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ORIGINAL ARTICLE

Chronic pain in patients with the hypermobility type of Ehlers–Danlos syndrome: evidence for generalized hyperalgesia

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Abstract Chronic widespread pain is highly present in patients with the Ehlers–Danlos syndrome hypermobility type (EDS-HT), but up to now, evidence for generalized hyperalgesia is lacking. The aim of this study is to investigate whether pressure pain thresholds (PPTs) at both symptomatic and asymptomatic body areas differ in EDS-HT patients compared to healthy subjects. Twenty-three women with EDS-HT and 23 gender- and age-matched healthy controls participated. All subjects marked on Margolis Pain Diagram where they felt pain lasting longer than 24 h in the past 4 weeks. Then, they completed several questionnaires assessing pain cognitions, fatigue, disability, and general health status, in order to take the possible influence of these factors on PPTs into account. Patients also completed a form concerning the type of pain they experienced. Thereupon, a blinded researcher assessed PPTs at 14 body locations on the trunk and extremities. PPTs were compared for the two complete groups. In addition, PPTs of patients and controls who did not report pain in a respective zone were compared. PPTs of the patients were significantly lower compared to those of the control group, also when pain-free samples per zone were compared. The mean (SD) PPT was 2.9 (1.62) kg/cm^2 in the EDS-HT patients and 5.2 (1.88) kg/cm^2 in the controls ($P<0.001$). No confounding factors responsible for the observed differences could be revealed. In half of the patient group, a predominantly neuropathic pain component was likely present. This study provides evidence for the existence of hyperalgesia even in asymptomatic areas (generalized secondary hyperalgesia). The generalized hyperalgesia may represent the involvement of a sensitized central nervous system, which inquires an adapted pain management for this patient group.

Keywords Central sensitization · Ehlers–Danlos syndrome · Hyperalgesia · Joint hypermobility · Pain · Pressure pain thresholds

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Introduction

The Ehlers–Danlos syndrome (EDS) comprises a heterogeneous group of inherited connective tissue disorders, characterized by fragility of the soft connective tissues and widespread manifestations in skin, ligaments, joints, blood vessels, and internal organs [1]. The current Villefranche classification recognizes six subtypes, of which the hypermobility type (EDS-HT) encompasses the majority of all cases [2]. It has been proposed that EDS-HT and JHS are the variable expression of the same disorder, as they show many common clinical features [3]. However, in our opinion, JHS comprises a broader spectrum of patients compared to EDS-HT. By definition and according to our clinical experience, nearly all patients diagnosed with EDS-HT will also meet the Brighton criteria for diagnosis of JHS, but this is not true in reverse, i.e. not nearly all JHS patients will meet the Villefranche criteria for EDS-HT. The main clinical manifestations of EDS-HT

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include severe generalized joint hypermobility, recurrent joint dislocations, mild skin involvement, and chronic joint and limb pain [2].

Recently, the natural history of EDS-HT has been re-delineated, at which three phases of disease evolution can be recognized based on the onset of specific symptoms affecting multiple systems, such as pain [4]. Regarding musculoskeletal pain, the first phase (onset in the first decade) is characterized by acute, local pain due to soft-tissue and joint injuries. In the second phase (onset in the second to third decade), widespread musculoskeletal pain is dominant, due to pain sensitization. And the third phase (onset in the third to fourth decades) shows that the chronic pain condition may worsen disability when maladaptive cognitions (e.g. pain catastrophizing, fear of pain) have been developed.

Indeed, the majority of adult patients with EDS-HT report to suffer from generalized pain complaints, with frequencies up to 100 % for joint pain and up to 87 % for muscle pain [5, 6]. The chronic pain is most frequently localized in shoulders, knees, hips, neck and back, and arms and legs, reflecting the musculoskeletal pain pattern [5–7]. In addition, pain intensity is perceived as moderate to severe and is continuously present, although with variable course [6].

Overall, pain problems associated with EDS-HT are complex and varied, and the origins of these pains are likely quite variable. Pain is usually described as nociceptive (caused by ongoing stimulation of nociceptors due to, e.g. ((sub)luxation of joints)) or neuropathic (caused by a primary lesion or dysfunction in the nervous system). In a pilot study, Camerota [8] suggested that pain in EDS might be partially of neuropathic nature in a cohort of 44 patients (classical and hypermobility type) measured by the ID pain questionnaire.

