

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

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Joint hypermobility syndrome (JHS), or Ehlers–Danlos syndrome (EDS) hypermobility type (EDS-HT), is a underdiagnosed heritable connective tissue disorder characterized by generalized joint hypermobility and a wide range of visceral, pelvic, neurologic, and cognitive dysfunctions. Deterioration of quality of life is mainly associated with pain and fatigue. Except for the recognized effectiveness of physiotherapy for some musculoskeletal features, there are no standardized guidelines for the assessment and treatment of pain and fatigue. In this work, a practical classification of pain presentations and factors contributing in generating painful sensations in JHS/EDS-HT is proposed. Pain can be topographically classified in articular limb (acute/subacute and chronic), muscular limb (myofascial and fibromyalgia), neuropathic limb, back/neck, abdominal and pelvic pain, and headache. For selected forms of pain, specific predisposing characteristics are outlined. Fatigue appears as the result of multiple factors, including muscle weakness, respiratory insufficiency, unrefreshing sleep, dysautonomia, intestinal malabsorption, reactive depression/anxiety, and excessive use of analgesics. A set of lifestyle recommendations to instruct patients as well as specific investigations aimed at characterizing pain and fatigue are identified. Available treatment options are discussed in the set of a structured multidisciplinary approach based on reliable outcome tools. © 2012 Wiley Periodicals, Inc.

Key words: disability; Ehlers–Danlos syndrome; joint hypermobility; multidisciplinary; physical therapy; treatment

INTRODUCTION

Joint hypermobility (JHM) refers to a condition in which one or more synovial joints move beyond the normal limits [Keer and Grahame, 2003]. It is a common, heritable trait being observed in

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up to 10–30% of males and 20–40% of females [Hakim and Grahame, 2003]. Appreciation of JHM is also influenced by many variables, including patient's age, ethnicity, past physical activity/fitness habits, and traumas, as well as familiarity of the observer with joint mobility evaluation. Specific maneuvers, such as Beighton score calculation [Beighton et al., 1973], are easy tools for assessing generalized JHM. However, many acquired factors may progressively limit the motion of congenitally lax joints. Consequently, JHM may go unnoticed in hypermobile individuals who have lost their “doublejointness” but still manifest a wide range of associated symptoms [Castori et al., 2011a].

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Generalized JHM is considered the physical marker of various heritable connective tissue disorders (hCTDs) recognized by additional somatic/visceral structural abnormalities. On the contrary, apparently “isolated” JHM is usually supposed irrelevant by the unexperienced practitioner or, perhaps, useful only in preoperative orthopedic evaluation and planning [Moriatis et al., 2011]. However, a growing number of musculoskeletal, visceral, and cognitive dysfunctions, such as dysautonomia, functional bowel disease, and fibromyalgia, have been described in association with generalized JHM outside a well-defined hCTD [Castori et al., 2011b]. This picture is defined joint hypermobility syndrome (JHS) [Grahame et al., 2000], which is now considered one and the same with the Ehlers–Danlos syndrome (EDS) hypermobility type (EDS-HT) by an international panel of experts [Tinkle et al., 2009]. However, such homogeneity between JHS and EDS-HT is still debated and only future molecular studies will solve the conundrum.

Due to the intrinsic difficulties in assessing JHS/EDS-HT, delayed diagnosis might result in excessive financial and time expense, superfluous investigations, wrong therapies, delay of appropriate treatments, and preventable worsening of the disease state [Kole and Faurisson, 2009]. After diagnosis achievement, JHS/EDS-HT patients still show marked disability mainly linked to pain and fatigue [Voermans and Knoop, 2011]. Nevertheless, besides the general acceptance of physiotherapy as an efficient treatment for some musculoskeletal complications of JHM [Keer and Simmonds, 2011], pathophysiology and manifestations of pain and fatigue are still largely obscure in JHS/EDS-HT. This gap has dramatic consequences on the long-term efficacy of available treatment options.

AIM AND METHODS

This work is aimed to systematize what actually is known concerning pain and fatigue in JHS/EDS-HT and to merge these relatively well-consolidated concepts with practice by illustrating our experience. Firstly, a PubMed search with the terms “hypermobility” combined with either “pain”, “fatigue”, or “dysautonomia” was carried out. Further papers were extracted from the bibliography of identified references. This assessment was preceded by a survey on disability and quality of life (QoL) of JHS/EDS-HT in order to integrate the following considerations within a wider picture reflecting the widespread derangement of homeostatic mechanisms in JHS/EDS-HT. After systematic presentation of what previously known on manifestations and treatments for pain and fatigue, we report our personal experience on assessment procedures for pain and fatigue and a proposal for a multidisciplinary approach for evaluating and, hopefully, more successfully treating patients with JHS/EDS-HT.

QUALITY OF LIFE AND DISABILITY

In medicine, QoL is a generally accepted term which evaluates the well-being of individuals affected by chronic, disabling conditions. QoL is generally poor in adults [Castori et al., 2010a; Rombaut et al., 2010] and children [Fatoye et al., 2012] with JHS/EDS-HT. In this condition, deterioration of QoL is likely linked to the degree of disability [Rombaut et al., 2010]. Disability, in turn, represents the

major factor impacting well-being and the needs of the affected individuals. This is in contrast with other hCTDs with significant cardiovascular involvement, in which sudden death represents the major burden. Deterioration of QoL is an emerging problem in JHS/EDS-HT, as this variant may be considered the most debilitating form of EDS [Rombaut et al., 2010]. Disability in JHS/EDS-HT includes both (i) physical impairment, and (ii) symptoms of central nervous system (CNS) fatigue (the “so-called” neuroasthenia). The latter is generally considered a mixture of symptoms, mainly fatigue, pain, and anxiety, related to exhaustion of CNS’s reserves. Both are linked, at different levels, to the complex, still largely uncharacterized pathophysiology of JHS/EDS-HT [Castori et al., 2011b].

A recent study shows comparable degree of disability of the lower limbs in JHS/EDS-HT and osteoarthritis patients, but this is observed 10 years earlier in the former group [Celletti et al., 2011a]. This may significantly impact healthcare in light of the presumed 0.75–2% prevalence of JHS/EDS-HT in the general population [Hakim and Sahota, 2006]. It also reflects early biomechanic dysfunctions affecting gait and posture [Mebes et al., 2008; Galli et al., 2011; Rombaut et al., 2011a]. Decreased proprioceptive functions and JHM are likely the major contributors of these dysfunctions as they associate with an abnormal pattern of muscle activation in both static and dynamic exercises [Greenwood et al., 2011]. On the other hand, recent literature highlights that chronic pain and fatigue are major features of various forms of EDS, in particular JHS/EDS-HT [Voermans et al., 2010a, 2010b], and that both contribute to disability [Voermans and Knoop, 2011]. Among the different forms of pain in JHS/EDS-HT, migraine seems particularly disabling [Bendik et al., 2011].

