



ORIGINAL ARTICLE

Pain in hypermobile Ehlers-Danlos syndrome: New insights using new criteria

Karelle Bénistan¹ | Valeria Martinez^{2,3,4}

¹Centre de référence des syndromes d'Ehlers-Danlos non vasculaires, Hôpital Raymond Poincaré, Garches, Assistance Publique Hôpitaux de Paris, Garches, France

²Département d'anesthésie et consultation douleur, Hôpital Raymond Poincaré, Garches, Assistance Publique Hôpitaux de Paris, Garches, France

³Centre d'Evaluation et de Traitement de la Douleur, F-92100 France, INSERM, U-987, Hôpital Ambroise Paré, Boulogne-Billancourt, France

⁴Université Versailles Saint-Quentin, Montigny-Le-Bretonneux, France

Correspondence

Karelle Benistan, Centre de référence des syndromes d'Ehlers-Danlos non vasculaires, Hôpital Raymond Poincaré, 104 bd Poincaré, Assistance Publique Hôpitaux de Paris, F-92380, 92380 Garches, France.
Email: karelle.benistan@aphp.fr

Abstract

Features of the pain in hypermobile Ehlers-Danlos syndrome (hEDS) are complex and insufficiently known by clinicians. We enrolled 37 hEDS patients. Disease status was ascertained using revised 2017 International Classification criteria, in the EDS French National Reference Center. Patients were evaluated with a clinical examination, quantitative sensory testing, and validated questionnaires. Thirty-seven patients were evaluated. Pain had appeared at 10 ± 5 years old and became chronic at 20 ± 9 years old. hEDS was diagnosed at only 24 ± 10 years old. Ninety-seven percent of them had severe chronic pain, which gradually increased over time in 75% of them. The main location of pain was in joints and predominated in lower limbs. Patients with a generalized presentation of pain had older chronic pain and a higher impact on the affective component. Neuropathic pain was frequent in the most painful joint and associated with heat hypoesthesia. An asymmetric proprioception was found in one third of the patients. A very high rate of attempted suicide was observed. To conclude, pain in hEDS is severe, chronic, and disabling. Sensorial and proprioceptive sensibilities are also affected. Peripheral neuropathic pain is frequent and central sensitization appears to be a key step in the evolution of disease.

KEYWORDS

hyperalgesia, hypermobile Ehlers-Danlos syndrome, neuropathic pain, pain, recurrent dislocation

1 | INTRODUCTION

Ehlers-Danlos syndromes (EDS) are a heterogeneous group of hereditary connective tissue disorders characterized by skin laxity, joint hypermobility, and tissue fragility. They are due to mutations in genes encoding structural proteins of connective tissue, for collagen modifiers or enzymes involved in their metabolism. The prevalence for all types of EDS collectively is estimated at 1/5,000 (Tinkle et al., 2017), if one does not take into account other hypermobility spectrum disorders.

The 2017 International Classification of the EDS now recognizes 13 subtypes and includes a set of stricter criteria for hypermobile

Ehlers-Danlos syndrome (hEDS), which reduces the number of hEDS diagnoses across the world in particular among patients with chronic pain and limits confusion around hEDS, joint hypermobility and related musculoskeletal manifestations (Challal, Minichiello, Funalot, & Boissier, 2015; Malfait et al., 2017). On the other end, this classification introduces the term "hypermobility spectrum disorders" to give some diagnostic label to other individuals suffering from chronic pain and presenting additional musculoskeletal features probably related to a pre-existent joint hypermobility, but who do not respect the criteria for any EDS. hEDS is the most frequent type of EDS; it affects over 80% of EDS patients and is now well characterized (Tinkle et al., 2017). Unlike the other subtypes, its diagnosis remains only clinical because genetic etiology has not been found yet (haploinsufficiency of *TNXXB* could explain 5% of hEDS (Zweers et al., 2003); possible

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candidate region on chromosome 8p22-8p21.1 (Syx et al., 2015). It has an autosomal dominant mode of inheritance. Symptoms begin during infancy. The diagnostic criteria of hEDS are summarized in Appendix. So far, there has been no specific etiological treatment available, but only symptomatic treatments and preventive measures designed to avoid complications. Although patients with hEDS suffer from pain, its underlying mechanisms are still unresolved and remain complex (Castori et al., 2017). Pain is the symptom by which patients most often enter the disease. The characteristics of pain in hEDS are now better described. However, literature has each time been interested in only certain aspects of these pains. In this study, we wanted to present an overview of the pain with all its components, and further explore neurophysiological aspects of pain in hEDS.