Besides, pain in EDS-HT is generally refractory to a variety of pharmacologic and physical interventions [9]. Consequently, pain has a detrimental effect on physical, social, and emotional function in patients with EDS-HT, with a substantial deterioration of their quality of life [7, 8, 10, 11]. In particular, a recent comparative study has shown a major negative impact of pain, in terms of pain severity, interference of pain with daily activities, control over pain, and emotional disturbances due to pain, in EDS-HT patients, which was higher compared to patients with rheumatoid arthritis (RA) and slightly lower compared to patients with fibromyalgia (FM) [11].

Although the pathophysiology is different, there are several clinical similarities between EDS-HT and FM, and EDS-HT and RA. A main similarity is the presence of daily musculoskeletal pain [12, 13]. Several studies could yet provide evidence for the involvement of central sensitization in the manifestation of chronic pain complaints in FM and RA [14–16]. Central sensitization represents hyperexcitability of the central nervous system due to the modulation or modification in central pain pathways causing hyperalgesia, allodynia, and referred pain and hypersensitivity beyond the area of tissue damage, leading to chronic widespread pain [17].

Up to now, the pathogenesis of pain in EDS is poorly understood, and evidence for central sensitization in patients with EDS, and especially in EDS-HT, is currently lacking.

Several studies in chronic pain disorders examined whether central sensitization could be existent by using algometry [18–20]. Through measuring pressure pain thresholds (PPTs) on both symptomatic and asymptomatic areas in patients and healthy control subjects, generalized secondary hyperalgesia can be detected. Whereas lower PPTs at symptomatic sites may represent primary hyperalgesia due to sensitized nociceptors within injured peripheral musculoskeletal structures (e.g. ligamentous rupture, joint capsule strain), it is known that lower PPTs in body areas outside and remote to the symptomatic site, together with a non-segmental general decrease in PPTs, represent generalized secondary hyperalgesia, due to prolonged or strong activity of dorsal horn neurons caused by repeated or sustained noxious stimulation, and infer a generalized hyperexcitability of central nociceptive pathways [20].

Therefore, the primary objective of the present study was to investigate PPTs in patients with EDS-HT compared to healthy matched control subjects, at both symptomatic and asymptomatic multiple body areas. The secondary objective was to examine the type of chronic pain EDS-HT patient experience.

Materials and methods

Subjects

Twenty-three adult patients diagnosed with EDS-HT participated. Patient selection was performed in the Centre for Medical Genetics at the Ghent University Hospital on the basis of the Villefranche Criteria for EDS-HT (see Table 1). As more than 90 % of the EDS-HT patients are female [2], the current study included only women. Also, 23 healthy volunteers, individually matched for gender, age, and ethnicity (all Caucasian), participated. Exclusion criteria for the control subjects were: (1) generalized joint hypermobility (Beighton score >4/9), (mean±SD control group: 1±1.7, range 0–3), (2) any musculoskeletal pain complaints at the moment, and (3) the use of analgesics or antidepressants. Subject characteristics are presented in Table 2.

Procedure

The study protocol was reviewed and approved by the Ethical Committee of the Ghent University Hospital, and written informed consent was obtained from all participants. All subjects filled out a Margolis Pain Diagram [21] followed by

Table 1 Villefranche criteria for diagnosis of EDS-HT

Villefranche criteria	EDS-HT group *n*=23 (*n*,%)	Control group *n*=23 (*n*,%)
Major criteria		
Generalized joint hypermobility	18 (78 %)	0 (0 %)
Skin involvement	21 (91 %)	0 (0 %)
Minor criteria		
Recurring joint dislocations	19 (83 %)	0 (0 %)
Chronic joint/limb pain	23 (100 %)	0 (0 %)
Positive family history	10 (43 %)	0 (0 %)

A subject is defined as having EDS-HT with the presence of generalized joint hypermobility (Beighton score ≥5/9 currently), and/or skin hyperextensibility/fragility, in combination with recurring joint dislocations, and/or chronic musculoskeletal pain, and/or a positive family history [2].