Such a dichotomy between physical impairment and CNS fatigue does not completely hold true in JHS/EDS-HT. This is demonstrated by the direct correlation between lower limb and foot disability and overall pain intensity [Berglund et al., 2005; Celletti et al., 2011a]. Such evidence suggests an unexpectedly tight link between biomechanic dysfunctions, which are peripheral in origin (i.e., lack of proprioception and joint laxity), and chronic pain and fatigue, which are, at least in part, consequences of CNS fatigue, in JHS/EDS-HT. *Kinesiophobia*, as a specific maladaptive cognition commonly acting in various disorders with chronic musculoskeletal pain, well represents the clinical counterpart of this assumption. In fact, it defines the fear of movements in patients affected by a chronic pain syndrome, which aggravates during physical activity [Vlaeyen and Linton, 2000]. This attitude, so commonly reported in JHS/EDS-HT [Grahame, 2009], amplifies muscular deconditioning, which in turn catastrophises physical impairment and general exhaustion.

In JHS/EDS-HT, disability is also strongly influenced by psychological factors as the result of inadequate adaptation to the physical and social consequences of the disease (i.e., distress). Anxiety, depression, and other features of CNS fatigue may be interpreted as the consequences of a complex chronic pain syndrome inadequately managed by available therapy [Lumley et al., 1994; Baeza-Velasco et al., 2011]. A further element of distress is the lack of recognition and knowledge of the disease by the various practitioners that have evaluated affected individuals before diagnosis establishment [Baeza-Velasco et al., 2011]. This

elicits patients' perception that their dignity is not fully upheld in healthcare environment [Berglund et al., 2010]. Sense of stigmatization and limitation of the possibility of self-actualization in daily living and social life are likely generated and induce the sensation of living "a restricted life" in the affected individuals [Berglund et al., 2000].

In JHS/EDS-HT, disability is multidimensional. At least five main determinants, including physical impairment, chronic pain, fatigue, maladaptive cognitions (i.e., *kinesiophobia*) and psychologic distress, are identified for such a deterioration of QoL. The present work is focused in reviewing two of them (i.e., pain and fatigue), while future studies are expected to systematize the remaining.

CLINICAL FEATURES OF PAIN

Pain is an unpleasant sensation often caused by an intense or damaging stimulus which leads to withdraw from the pain trigger, to protect the damaged body part and to avoid behaviors/situations generating similar experiences in the future. Classically, pain is distinguished in "nociceptive/inflammatory" pain, which is a physiologic sensation generated by damaged tissues and elicitation of pain receptors, and "neuropathic/neurogenic" pain, which is inherently pathologic and directly related to an injury of components of the nervous system (either peripheral or central) involved in pain stimuli transmission and/or modulation. A further subtype of pain is the "dysfunctional" pain, which refers to poorly localized forms of "organic" pain, such as fibromyalgia, headache, and irritable bowel disease. It is possibly related to an abnormal and intense enhancement of pain generated from external and visceral stimuli by CNS mechanisms (i.e., central sensitization) [Yunus, 2007]. Whether "dysfunctional" and typical "neuropathic" pains can be grouped together or not is still debated [Scadding, 2003].

Chronic/recurrent pain is extremely common in JHS/EDS-HT [Sacheti et al., 1997]. It is associated with regular analgesic use, JHM, dislocations and previous surgery, and related to functional impairment independently from fatigue [Voermans et al., 2010a]. Pain is included in the Villefranche criteria for EDS-HT [Beighton et al., 1998] and Brighton criteria for JHS [Grahame et al., 2000] as a minor and major item, respectively. Although mainly considered musculoskeletal in origin and primarily linked to repeated/chronic joint damage, recent evidence strongly indicates a wider spectrum of pain features in JHS/EDS-HT to include all pain types described above. For this reason, JHS/EDS-HT may be considered a prototype of mixed chronic pain syndrome, for which the identification of more effective pain-relief strategies could lead to generalizations relevant for a wider spectrum of chronic painful disorders (Table I).

Inflammatory/Nociceptive Limb Pain

Limb pain is the best known pain in JHS/EDS-HT. Accordingly, joint/limb pain is the sole subtype included in the Villefranche criteria [Beighton et al., 1998]. Recurrent and chronic arthralgias are considered the most common manifestations of limb pain in JHS [Grahame et al., 2000]. Most JHS/EDS-HT patients first complain of acute arthralgias recurring mainly at shoulders, knees, and hands [Sacheti et al., 1997]. Foot pain is an additional strongly debilitating pain likely arising from multiple joints dysfunction

[Berglund et al., 2005]. Acute arthralgias are likely the result of soft-tissue rheumatism [Hudson et al., 1998] and dislocations [Voermans et al., 2009], both facilitated by laxity of capsules, ligaments, and tendons as well as delayed repair process. Subsequently, recurring arthralgias become fixed (i.e., chronic) with unpredictable episodes of intensification. Mechanisms underlying chronic arthralgias in JHS/EDS-HT are still obscure. In the past, precocious osteoarthritis was considered a late complication of JHM, but more recent studies raise the question whether JHM is a predisposing or protective factor for osteoarthritis [Dolan et al., 2003]. Theoretically, the lower bone mass frequently reported in young adults and adults with JHS/EDS-HT [Gulbahar et al., 2006] may delay the repair of fractures with various consequences including pain amplification.

Skeletal muscle pain (i.e., myalgias) with or without muscle cramps [Castori et al., 2011a] is a further form of limb pain frequently reported in various forms of EDS, such as JHS/EDS-HT [Voermans et al., 2009]. Specific forms of localized and generalized pain of muscle origin are or are likely to be reported in JHS/EDS-HT. In particular, myofascial pain is described as a common unilateral manifestation of temporomandibular joint dysfunction in 31 patients [De Coster et al., 2005]. In theory, myofascial pain should be a relatively common form of muscle pain in JHS/EDS-HT and it could affect various body areas. In line with this, Sahin et al. [2008] find JHS in ~18% patients with cervical myofascial pain. Relationship between JHM/JHS/EDS-HT and fibromyalgia is well known since early '90s [Goldman, 1991]. Accordingly, a strong association was subsequently demonstrated in females [Oflooglu et al., 2006; Sendur et al., 2007] and schoolchildren [Gedalia et al., 1993]. Though not involving limbs, back pain (localized or generalized) is a further common manifestation of musculoskeletal pain in JHS/EDS-HT [Simmonds and Keer, 2008; Castori et al., 2011a].

