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.

© 2015 Wiley Periodicals, Inc.

KEY WORDS: cervical spine; connective tissue; ligamentous laxity; meninges; occipitotlandoaxial; 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, occipitotlandoaxial joint; TMJ, temporomandibular joint; vEDS, vascular Ehlers–Danlos syndrome.


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, neurodegenerative 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).
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 \( \sim 1/5,000 \) [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 \( \sim 1\% \) [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 [Hermans-Lé 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 terms 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 EDS 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 gHM/EDS and specific subsets of primary and secondary types of headache, including new daily persistent headache (NDPH) [Rozen 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 [Havlík 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 H2O). 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 gHM 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
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

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.
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 [Pasino 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 para-vertebral muscles involvement [Bennett, 2007]. In the presence of gHM, 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 gHM/EDS is still a matter of debate. An early literature review of 14 previous works concluded that a clear association between gHM 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 [Pasino 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 gHM, 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 gHM 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 gHM 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 [Kakhkeshani 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 Bright 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-morbidity 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 osteoarthritides [Dolan et al., 2003]. In contrast to limb joints for which causal correlation between gJHM and precarious 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 lumentous 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 cranio-cervical 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
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 unstable 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 may fail to demonstrate significant changes. This implies a general underestimation of cervical spine pathologies. 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; Voernmans 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; Pratiparnawat 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.

### Table 1. EDSs and JHS Ancillary Features Which May Be Influenced by an Underlying Cervical Spine Pathology

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

Hand interosseous muscles hypotrophy

Minor memory and concentration disturbances

Unexplained ocular/visual and auditory disturbances (e.g., tinnitus, diplopia)

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

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; Voernmans 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 dis-
painful manifestations is crucial for drug medical use for headache and other 

Martin and Neil- 

overuse may be frequently reported in 

Castori et al., 2012], pain-killer drugs 

Castori et al., 2012], and its usual 

Nasal resistance [Guillemainault et al., 2013]. 

The third edition of the Interna- 

assessing headache with specific entries for simple alcoholic, opioid and combined alcoholic 

Rains and Poceta, 2006], 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 [Guillemainault et al., 2013]. 

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, chronicification, 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 out carefully following specific “red flags”, whose adherence may be useful

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

Consolidated evidence indicates improvement of symptoms by orthosis applications in various forms of headache possibly related to gHM. 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 gHM.

Formally, surgery has a very limited application for the treatment of headache in EDS. Occasionally, headache may be associated with Chiari

<table>
<thead>
<tr>
<th>TABLE IV. Red Flags in Treating Headache in the Ehlers-Danlos Syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red flag</td>
</tr>
<tr>
<td>Classify accurately (co-) existent headache disorder(s)</td>
</tr>
<tr>
<td>Support symptomatic classification by searching organic triggers, as proposed in Table II</td>
</tr>
<tr>
<td>Promote an integrated approach by using simultaneously multiple therapeutic resources</td>
</tr>
<tr>
<td>Postpone the use of drugs with presumed higher rate of side effects in Ehlers–Danlos syndrome*</td>
</tr>
<tr>
<td>Consider first physical therapy and conservative approaches</td>
</tr>
<tr>
<td>Promote adhesion to general lifestyle recommendations, as proposed in Table V</td>
</tr>
<tr>
<td>*Including acetilsalicylic acid, myorelaxants, corticosteroids (chronic treatments), opioids and anti-epileptics.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE V. Lifestyle Recommendations and Prevention Strategies for the Ehlers-Danlos Syndrome Patient with Focus on Headache</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendations</td>
</tr>
<tr>
<td>Promote regular, aerobic fitness</td>
</tr>
<tr>
<td>Promote postural and ergonomic hygiene of the spine and upper limbs</td>
</tr>
<tr>
<td>Promote daily relaxation activities</td>
</tr>
<tr>
<td>Promote early treatment of malocclusion</td>
</tr>
<tr>
<td>Avoid hard foods intake and excessive jaw movements (ice, gums, etc.)</td>
</tr>
<tr>
<td>Avoid high-impact sports/activities</td>
</tr>
<tr>
<td>Avoid excessive weight lifting/carrying</td>
</tr>
<tr>
<td>In case of orthostatic intolerance (or documented cardiovascular dysautonomia):</td>
</tr>
<tr>
<td>Promote assumption of generous isotonic liquid intake (2–2.5 L/day)</td>
</tr>
<tr>
<td>Promote assumption of high salt intake (avoided in case of arterial hypertension)</td>
</tr>
<tr>
<td>Promote use of elastic stocks (and/or abdominal binders)</td>
</tr>
<tr>
<td>Promote sleeping on a sloping surface (10–15 degree grade)</td>
</tr>
<tr>
<td>Avoid large meals (especially of refined carbohydrate)</td>
</tr>
<tr>
<td>Avoid prolonged sitting positions and prolonged recumbency</td>
</tr>
<tr>
<td>Avoid sudden head-up postural changes</td>
</tr>
<tr>
<td>Illustrate counter-maneuvers to apply in case of exacerbation of symptoms</td>
</tr>
</tbody>
</table>
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]. Proltherapy 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 [Burchard 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 gHMD/EDS and, consequently, of the underlying pathophysiological 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


Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delmas PL, Delma...