EDS-HT Ehlers–Danlos syndrome hypermobility type, *n* number of subjects

questionnaires assessing psychosocial factors, fatigue, disability, and general health status, in order to exclude the possible influence of these factors on PPTs (confounding factors). Only patients also completed a form regarding the type of pain they experienced. Thereupon, each subject was referred to a second blind researcher who was not aware of the results of the pain drawings. This second researcher, experienced in algometry, assessed PPTs on 14 anatomically well-defined body locations.

Measurements

Type of pain

The Pain Detect Questionnaire (PD-Q) is a self-reported questionnaire designed and validated to detect neuropathic pain components in patients suffering from chronic pain [22]. It comprises nine questions regarding the severity, course, quality, and nature of the patient's pain and specific neuropathic pain symptoms. A validated algorithm was used to calculate a total score ranging from 0 to 38 based on the patient's answers. A total score >18 indicates that a predominantly neuropathic pain component is likely, whereas a total score ≤12 indicates that the pain is likely predominantly nociceptive. With a total score of 13–18, the presence of neuropathic pain is ambiguous [22]. PD-Q has been applied in several studies of clinical manifestations of central sensitization in musculoskeletal pain conditions [23, 24] and was found to be appropriate for the present investigation.

Margolis Pain Diagram

The Margolis Pain Diagram uses two body outlines, front and back, in which subjects have to shade the body parts were they felt pain lasting for more than 24 h in the past 4 weeks. Plastic templates, as shown in Fig. 1, that contained the 45 different areas as defined by Margolis [21] were used to interpret the pain drawings. A score of 1 was assigned if the subjects' drawing indicated pain, for each of the 45 areas, and weights were assigned to the different body areas equal to the covering body surface percentage, resulting in a weighted score that reflected the total percentage of body surface shaded as painful [21]. The present study focused on the body areas in which algometry was executed to compare the pain drawings with the PPTs in the respective zones. The zones of interest are marked in grey in Fig. 1.

PPTs

PPTs were bilaterally measured using an analogue algometer with a circular silicon rubber tip of 0.79 cm^2 (Wagner instruments, Greenwich, USA). In order to test pain thresholds both on the extremities and the trunk, PPTs were assessed at the adductor pollicis muscle, in the middle of the skin web between thumb and index finger [20]; at the paraspinal muscles

Table 2 Subject's characteristics

Variable	EDS-HT group *n*=23	Control group *n*=23	*P* value
Age (years)	40±10.6	39±10.0	0.721
Duration of mss. symptoms (years)	24±12.4 (*n*=23)	–	–
Duration of gastro-int. symptoms (years)	14±13.5 (*n*=20)	–	–
Duration of fatigue (years)	15±11.0 (*n*=21)	–	–
Duration of pain (years)	24±12.5 (*n*=23)	–	–
Use of analgesics and/or antidepressants (*n*,%)	17 (74 %)	0 (0 %)	**<0.001**
Use of neuropathic pain medication (*n*,%)	2 (9 %)	0 (0 %)	**<0.001**

EDS-HT Ehlers–Danlos syndrome hypermobility type, *VAS* Visual Analogue Scale (0–10); *mss.* musculoskeletal, *gastro-int.* gastro-intestinal, *n* number of subjects. Descriptive statistics are shown as mean±standard deviation (SD) for continuous data and as percentages or absolute frequencies for categorical data. Bold: $p<0.05$