Neuropathic Limb Pain

In addition to arthralgias/myalgias, JHS/EDS-HT limb pain may also reflect a peripheral neuropathic component, as recently suspected in >60% patients [Camerota et al., 2011]. This preliminary observation may be the clinical counterpart of the increased rate of compressive neuropathy and axonal polyneuropathy in EDS [Voermans et al., 2011a]. Recurrent limb paresthesias, frequently reported in adults with JHS/EDS-HT [Castori et al., 2011a], may be a clue for primary nerve involvement. Complex regional pain syndrome, either type I or II, may be a rare complication of JHS/EDS-HT, as reported in single patients [Stoler and Oaklander, 2006]. It is postulated that, in EDSs, complex regional pain syndrome may be caused by stretch injuries as a result of proneness to joint dislocations, excessive exposure to medical procedures, and/or primary abnormalities of the connective tissue surrounding nerves. However, the subjective descriptions of limb/generalized pain offered by JHS/EDS-HT adults is only in part explained by typical arthralgias/myalgias and peripheral neuropathic pain. In the future, the role of the "co-called" dysfunctional pain and, perhaps, the mechanisms underlying central sensitization should be investigated in order to better assessing patients with JHS/EDS-HT [Reply to Voermans and Knoop, 2011].

TABLE I. Forms of Pain and Management Options

Presentation	Possible triggers/causes	Possible prevention strategies	First line treatments	Treatments with possible disease-related side effects
Limb pain, articular (acute/subacute)	Limb joint instability Trauma amplification due to lax tissues	Aerobic fitness Avoiding high impact sports/activities Strengthening exercises	Active rest Conservative joint stabilization Cold applications Paracetamol Paracetamol	NSAIDs ^a Corticosteroids (oral) ^b
Limb pain, articular (chronic)	Excessive mechanical joint stress	Aerobic fitness Avoiding high impact sports/activities Weight control (BMI <25) Ergonomic and postural hygiene Strengthening exercises Avoiding cold	COXIBs ^c Stretching exercises	NSAIDs ^a Corticosteroids (oral/injections) ^b Opioids ^d Hyaluronic acid injections ^e Surgery ^f NSAIDs ^a
Limb pain, muscular localized (myofascial pain)	Proneness to muscle injury/sprains	Stretching exercises Ergonomic and postural hygiene	Manipulation Paracetamol	Myorelaxants ^g Amytriptyline and other tricyclic antidepressants ^h Trigger-point injections ^e
Limb pain, muscular generalized (fibromyalgia)	?	Aerobic fitness Balneo- and spa therapy Vegetarian diet ^l	Duloxetine and other SSRI/SNRI Psychologic therapy ^j Duloxetine and other SSRI/SNRI	Opioids ^d Myorelaxants ^g
Limb pain, neuropathic	Proneness to nerve entrapment Proneness to disk hernia formation Trauma amplification due to lax tissues Axonal neuropathy	Ergonomic and postural hygiene	Balneo- and spa therapy Whole body heat-therapy Mindfulness meditation Homeopathy Physical therapy Psychologic therapy ^j Duloxetine and other SSRI/SNRI Calcitonin ^m Biphosphonates ^m Spinal cord stimulation ^m Mirror visual feedback ^m Hand laterality recognition ^m Movement imagination ^m	Amytriptyline and other tricyclic antidepressants ^h Pregabalin/gabapentin ^k Corticosteroids (oral) ^d Amytriptyline and other tricyclic antidepressants ^h Pregabalin/gabapentin ^k Surgery ^f Spinal cord drug injection ^{e,m}

(Continued)

TABLE 1. (Continued)

Presentation	Possible triggers/causes	Possible prevention strategies	First line treatments	Treatments with possible disease-related side effects
Back/neck pain	Spine hypermobility	Avoiding cold Weight control (BMI <25) Aerobic fitness Stretching exercises Avoiding excessive weight lifting/carrying Back school Ergonomic and postural hygiene	Stretching exercises Manipulation Back school Paracetamol Duloxetine and other SSRI/SNRI Acupuncture	NSAIDs ^a Opioids ^d Myorelaxants ^g Amytriptyline and other tricyclic antidepressants ^h
Headache	Cervical spine instability Temporomandibular joint dysfunction Intracranial hypotension	Generous isotonic liquid intake Neck strengthening exercises Avoiding hard foods and excessive jaw movements (gums/ice) Avoiding alcohol intake Early treatment of malocclusion	Generous isotonic liquid intake Temporomandibular joint rehabilitation Paracetamol Caffein Duloxetine and other SSRI/SNRI Cognitive behavioral therapy	NSAIDs ^a Amytriptyline and other tricyclic antidepressants ^h Pregabalin/gabapentin ^k Ergotamin (oral/intra-rectal) ⁿ
Abdominal pain	Bowel dysfunction	Dietary and pharmacologic treatment of concomitant constipation/diarrhea General relaxation	Duloxetine and other SSRI/SNRI Anti-muscarinic drugs Stretching exercises	Amytriptyline and other tricyclic antidepressants ^h Surgery (e.g., dolico-colon) ^f
Pelvic pain, visceral	Bladder dysfunction Rectal dysfunction Organ prolapses	Avoiding bladder irritant foods (e.g., coffee and citrus products) Avoiding tight-fitting clothing Dietary and pharmacologic treatment of concomitant constipation/diarrhea General relaxation	Manipulation Duloxetine and other SSRI/SNRI Anti-histaminic drugs (cimetidine, hydroxyzine) Pentosan polysulfate Neurostimulation Cyclosporine A Pelvic massage	Amytriptyline and other tricyclic antidepressants ^h Intravesical drug injections ^e Cystoscopy ^o Intraderstrusor botulinum toxin injections ^o Surgery ^f
Pelvic pain, vulvodinia/dyspareunia/	Endometriosis	Lubrication during sexual intercourse		NSAIDs (endometriosis) ^a (Continued)

TABLE 1. (Continued)

