredriksen TA, Pfaffenrath V. 1998. Cervicogenic headache: Diagnostic criteria. The Cervicogenic Headache International Study Group. Headache 38:442–445.

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: Wiley-Liss pp. 431–524.

Taggard DA, Menezes AH, Ryken TC. 1999. Instability of the craniovertebral junction and treatment outcomes in patients with Down's syndrome. Neurosurg Focus 6:e3.

Tanaka T, Hayakawa M, Sadato A, Adachi K, Watabe T, Maeda S, Ohmura M, Hirose Y. 2014. Transvenous embolization for carotid-cavernous fistula in a patient with vascular type of Ehlers-Danlos syndrome–direct superior ophthalmic vein approach: Case report. Neurol Med Chir (Tokyo) 54: 155–60.

Tinkle BT, Bird HA, Grahame R, Lavallee 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 A 149A:2368–2370.

Tinkle BT., 2010. *Joint hypermobility handbook – a guide for the issues & management of Ehlers-Danlos syndrome hypermobility type and the hypermobility syndrome.* Greens Fork: Left Paw Press.

Triantafillidou K, Venetis G, Markos A. 2012. Short-term results of autologous blood injection for treatment of habitual TMJ luxation. J Craniofac Surg 23:689–692.

Turnbull DK, Shepherd DB. 2003. Post-dural puncture headache: Pathogenesis, prevention and treatment. Br J Anaesth 91: 718–29.

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.

Vernon H, Humphreys BK. 2008. Chronic mechanical neck pain in adults treated by manual therapy: a systematic review of change scores in randomized controlled trials of a single session. J Man Manip Ther 16:E42–E52.

Voermans NC, Dijk KG, Bos MM, Geus-Oei LF, Verrips A, Lindert EJ. 2009. Postural headache in Marfan syndrome associated with spinal cysts and liquor hypotension. Neuropediatrics 40:201–204.

Voermans NC, Knoop H, Bleijenberg G, van Engelen BG. 2010a. Pain in ehlers-danlos syndrome is common, severe, and associated with functional impairment. J Pain Symptom Manage 40:370–378.

Voermans NC, Knoop H, van de Kamp N, Hamel BC, Bleijenberg G, van Engelen BG. 2010b. Fatigue is a frequent and clinically relevant problem in Ehlers-Danlos Syndrome. Semin Arthritis Rheum 40:267–274.

Voermans NC, Knoop H. 2011. Both pain and fatigue are important possible determinants of disability in patients with the Ehlers-Danlos syndrome hypermobility type. Disabil Rehabil 33:706–707.

Wasserman BR, Moskovich R, Razi AE. 2011. Rheumatoid arthritis of the cervical spine–clinical considerations. Bull NYU Hosp Jt Dis 69:136–148.

Williams B. 1981. Chronic herniation of the hindbrain. Ann R Coll Surg Engl 63: 9–17.

Yazici M, Ataoglu S, Makarc S, Sari I, Erbilen E, Albayrak S, Yazici S, Uyan C. 2004. The relationship between echocardiographic features of mitral valve and elastic properties of aortic wall and Beighton hypermobility score in patients with mitral valve prolapse. Jpn Heart J 45:447–460.