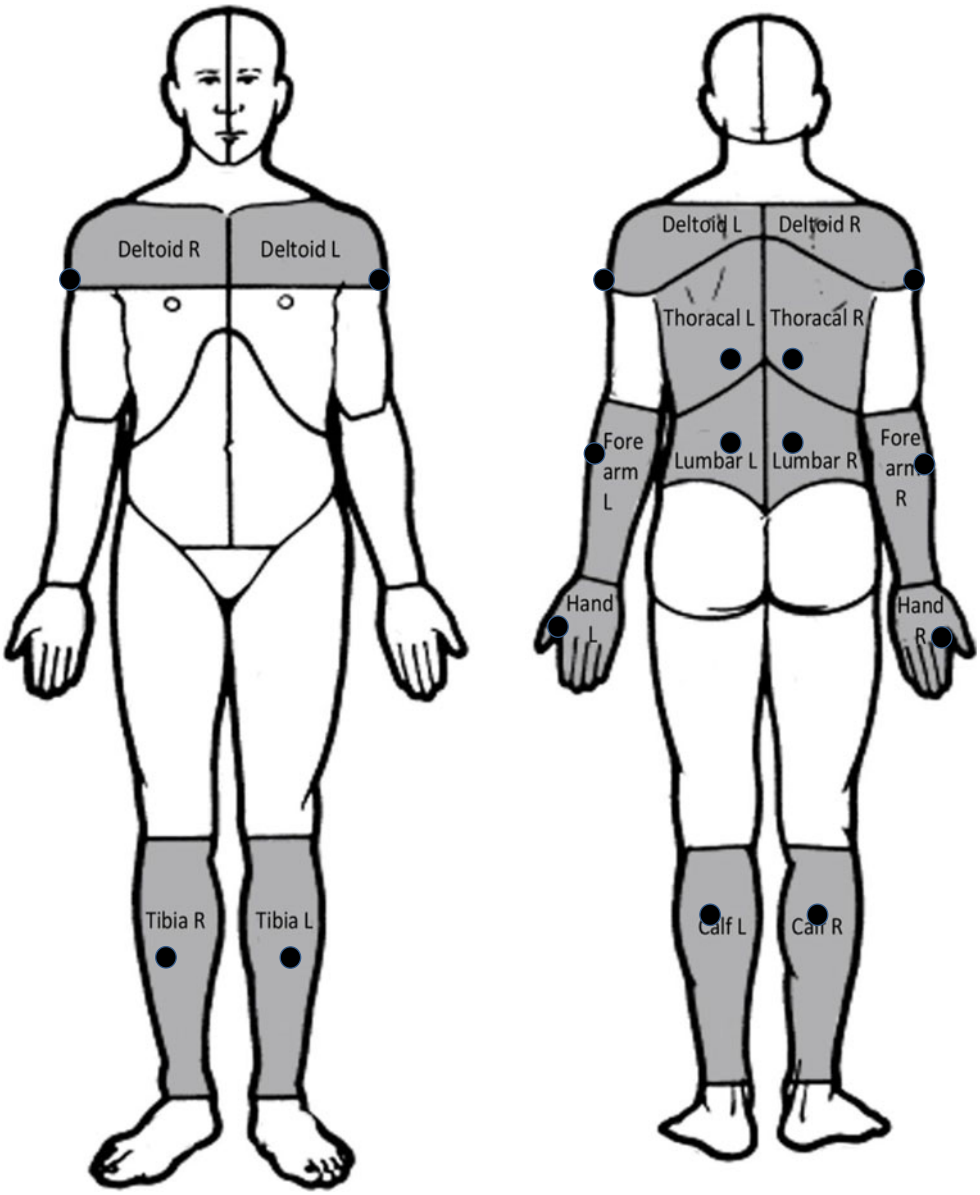

Fig. 1 Template for scoring pain diagrams with focused zones for algometry. The *grey zones* are the body areas of interest for algometry according to Margolis pain diagram. The *dots* are the locations at which pressure pain thresholds were assessed (*L*=left, *R*=right)

at 5 cm lateral to the spinous process of L3 and of T8 [20]; at the middle of the deltoid muscle at the latitude of the axilla; at the middle of the gastrocnemius muscle at the proximal third of the calf [20]; at the extensor carpi radialis longus muscle at the proximal third of the forearm [20]; and at the anterior tibial muscle, halfway and just lateral to the tibia [20]. These locations are marked with dots in Fig. 1. The pressure was gradually increased at a rate of 1 kg/s until the subject indicated that the pain level has been reached [20, 25, 26]. The threshold was determined as the mean of the two last values out of the three consecutive (10s in between) measurements, since this procedure has found to be reliable in healthy controls [26]. Pressure algometry has been found to be efficient and reliable in the exploration of pathophysiological mechanisms involved in pain [27].

Possible confounders

Psychosocial factors, fatigue, disability, and general health status The Dutch version of the Hospital Anxiety and Depression Scale (HADS) was used for the assessment of depression and anxiety. It is a 14-item, self-rating instrument, divided into an anxiety subscale and a depression subscale with seven items each [28]. The HADS appears to be a reliable and valid tool [29].