Presentation	Possible triggers/causes	Possible prevention strategies	First line treatments	Treatments with possible disease-related side effects
dysmenorrhea	Dry/atrophic vaginal mucosa	General relaxation	Topical estrogen/lidocaine	Amytriptyline and other tricyclic antidepressants ^h
Pelvic pain, musculoskeletal/neuropathic	Pelvic ring hypermobility Coccygeal joint dysfunction Trauma amplification due to lax tissues (compression)	Aerobic fitness Avoiding prolonged sitting positions Weight control (BMI <25) Ergonomic and postural hygiene	Cognitive behavioral therapy Duloxetine and other SSRI/SNRI Neuromodulation Mechanical dilators Paracetamol (endometriosis) Hormonal therapy (endometriosis)	Pregabalin/gabapentin ^k Botulinum toxin injections ^o Local anesthetic and steroid injections ^{b,e} Cryoneurolysis ^o Surgery (endometriosis) ^o
			Stretching exercises Manipulation Trunk stabilization Neural mobilization Neuromodulation Duloxetine and other SSRI/SNRI Radiofrequency therapy	Amytriptyline and other tricyclic antidepressants ^h Pregabalin/gabapentin ⁱ Surgery ^f Local anesthetic and steroid injections ^{b,e} Cryoneurolysis ^o

Note: Treatment options are distinguished between those with possible contraindications in JHS/EDS-HT patients and those without. This distinction was performed essentially based on JHS/EDS-HT specific features, such as recurrent gastritis, joint instability, dysautonomia, and osteopenia/osteoporosis, which could amplify specific side-effects.

^aFor NSAIDs, always consider gastroprotection due to the increased rate of gastritis in JHS/EDS-HT.

^bUse with care due to the increased rate of osteopenia/porosis and striae distensae in JHS/EDS-HT.

^cConsider the risk of myocardial infarction associated with chronic use of COXIBs.

^dUse with care due to the risk of worsening constipation, a feature common in JHS/EDS-HT.

^ePotentially useful, but no information available on the effects of repeated injections in constitutionally lax tissues.

^fUsually ineffective due to the extremely high risk of recurrence of joint instability/nerve entrapment/organ dysfunction.

^gUse with care due to the risk of generalized joint instability/amplification.

^hUse with care due to the risk of weight gain, cognitive impairment and urinary retention, all potentially harmful/more common in JHS.

ⁱIncluding cognitive behavioral therapy, hypnotherapy/guided imagery, patient-centered communication, and written emotional disclosure.

^jConsider with caution due to the possible side effects of a restricted diet in JHS/EDS-HT (e.g., insufficient calcium and vitamin D assumption related to disease-specific proneness to osteopenia/porosis).

^kManage with care due to the risk of amplifying dysautonomic symptoms.

^lIncluding cognitive behavioral therapy, graded exposure training, and disease education.

^mIn case of complex regional pain syndromes only.

ⁿNot indicated in pregnant women and in presence of systemic hypertension; use with care due to the risk of amplifying dysautonomic symptoms.

^oInvasive techniques should be considered with caution in patients with heritable connective tissue disorders.

Headache

Jacome [1999] first described headache as a possible neurologic presentation of EDS. In the originally reported nine patients, clinical forms of headaches include migraine with aura, migraine without aura, tension headache, a combination of tension headache and migraine, and post-traumatic headache. This finding was repeatedly confirmed [Rombaut et al., 2010; Castori et al., 2011a]. Among the various forms of headache, migraine is considered a common presentation of head pain in JHS/EDS-HT with a marked disability potential [Bendik et al., 2011]. New daily persistent headache may be an additional, prevalent form of headache in JHS/EDS-HT. In fact, cervical spine hypermobility is considered a common predisposing factor for this form of headache [Rozen et al., 2006]. Furthermore, instability at the occipitoatlantoaxial junction may present as a Chiari malformation type I in various hCTDs, including JHS/EDS-HT [Jacome, 1999; Milhorat et al., 2007; Castori et al., 2010b]. Temporomandibular joint dysfunction is an additional predisposing factor to multiple forms of craniofacial pain in JHS/EDS-HT [De Coster et al., 2005]. Finally, intra-

cranial hypotension might be a further mechanism of headache in hCTDs. This may result from dysautonomia and/or spontaneous spinal cerebrospinal fluid leaks likely due to increased fragility of the meninges [Schievink, 2006], with or without formation of dilations (i.e., dural ectasia and cysts) evident at spine magnetic resonance imaging (Fig. 1).

Abdominal/Pelvic Pain

Unexplained and unpredictable abdominal pain is extremely common in JHS/EDS-HT, as it may be reported in up to 86% of cases [Hakim and Grahame, 2004; Castori et al., 2010b, 2011a; Zarate et al., 2010]. It is frequently associated with functional gastrointestinal symptoms such as bloating, reflux, heartburns, nausea, vomiting, diarrhea, and constipation. Accordingly, the association between JHM/JHS/EDS-HT and functional gastrointestinal disorders is a well-consolidated concept [Zarate et al., 2010]. The pathophysiologic mechanism leading to such a severe involvement of the gut is still unknown. A few reports demonstrate a higher

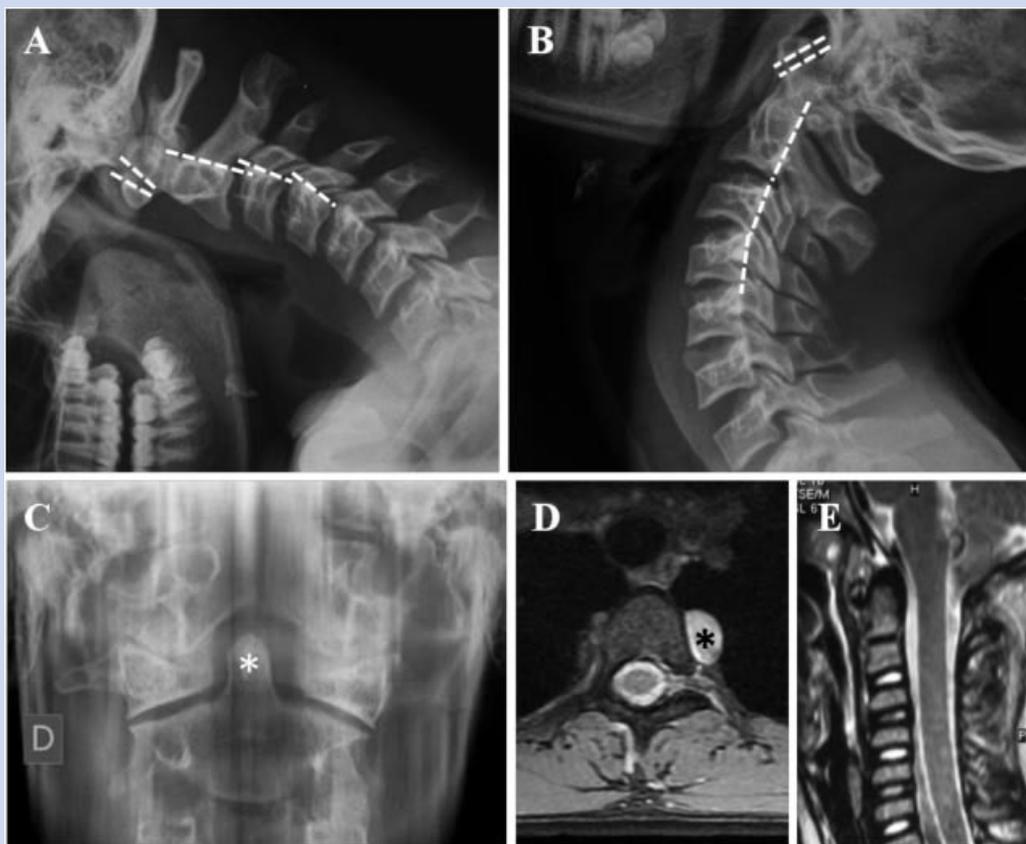


FIG. 1. Radiologic findings related to headache in JHS/EDS-HT. Latero-lateral view of neck spine X-rays in flexed (A) and extended (B) positions in a 16-year-old boy. Instability of cervical vertebrae is more evident on flexion with antero-listhesis of C2 and, in a minor extent, C3. On flexion, the odontoid process of C2 is more distant from the anterior arch of C1 with possible (intermittent) compression on the brainstem (dot lines). X-ray stratigraphy of the occipitoatlantoaxial junction showing right deviation of the odontoid process (white asterisk) at rest in a 24-year-old boy (C). A large meningeal cyst (black asterisk) of the thoracic spine on T2-weighted MRI in a 25-year-old woman (D). Arnold–Chiari malformation type I in a 11-year-old boy (E).

rate of hiatus hernia [Al-Rawi et al., 2004], Crohn's disease [Vounotrypidis et al., 2009], slow transit constipation [de Kort et al., 2003; Manning et al., 2003; Reilly et al., 2008], and rectal evacuatory dysfunction [Mohammed et al., 2010] in JHS/EDS-HT. However, taken together, all these abnormalities do not explain the entire spectrum of abdominal features in JHS/EDS-HT.

Pelvis is a further common site of pain complaints in JHS/EDS-HT. Research in this field is extremely limited, but clinical evidence indicates this structure as extremely prone to multiple dysfunctions in JHS/EDS-HT. Rectal, genital and bladder prolapses [Lammers et al., 2012] are possible, commonly encountered sources of pain/discomfort. Accordingly, multiple/severe pelvic prolapse(s) in a nulliparous woman is a possible presentation of JHS/EDS-HT [Castori et al., 2010b]. Pelvic prolapses may cause pain/discomfort also due to specific complications such as constipation and recurrent urinary infections [de Kort et al., 2003]. Dyspareunia [McIntosh et al., 1995] partly due to vaginal dryness [Sorokin et al., 1994] is a common form of pelvic pain in JHS/EDS-HT. Primitive bladder and colonic dysfunction, possibly linked to the underlying disautonomia, may be major contributing factors to primary pelvic visceral pain, but such a hypothesis remains unproved. Finally, other gynecological and musculoskeletal features, such as endometriosis, pelvic ring instability, and coccygeal joint dysfunction, are likely more common in JHS/EDS-HT and may equally trigger various forms of pelvic pain.

TREATMENT OF PAIN

Treating pain in JHS/EDS-HT is challenging due to the lack of convincing evidence-based studies on the effectiveness of specific treatments. The sole published evidences are a handful of papers on small cohorts or single patients. In particular, proprioceptive exercises resulted effective in reducing symptoms in 18 JHS patients [Ferrell et al., 2004], while the possible effectiveness of chiropractic [Colloca and Polkinghorn, 2003] and repetitive muscle vibration [Celletti et al., 2011b] was suggested in single patients. Concerning chiropractic, JHS/EDS-HT patients are typical subjects for whom standard low-amplitude manipulation is contraindicated due to the intrinsically lax connective tissue [Haldeman et al., 1993; Mierau, 2000]. However, the application of low-force chiropractic adjusting techniques may be successful in JHS/EDS-HT. Additionally, 10% dextrose prolotherapy demonstrated effective in reducing pain at palpation in patients with complications of temporomandibular JHM [Refai et al., 2011]. Therefore, the unique way to manage pain in this condition is to select and adapt options among those available for the general population. Table I summarizes what is generally known to be efficacious for treating and possibly preventing the various forms of pain observed in JHS/EDS-HT (review of the efficacy of listed treatments in the general population is beyond the scope of this work).

Among the various conservative approaches, physiotherapy is considered the most successful strategy. Except for the monograph by Keer and Grahame [2003], recently updated in a multi-authored work [Hakim et al., 2010], the most effective procedure for physiotherapy in JHS/EDS-HT is summarized in a few papers only [Simmonds and Keer, 2007, 2008; Keer and Simmonds, 2011]. The basic approach includes strengthening and proprio-

ception improving exercises, and gentle stretching. A detailed description of exercises and additional treatment options for pelvic pain is offered by Nelson et al. [2012]. However, physiotherapy has limits especially concerning time spent (by both the practitioner and the patient), inter-operator variability, and long-term efficacy. Alternative, possibly efficacious supportive approaches are the various psychological therapies, mainly cognitive behavioral therapy (CBT), massage, and non-conventional treatments. In particular, CBT seems the best approach for treating pain in JHS/EDS-HT [Grahame, 2009]. This hypothesis, though still not supported by specific studies, is emphasized by the documented CBT efficacy in treating pain in other chronic pain rheumatologic conditions, such as fibromyalgia [Rossy et al., 1999; Glombiewski et al., 2010], and osteoarthritis satellite symptoms, including insomnia [Vitiello et al., 2009] and depression [Yohannes and Caton, 2010]. Psychotherapy is of utmost relevance in chronic pain syndromes, such as JHS/EDS-HT, especially when there is a gap between individual's symptom perception and signs visible at family members, friends, and colleagues. In this setting, CBT may help patients in learning how to live with their untreatable disease.