In addition, The Dutch translation of the Pain Catastrophizing Scale (PCS) was used aiming at assessing pain catastrophizing with 13 items describing different thoughts and feelings that individuals may experience when they are experiencing pain. The psychometric quality of the PCS has found to be good [30]. Also, the Pain Vigilance and

Awareness Questionnaire (PVAQ), to investigate attention to pain in subjects with chronic pain, was used. The questionnaire demonstrates good methodological quality in for example fibromyalgia patients [31].

The Checklist Individual Strength (CIS) subscale fatigue was used to assess the subjective fatigue severity. The CIS has shown good reliability and validity in chronic pain patients [32].

The validated Dutch version of the Health Assessment Questionnaire (HAQ) was used and is designed to measure self-reported physical disability in patients with chronic disorders [33].

The Short Form Health Survey-36 items (SF-36) assesses general health and well-being or quality of life. The psychometric properties of the SF-36 are well characterized in a wide variety of patient populations [34].

Statistical analyses

Data analysis was performed using PASW Statistics 20. Descriptive data are shown as mean±standard deviation (SD) for continuous data and as absolute frequencies or percentage for categorical data. Comparison of subject characteristics (age and medication use), percentage of painful body surface, and PPTs between groups was performed by independent *t* tests for means and chi-square tests for frequencies, respectively.

To compare PPTs between EDS-HT patients and healthy controls on asymptomatic places, only subjects who did not report pain in a specific area subjected to algometry, as presented in Fig. 1, were used. This means, pain thresholds between pain-free (for the respective zone) EDS-HT patients and pain-free controls were compared [18]. The comparability for age of the pain-free groups was even so assessed with the independent-samples *t* test. Significance level was set on $P<0.05$. *P* values for the differences in PPTs were post hoc Bonferroni corrected, because of multiple testing.

The influence of possible confounders, i.e. psychosocial factors (pain catastrophizing, depression and anxiety, pain vigilance and awareness) fatigue, disability, general health status, and duration of symptoms, on algometry was evaluated by performing a Univariate Analysis of Variance for variables which significantly correlated (Pearson correlation coefficient) with the mean PPT.

Results

Subject characteristics

Subject characteristics are presented in Table 2. The two groups were homogenous with respect to age ($p=0.721$) and gender. The principal complaints of the EDS-HT patients protracted for 14 to 24 years. Seventeen patients (74 %) used analgesics and/or antidepressants, two of whom used neuropathic pain medication (opioids, tricyclic antidepressant), in contrast to the pain- and medication-free control subjects ($p<0.001$).

Type of pain

All EDS-HT patients reported long-lasting generalized musculoskeletal pain. The mean total score on the PD-Q was 16.6 ±7.09, whereby the presence of neuropathic pain is unclear. However, nine patients (39.1 %) scored ≤12 corresponding to a predominantly nociceptive pain, while 11 (47.8 %) of the patients had a PD-Q score >18, indicating a predominantly neuropathic pain component being present in approximately half of the patient group.

Margolis Pain Diagram

The percentage of painful body surface was significantly higher in the EDS-HT group in comparison to the healthy control group ($p<0.001$). EDS-HT patients experienced pain for more than 24 h in the past 4 weeks on an average of 31 % (± 17.8) of their body surface, compared to 1 % (± 2.4) in the control group ($P<0.01$). Seventy-eight percent (18/23) of the controls submitted a blank pain diagram.

Algometry (PPTs)

A significant difference between the patient and control group was revealed for all PPTs. The mean (SD) PPT was 2.9 (1.62) kg/cm^2 in all EDS-HT patients and 5.2 (1.88) kg/cm^2 in the controls ($p<0.001$). EDS-HT patients systematically scored significantly lower on the algometry, as presented in Table 3.

Further, pain thresholds were compared per zone between EDS-HT patients and controls who did not report pain in the respective zone as presented in Table 4. For each respective zone, the mean age of the pain-free EDS-HT patients and controls was not significantly different.

Although the EDS-HT patients did not report pain in a specific area, PPTs were always, with the exception of the right calf reference point, significantly lower in comparison to the control group (Table 4).