Drug use and surgery are generally associated with pain [Voermans et al., 2010a]. Surgery is generally not effective in pain relief and may generate unexpected complications (mainly due to abnormal tissue post-surgical recovery and muscle deconditioning). Pain-relieving drug use is often inefficacious and may induce side-effects, mainly gastrointestinal. The classic approach combines non-steroidal anti-inflammatory drugs/paracetamol and Opioids. However, physiotherapy (with or without CBT) may be supported by adjuvants drugs for chronic pain management. Among them, amitriptyline, duloxetine, and other SSRI/SNRI are the most promising due to the apparently limited range of possible side effects and the wide spectrum of pains positively influenced by them (Table I). Pharmacologic prevention and treatment of osteoporosis is warranted in case of documented low bone mass, being associated with an increased risk of fracture.

CLINICAL FEATURES OF FATIGUE

Chronic fatigue is a persistent overwhelming sense of tiredness, lack of energy, and feeling of exhaustion [Vercoulen et al., 1994]. Such a mixture of unpleasant perceptions is nearly universal in adults with JHS/EDS-HT. This well-known evidence was recently quantified in several studies [Castori et al., 2011a; Rombaut et al., 2010; Voermans et al., 2010b]. Manifestations of fatigue-related features in JHS/EDS-HT are wide and overlap criteria for the chronic fatigue syndrome (CFS) in more than 80% of the patients [Castori et al., 2011c]. The correlation between JHM and CFS was explored by various research groups [Rowe et al., 1999; Barron et al., 2002; Nijs et al., 2004, 2006a], which inconstantly demonstrate a unexpected higher rate of generalized JHM in patients with CFS. It is possible that JHS/EDS-HT really affects a significant number of CFS patients with primary musculoskeletal dysfunction and a lower rate of symptoms related to impairment of the immune system (e.g., tender lymph nodes and sore throat). This anticipates etiological heterogeneity for CFS and the possible role for JHM in characterizing a specific subtype of CFS. This point still needs further investigations [Nijs et al., 2006b].

The cause(s) of fatigue in JHS/EDS-HT is(are) debated. In a questionnaire study on 276 patients with various forms of EDS (162 with JHS/EDS-HT) [Voermans et al., 2010b], five major determinants of fatigue are delineated, namely sleep disturbances, concentration problems, social functioning, self-efficacy concerning fatigue, and pain. Besides concentration problems, which are likely a result of chronic fatigue, all the remaining are possible causes for fatigue combining together in different ways case by case. In particular, obstruction sleep apnea syndrome is common in EDSs [Verbraecken et al., 2001] and may represent a leading cause of unrefreshing sleep. Similarly, also restless leg syndrome/periodic limb movements are considered frequent in this condition [Tinkle, 2010]. Nocturnal chronic pain is an additional factor influencing sleep effectiveness [Voermans et al., 2010a]. Furthermore, muscle weakness has been recently outlined as a contributing factor to fatigue in EDS [Voermans et al., 2011b], maybe in term of post-exertional malaise.

On a pathogenic perspective, additional systemic characteristics of JHS/EDS-HT can be involved in generating a persistent feeling of exhaustion. In particular, the link between JHM and dysautonomia is a relatively consolidated concept [Rowe et al., 1999]. Accordingly, dysautonomia is considered a major factor contributing to fatigue [Gazit et al., 2003; Hakim and Grahame, 2004]. In addition, an increased rate of celiac disease was demonstrated in JHS/EDS-HT and this evidence may indicate intestinal malabsorption as a possible trigger for fatigue, at least in a subset of patients [Danese et al., 2011]. The apparently high rate of excessive use of analgesics amplifying disautonomic symptoms [Voermans et al., 2010b] and obstructive/restrictive respiratory dysfunction [Castori et al., 2010b; Tinkle, 2010] may be considered further co-factors precipitating fatigue in JHS/EDS-HT. Finally, Morgan et al. [2007] find an increased rate of asthmatic symptoms and atopy associated with increased lung volumes, impaired gas exchange, and an increased tendency of both the lower and upper airways to collapse in JHS/EDS-HT.

TREATMENT OF FATIGUE

In light of the recent findings, various disease characteristics may be identified as contributors to fatigue in JHS/EDS-HT (Table II). For each of them, a series of lifestyle recommendations and possible therapeutic options can be outlined. Similarly to pain, it should be emphasized that none of the listed treatments, perhaps except for gluten-free diet [Danese et al., 2011], was demonstrated effective in JHS/EDS-HT patients. In addition to tabulated treatment options, daily intake of 250 mg of L-carnitine and 100 mg of coenzyme Q₁₀ is proposed as possibly ameliorative for fatigue in EDS [Mantle et al., 2005]. A work suggests improvement of fatigue with modafinil in patients with orthostatic intolerance [Kanjwal et al., 2011], a feature apparently common in JHS/EDS-HT. Finally, a recent review outlines that postural tachycardia syndrome seems to be the most common presentation of disautonomia in JHS/EDS-HT [Mathias et al., 2011]. In this paper a list of possible treatments and prevention strategies is defined (partly summarized in Table II).

DISCUSSION

The main finding of this study is that practically nothing has been published to date providing an evidence-based approach the

TABLE II. Contributing Factors to Fatigue

Factors	Possible treatments/prevention strategies
Muscle weakness	Aerobic fitness Strengthening exercises Proprioception exercises
Respiratory insufficiency	Respiratory/diaphragmatic exercises
Poor sleep	
Obstruction sleep apnea syndrome	Weight control (BMI <25) Nasal dilators Continuous positive airway pressure ^a Mandibular advancement devices Antidepressant drugs Nasal/pharyngeal surgery ^b Modafinil/armodafinil [adjuvant] Cognitive behavioral therapy [adjuvant] Heated humidification [adjuvant]
Restless leg syndrome	Avoiding caffeine, nicotine, and alcohol Levodopa and dopamine agonists Gabapentin and lamotrigine ^c Benzodiazepines
Nocturnal limb/back pain	See Table I
Dysautonomia	Generous isotonic liquid intake High salt intake Avoiding alcohol, heat, large meals, prolonged recumbency and undue exertion Judicious regular exercise Hypertensive drugs
Malabsorption (celiac disease)	Gluten-free diet
Reactive depression/anxiety disorder	Psychologic therapy Psychopharmacologic therapy
Excessive use of analgesics	Modulation of pain treatment

^aContinuous positive airway pressure is the gold-standard for the treatment of obstruction sleep apnea syndrome.

^bInvasive techniques should be considered with caution in patients with heritable connective tissue disorders.

^cManage with care due to the risk of amplifying dysautonomic symptoms.

effectiveness of any of the above mentioned treatment options for pain and fatigue in JHS/EDS-HT. This reflects the scant attention posed by healthcare providers to the needs of JHS/EDS-HT patients and the lack of a sufficient number of European hospitals with services specifically dedicated to hCTDs [Voermans et al., 2010a]. We, therefore, report here the outlook of our service dedicated to the management of JHS/EDS-HT along with a model for better assessing pain and fatigue in this condition.

Structure of the Clinic

Since June 2008, the Clinical Genetics outpatient service at the "San Camillo-Forlanini" Hospital in Rome (Italy) is involved in

TABLE III. Suggested Investigations by Pain Feature

Pain features	Suggested investigations
Neuropathic pain	Electroneurography/electromyography
Myalgias with post-exertional malaise and/or cramps (Peripheral) polyarthralgias	Serum lactate dehydrogenase and creatine kinase dosage, and electromyography
Headache	Rheumatoid factor, erythrocyte sedimentation rate, and C-reactive protein dosage, HLA-B27 and X-rays of hands and feet ^a
	Dynamic X-ray/MRI of the cervical spine, total spine and brain MRI, temporomandibular joint evaluation, check for signs/symptoms of orthostatic hypotension

^aAs for undifferentiated peripheral inflammatory arthritis, according to Villeneuve et al. [2011].

eyesight of the experienced pain sensations (Fig. 2). Administration of standardized questionnaires (e.g., ID Pain™, Neuropathic Pain Symptom Inventory, and McGill Pain Questionnaire) [Voermans et al., 2010a; Camerota et al., 2011] may be extremely useful for better classifying pain, especially for suspected neuropathic pain. Various investigations could be considered in order to test and characterize pain features (Table III). In consideration of the high rate of osteopenia/porosis in JHS/EDS-HT [Gulbahar et al., 2006], bone densitometry at spine and femur head should be requested especially in adults and in all patients after periods of reduced physical activity.

At the moment, both abdominal and pelvic pain are insufficiently known features in JHS/EDS-HT. Therefore, it appears too premature to select standardized investigations useful to study these forms of pain. The works by Nelson et al. [2012] and Fields and Dean [2011] are good reviews to consult, illustrating possible causes and differential diagnosis of abdominal/pelvic pain.

Assessment of Fatigue

Fatigue associated with JHS/EDS-HT appears pathogenic heterogeneous. At first evaluation, baseline investigations for CFS [Baker et al., 2007] are indicated in patients complaining prolonged (>6 months) fatigue especially when they meet CFS diagnostic criteria (Table IV). This is aimed at identifying possible co-morbidities (e.g., thyroid dysfunction) which could combine with JHS/EDS-HT and need specific treatments. Similarly to pain, further investigations can be performed in presence of specific fatigue features (Table V). In order to quantify fatigue, the Checklist Individual Strength has been previously applied in JHS/EDS-HT [Voermans et al., 2010b]. Rough evaluation of sleep quality can be investigated by the Pittsburgh Sleep Quality Index or Epworth Sleepiness Scale [Tinkle, 2010].

A list of things to ask during history taking with emphasis on pain and fatigue features is presented in Table VI.

Operative Workout

After having revised available literature, the need of a multidisciplinary approach is overwhelming. Based on our experience, such a multidisciplinary team should include the

professionals listed in Table VII. It is expected that future researches will open still premature links between JHM and developmental coordination disorder [Kirby and Davies, 2007] and other developmental disorders, which will expand

TABLE IV. Baseline Laboratory Investigations for Patients With Chronic Fatigue/Chronic Fatigue Syndrome (Modified From Baker et al., 2007)

Investigation

Urinalysis for blood, protein, and glucose
 Complete blood count
 Erythrocyte sedimentation rate
 C reactive protein
 Serum urea, creatinine, electrolytes, calcium
 Random blood glucose
 Creatine kinase
 Liver function (PT/INR, aPTT, albumin, direct/indirect bilirubin, and transaminases)
 Thyroid stimulating hormone, FT3, FT4
 Celiac antibody screening (IgG and IgA for AGA, EMA, and anti-tTG)
 Serum ferritin (children and young adults only)

TABLE V. Suggested Investigations by Fatigue Feature

Fatigue features	Suggested investigations
Exertional dyspnea	Pulmonary function tests
Poor sleep	Polysomnography
Signs/symptoms of disautonomia	Autonomic screening tests (e.g., measurement of pressure and heart rate after head-up tilt and Valsalva maneuver, plasma norepinephrine and epinephrine levels supine and standing or during head-up tilt) ^a
Depressed mood/anxiety	Psychiatrist/neuropsychologist evaluation

^aFor a more complete list of investigations see Mathias et al. [2011].

TABLE VI. A List of Possibly Useful Questions for History Taking

Symptoms/history feature to check

Limb/back pain

1. Age at onset
2. Location/distribution
3. Intensity (by location)
4. Quality and type (by location)
5. Progression (chronic versus recurrent)
6. Frequency (for recurrent/fluctuating pain)
7. Possible triggers/aggravating factors
8. Associated symptoms (paresthesias, muscle cramps, swelling, allodynia, hyperalgesia, redness, etc.)

Headache

1. Age at onset
2. Location/distribution
3. Intensity (by location)
4. Quality and type (e.g., pulsating versus pressing)
5. Frequency (episodic versus recurrent versus chronic)
6. Possible triggers/aggravating factors (head-up tilt, neck hyperextension/flexion, heat/cold temperature, menses, etc.)
7. Presence/absence of aura
8. Associated symptoms (features of temporomandibular joint dysfunction, tinnitus, nausea, vomiting, photophobia, phonophobia, etc.)

Fatigue

1. Age at onset
2. Intensity
3. Consequences on daily living (dressing, washing, walking autonomy, workplace, household activities, etc.)
4. Associated symptoms (exertional dyspnea, post-exertional malaise, unrefreshing sleep, memory/concentration problems, depression, anxiety, symptoms of orthostatic hypotension/tachycardia, etc.)