Possible confounders

Significant correlations were found between psychosocial and other factors and PPTs, as shown in Table 5. However, none of these psychosocial factors nor fatigue, disability, general health status, or duration of symptoms did affect the difference in PPTs between the two groups (data not shown).

Table 3 Comparison of pressure pain thresholds (kg/cm^2) between the total EDS-HT group (n=23) and control group (n=23)

Body area*	PPT EDS-HT group Mean±SD	PPT control group Mean±SD	*P* value
Hand left	3.5±1.57	5.5±1.76	**<0.001**
Hand right	3.1±1.28	5.6±1.87	**<0.001**
Forearm left	2.2±0.89	3.8±1.30	**<0.001**
Forearm right	2.3±1.58	4.1±1.53	**<0.001**
Deltoid left	2.3±1.22	4.0±1.79	**<0.001**
Deltoid right	2.3±1.42	4.1±1.63	**<0.001**
Thoracic left	3.3±1.61	5.5±3.10	**0.005**
Thoracic right	3.3±1.82	5.1±2.41	**0.007**
Lumbar left	3.8±2.39	6.4±3.04	**0.001**
Lumbar right	3.3±1.73	6.5±2.84	**<0.001**
Tibia left	3.1±1.77	5.7±3.04	**0.001**
Tibia right	3.1±1.96	5.9±2.73	**<0.001**
Calf left	2.9±1.71	5.0±2.44	**0.001**
Calf right	3.3±1.82	5.0±2.46	**0.012**

*Body area: description of exact body locations of PPT measurements, see methodology. *EDS-HT* Ehlers–Danlos syndrome hypermobility type, *PPT* pressure pain threshold. Bold: significant p value after Holm–Bonferroni correction

Discussion

This study is the first to investigate pain by pressure pain thresholds and questionnaires in patients with EDS-HT and to provide insights into possible mechanisms and origins for persistent, chronic pain in this patient population. The results of the present study demonstrate lower PPTs in patients with EDS-HT compared to healthy control subjects without pain. Moreover, also at asymptomatic (pain-free) locations, EDS-HT patients systematically show significantly lower pain thresholds. Furthermore, approximately 40 % of the patients present with a nociceptive pain pattern, whereas in about 50 % a predominantly neuropathic pain component is likely present.

Our results concerning the PPT scores in the EDS-HT group, generally as well as on asymptomatic locations, are comparable with the findings of previous reports on pain algometry in other chronic pain populations such as in patients with FM [35], chronic fatigue syndrome (CFS) [20], and chronic whiplash-associated disorder [18] but were lower compared to patients with chronic low back pain (CLBP) (mean PPT: 6 to 8 kg/cm^2) [36]. In addition, the differences in PPTs between the EDS-HT patients and control subjects can be considered pathological according to the definition of Fisher since the difference between both groups was >2 kg/cm^2 (mean PPT 2.98 kg/cm^2 versus 5.15 kg/cm^2, respectively) [37].

The EDS-HT patients systematically scored significantly lower on PPT, also when pain-free samples per zone were compared, with exception of the PPT of the right calf, compared to healthy controls. Why the outcome at the right calf is deviant is unclear but is probably due to fact that two control subjects scored very low for this measurement (PPTs of 1.50 and 1.85 kg/cm^2) compared to the other controls. When excluding these subjects from analysis, the observed difference did reach significance, and the effect could be labeled as the result from outlying data.

According to the Margolis Pain Diagram, EDS-HT patients experienced pain lasting longer than 24 h in the past 4 weeks on more than 30 % of their total body surface, which underlines the widespread character of the pain in EDS-HT and which supports the findings of a general decrease in PPT in the patient group. But what is more, this widespread pain lacking local distinction together with the lower PPTs in body areas outside and remote to the symptomatic site infers a generalized hyperexcitability of central nociceptive pathways. Consequently, this study is the first to provide evidence for the involvement of central sensitization in EDS-HT patients. Central sensitization encompasses altered sensory processing in the brain, malfunctioning of descending anti-nociceptive mechanisms, increased activity of pain facilitatory pathways, and temporal summation of second pain or wind-up [38]. Which of these pathological pain mechanisms play a major role in EDS needs to be further investigated.