Musculoskeletal system

1. History of infancy/childhood joint hypermobility (pre-existing to specific sports, such as ballet and gymnastics)
2. Tendency to fall/clumsiness
3. Psychomotor development milestones
4. Sports performed
5. Problems/limitations in specific activities (e.g., running, writing, sitting/standing for long periods, etc.)
6. Sprains: Involved joints, number, treatments
7. Dislocations: Involved joints, number, treatments
8. Soft tissue injuries (bursitis, tendonitis, etc.): Involved joints, number, treatments
9. Tendon stress/overuse damage (including ruptures)
10. Muscle strains
11. Muscle ruptures
12. Previous evidence(s) of early-onset osteoarthritis
13. Treatments for spinal curvature anomalies, flatfoot, genu valgum, cubitus valgus

Gastrointestinal system

1. Oral cavity dryness (xerostomia)
2. Deglutition problems
3. Gastroesophageal reflux complaints
4. Recurrent/chronic heartburns

(Continued)

TABLE VI. (Continued)

Symptoms/history feature to check

5. Bloating
6. Delayed digestion
7. Recurrent abdominal pain
8. Diarrhea/stipsis

Gynecology

1. Irregular menses
2. Pain during menses (dysmenorrhea)
3. Pain during sexual intercourse (dyspareunia)
4. Spontaneous vulvar pain (vulvodinia)
5. Excessive menses flow (menorrhagia)
6. Recurrent cystitis
7. Symptoms of stress incontinence
8. Symptoms of uterine prolapses
9. Symptoms of rectal prolapse/hemorrhoids
10. Disease characteristics during pregnancy(ies)

TABLE VII. Specialists Involved in the Multidisciplinary Team for Management of Pain and Fatigue in JHS/EDS-HT

Specialist

Pediatrician/clinical geneticist^a
 Psychiatrist/rheumatologist^a
 Pain specialist/neurologist^a
 Psychiatrist/neuropsychologist^a
 Physiotherapist^a
 Occupational therapist^a
 Urologist-gynecologist
 Orthopedist
 Cardiologist
 Pneumologist
 Gastroenterologist
 Specialist(s) in non-conventional medicine (e.g., acupuncturist, osteopath, etc.)

^aThese specialists should take part to the core evaluating group involved in globally assessing the patient and planning interventions of the following listed professionals.

the list of core professionals to, for example, child neurologists and logopedists. As JHS/EDS-HT is a disorder strikingly affecting daily living, the multidisciplinary team should also instruct patients in improving their lifestyle with behaviors contrasting the deleterious effects of JHM and a congenitally lax connective tissue (Table VIII).

Not only the assessment but also the monitoring of prescribed treatments is difficult in JHS/EDS-HT. This, once more, reflects the absence of standardized procedures. A possibly effective strategy is depicted in Figure 3 and its validation is still ongoing in our service. The key point of this approach is to identify validated and handy tools (usually, questionnaires) which are used to quantify baseline levels of disability and severity of symptoms and to more objectively evaluate the ameliorative/deleterious consequences of treatment. In addition to the scales/questionnaires used for the assessment of pain and fatigue,

TABLE VIII. Lifestyle Recommendations Concerning Pain and Fatigue in JHS/EDS-HT

Recommendation

- Promote regular, aerobic fitness
- Promote fitness support with strengthening, gentle stretching and proprioception exercises
- Promote postural and ergonomic hygiene especially during sleep, at school and workplace
- Promote weight control (BMI <25)
- Promote daily relaxation activities
- Promote lubrication during sexual intercourse (women)
- 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 early treatment of malocclusion
- Avoid high impact sports/activities
- Avoid low environmental temperatures
- Avoid prolonged sitting positions and prolonged recumbency
- Avoid sudden head-up postural change
- Avoid excessive weight lifting/carrying
- Avoid large meals (especially of refined carbohydrates)
- Avoid hard foods intake and excessive jaw movements (ice, gums, etc.)
- Avoid bladder irritant foods (e.g., coffee and citrus products) intake
- Avoid nicotine and alcohol intake

Note: These recommendations are based on authors' experience as well as basic pathophysiologic principles related to laxity of the connective tissue.

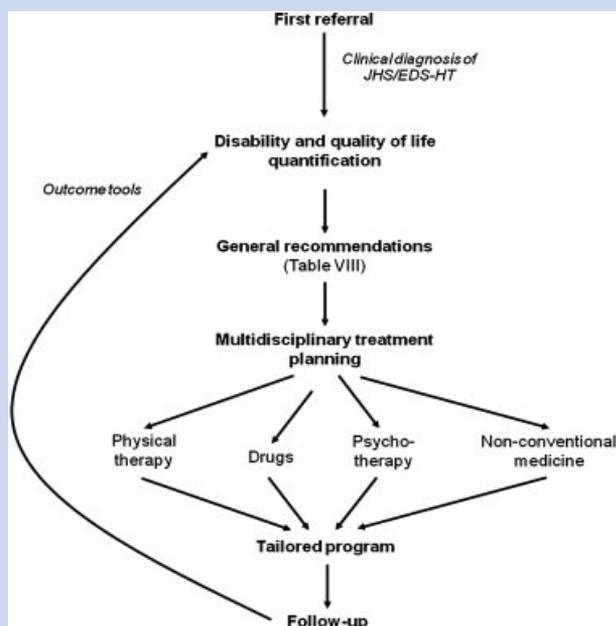


FIG. 3. The flow-chart of the proposed process for evaluating and treating pain and fatigue in JHS/EDS-HT.

further tools, including the Short Form Health Survey [Castori et al., 2010a], Lower Extremity Functional Scale [Celletti et al., 2011a], and Sickness Impact Profile [Rombaut et al., 2011b; Voermans et al., 2010a], can be used for global evaluation of QoL and disability.

CONCLUSIONS

This work was aimed to address the question as to whether an evidence-oriented approach for assessing and treating pain and fatigue in JHS/EDS-HT can be outlined or not. This search solely allowed us to identify possible useful investigations to be considered by the practitioner and a list of daily living recommendations for the patients. Literature review and the illustrated personal experience highlight the need for further studies focused on investigating the apparently complex pathophysiology of JHS/EDS-HT. This understanding should represent the starting point for better characterizing and investigating pathologic processes in any given patient. In the future, the final goal of such an inductive and multidisciplinary process is to define more tailored therapeutic programs and, hopefully, identify new approaches for treating symptoms and preventing disability.

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