Next to pain algometry, this study also investigated the type of chronic pain EDS-HT patients experienced, specifically, the presence of neuropathic pain symptoms. Our results showed that approximately half of the patients most likely suffered

Table 4 Comparison of pressure pain thresholds (kg/cm^2) between pain-free EDS-HT patients and control subjects

Body area*	PPT EDS-HT group		PPT control group		*P* value
	n	Mean±SD	*n*	Mean±SD	
Hand left	16	3.7±1.44	23	5.5±1.76	**0.001**
Hand right	16	3.4±1.26	23	5.6±1.87	**<0.001**
Forearm left	19	2.0±0.81	23	3.9±1.31	**<0.001**
Forearm right	20	2.2±0.63	23	4.1±1.53	**<0.001**
Deltoid left	13	1.8±0.62	23	4.0±1.79	**<0.001**
Deltoid right	16	2.0±0.93	22	4.0±1.60	**<0.001**
Thoracic left	15	2.8±1.05	23	5.5±3.10	**0.001**
Thoracic right	15	2.6±1.03	23	5.1±2.41	**<0.001**
Lumbar left	9	3.4±1.48	23	6.4±3.04	**0.008**
Lumbar right	10	2.9±1.57	22	6.6±2.82	**0.001**
Tibia left	18	3.0±1.97	23	5.7±3.04	**0.003**
Tibia right	15	2.6±1.63	22	6.0±2.78	**<0.001**
Calf left	15	3.1±1.81	23	5.0±2.44	**0.013**
Calf right	16	3.7±1.90	23	5.0±2.46	0.093

*Body area: description of exact body locations of PPT measurements, see methodology. *EDS-HT* Ehlers–Danlos syndrome hypermobility type, *PPT* pressure pain threshold, *n* number of pain-free subjects for that respective zone. Bold: significant p value after Bonferroni correction

Table 5 Pearson correlation coefficients between the mean pressure pain threshold (PPT) and psychosocial factors, fatigue, disability, health status, and duration of symptoms

	Correlation with mean PPT
Pain catastrophizing (PCS score)	−0.308*
Pain vigilance and awareness (PVAQ score)	−0.277
Degree of depression (HADS-D score)	−0.170
Degree of anxiety (HADS-A score)	−0.011
Fatigue (CIS fatigue score)	−0.416**
Disability (HAQ total score)	−0.452**
General health status (items of SF-36)	Varying between −0.257 and 0.491**
Duration of symptoms	Varying between −0.311* and −0.422**

PCS pain catastrophizing scale, *PVAQ* pain vigilance and awareness questionnaire, *HADS-D* Hospital Anxiety and Depression Scale-subscale depression, *HADS-A* Hospital Anxiety and Depression Scale-subscale anxiety, *CIS* checklist individual strength, *SF-36* Short Form Health Survey-36 items

* and **significant Pearson correlation at $p<0.05$ and $p<0.01$, respectively

from neuropathic pain, according to the Pain Detect. This finding confirms the recent research letter by Camerota et al. [8] who reported that, according to the ID Pain questionnaire, two thirds of the EDS patients (hypermobility and classic type) suffered from at least "probable" neuropathic pain (probably in 32 % and likely in 36 %).

Therefore, it is likely that pain symptoms in EDS-HT have a compound origin and are the result of different pain-triggering mechanisms. Sacheti et al. [5] suggested that nociceptive pain in EDS can have several causes: it may be secondary to frequent dislocations, result from repeated soft-tissue injury, or be related to multiple surgical procedures. The underlying mechanisms of neuropathic pain in EDS-HT are even more unclear. However, a study of Voermans et al. on neuromuscular features in EDS patients may shed a light on this issue. The results showed that axonal polyneuropathy occurs in various EDS types [39]. Since extracellular matrix proteins, which are involved in EDS, are distributed throughout the connective tissue of peripheral nerve, the authors hypothesized that axonal function of peripheral nerves is influenced by the inherited connective tissue defect in EDS [39]. Furthermore, also compression neuropathy is associated with EDS in some cases [40] and may play a role in neuropathic pain in this patient population, at which collagen-deficient perineurium and endoneurium might fail to limit excessive stretching of or pressure on nerves [41]. However, these conditions cannot explain the entire range of neuropathic pain in EDS, and more elusive mechanisms may coexist in several patients.

Moreover, the existence of a central component, central sensitization, probably plays an important role in the widespread chronic pain in EDS. From a musculoskeletal perspective, it is important to realize that peripheral mechanisms take part in the pathophysiology of central sensitization. Many cases of chronic musculoskeletal pain evolve from traumatic and non-traumatic local nociceptive and neuropathic musculoskeletal problems characterized by a period of massive peripheral input in the (sub)acute to chronic stage [42]. In response, the central nervous system modulates the sensitivity of the somatosensory system. Once central sensitization is established, any new peripheral injury may serve as a new source of input, which sustains or aggravates the process of central sensitization [43]. This also may be the case in many patients with EDS-HT.

Overall, it is apparent that several forms of pain coexist in EDS-HT with diverse and possibly distinguishable clinical features. Nociceptive and neuropathic pain, as well as central sensitization, can contribute to the widespread chronic pain in EDS-HT. In order to develop a more tailored pain therapy for EDS-HT patients, correct pain diagnosis is highly necessary. The need for this is underlined by our finding that half of the EDS-HT patients in our study likely suffer from neuropathic pain, whereas we showed that only 9 % of the patients used neuropathic pain medication. Furthermore, the involvement of central sensitization in EDS-HT should be addressed in the pain management of these patients. The presence of central sensitization implies an increased complexity of the clinical picture (i.e. an increase in unrelated symptoms and hence a more difficult clinical reasoning process), as well as decreased odds for a favorable rehabilitation outcome [44]. Although currently little is known about the effect in humans, some approaches might be introduced, among which pharmacotherapy potentially targeting central sensitization (e.g. serotonin- and norepinephrine-reuptake inhibitors), transcranial magnetic stimulation, and transcutaneous electrical nerve stimulation [38]. In addition, it is known that the dysfunctional descending nociceptive inhibitory mechanism is influenced by negative and maladaptive thoughts, emotions, cognitions, and behaviours like catastrophizing, hypervigilance, and avoidance behaviour [45]. These negative cognitions can develop when EDS-HT patients do not understand the origin of their generalized musculoskeletal chronic pain and can facilitate pain. Therefore, pain education about central sensitization and its role in chronic pain, known as pain physiology education, might be crucial in order to change to the patient's perception and cognition about pain. Positive results of this approach can be expected from recent findings in various chronic musculoskeletal pain populations such as FM [46], CFS [47], and CLBP [48] but require future evaluation in patients with EDS-HT. However, despite the important role of cognitions and behaviour in pain, neither depression, nor anxiety, pain catastrophizing, pain vigilance, and awareness were found to be confounders responsible for the observed differences in PPTs between EDS-HT patients and healthy controls in our study.

Notwithstanding, according to the disease evolution presented by Castori et al. [4], EDS-HT patients characterized by full-blown central sensitization manifestations will develop/worsen disability when long-lasting maladaptive cognitions sustain. Consequently, it is highly necessary to design tailored pain treatment strategies, including also physical therapy and cognitive–behavioural therapy, in order to prevent/slow down disability and deterioration in quality of life [49].

The results of the study must be viewed within the limitations of the study. First, we included only female patients, so we should be cautious with generalization of the results. However, 90 % of the patients with EDS-HT are women [2]. Second, we did not take into account the potential impact of pain medication on PPTs in the EDS-HT group. In fact, 74 % of the patients in our study sample indicated to use analgesics and/or antidepressants on a regular basis. Notwithstanding, we are convinced that our results are clinically relevant, because even with the use of pain alleviating medication, the PPTs were consistently significantly lower in the EDS-HT patient group compared to the control group. Third and final, the current study was of cross-sectional design, so no causative underlying mechanisms could be identified. However, the results as presented in this study do warrant further scientific exploration.

In conclusion, the present study demonstrates the different types of pain in EDS-HT and suggests the existence of a central hyperexcitability as an important mechanism involved in the chronic pain problems in this patient group. EDS-HT patients present with decreased PPTs and generalized widespread areas of hyperalgesia. These findings may represent the involvement of a sensitized central nervous system. Future research is needed to further gain insight into the pain mechanisms and the sources of pain in patients with EDS-HT, which will hopefully contribute to the development of an appropriate and adequate pain management for this challenging but very rewarding group of patients.

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