2 | METHOD

Patients were consecutively recruited during 1 year in 2017 and disease status has been systematically ascertained using validated diagnostic criteria in the French EDS National Reference Center (Raymond Poincaré Hospital, Garches). Inclusion criterion was a hEDS diagnosis according to the new 2017 EDS criteria (Malfait et al., 2017; Appendix). We collected demographic data, medical history, pain history, physical examination, echocardiography, and completed questionnaires. Evaluations were always performed by the two same senior investigators, on the one hand, the EDS specialist for the physical examination, and on the other hand, the pain specialist for the pain evaluation. In this observational study, the data collection was approved by National Commission for Informatics and Liberties (CNIL). All data were anonymized.

2.1 | Assessment of pain and its impact

All the patients were asked to describe their pain and its impacts. We asked them at what age the first symptoms occurred, their age at hEDS diagnosis, their age at chronic pain onset, and the duration of their pain. We asked patients to enumerate currently painful joints, and to rank the three most painful. They were also asked about the frequency of subluxations, luxations, or sprains during the last month and the number of emergency department visits in the last 12 months. Patients were asked to record school or absenteeism at work measured in days off work/school in the last 12 months. We also questioned them about diagnostic wandering, suicide attempts, analgesic treatment history, and previous orthopedic surgery. The Brief Pain Inventory short form was used to assess the interference of pain in the daily life (Cleeland & Ryan, 1994). Average and worst pain intensity over the last 24 hr were assessed using numerical rating scale (NRS; 0: no pain; 10: worst possible pain). The areas of pain including maximal pain were reported on the body map from the Brief Pain Inventory (BPI) (Cleeland & Ryan, 1994). The QDSA scale (Questionnaire Douleur de Saint-Antoine, the validated French version of the McGill Pain Questionnaire; Boureau, Luu, & Doubreire, 1992) was used to evaluate the different components of the

subjective pain experience, describing the sensory and the affective dimensions. Fatigue intensity was evaluated by a visual analog scale (VAS). In the most painful joint, we searched for neuropathic characteristics with the validated DN4 questionnaire (Bouhassira et al., 2005). Patients with NP had to fill in the neuropathic pain symptom inventory (NPSI; Bouhassira et al., 2004) which includes 10 symptoms rated on 0–10 numerical scales (burning, squeezing, pressure, electric shocks, stabbing, pain evoked by brush, pressure, cold, tingling, pins, and needles). The total score is based on a 100-point scale.

We also assessed psychological vulnerability with the hospital anxiety and depression (HAD) scale which includes an anxiety subscale (HAD-A) and a depression subscale (HAD-D), both of them containing seven intermingled items, providing a total score for each subscale ranging from 0 to 21 (Zigmond & Snaith, 1983). Digital palpation of 18 specified locations of tenderness described in 1990 by the American College of Rheumatology for the diagnosis of fibromyalgia. We also performed a manual palpation of quadriceps to test for a muscular pain.

2.2 | Quantitative sensory testing

Quantitative sensory testing was performed on the area of the joint described by the patient as the most painful. Contralateral joint were used as control. Brush-induced allodynia was assessed using a paintbrush (Somedic AB, Stockholm, Sweden); intensity was assessed on a 100 mm VAS. Thermal sensations and pains were assessed with a Somedic thermotest (Somedic AB, Stockholm, Sweden), using the Marstock method according to the method of limits (Fruhstorfer, Lindblom, & Schmidt, 1976). The baseline temperature of the thermode was set at 32°C. The maximum and minimum temperatures were set at 50°C for heat, 10°C for cold detection, and 4°C for cold pain. A thermal rate of change of 1°C/s was used. All thresholds were calculated as the average of three successive determinations. Hypoesthesia to mechanical, warm, or cold stimuli was considered in case of increased warm detection thresholds or decreased cold detection thresholds of at least 2 SD in comparison with contralateral sides.

2.3 | Vibratory perception sense

Patients underwent testing for vibratory perception sense by assessment of the vibratory perception threshold (VPT). Therefore, a biothesiometer (Somedic AB, Stockholm, Sweden) was used according to previously published methods (Frenette, Mergler, & Ferraris, 1990). The tractor of the device was applied with uniform pressure on three points bilaterally: trochanter at the hip, femoral condyle at the knee, and fibula condyle at the ankle. Patients were asked to inform the examiner of the first sensation of vibration as the amplitude of vibration was slowly increased by one vibration per second. The average (V) of the three VPT measurements at each site was calculated. An asymmetry of proprioception was considered if a difference of two standard deviations was observed between the two sides.

2.4 | Temporal summation tests with Von Frey filaments

This test evaluates the pain triggered by the application of a 180 g Von Frey filament (Bioseb, in vivo Research Instruments, <http://www.bioseb.com>) to the inner surface of the right upper arm until the filament curves. The pain induced was evaluated on an 11-point NRS after the first stimulation, and then again after 10 consecutive applications to an area of 1 cm², at a frequency of 1 Hz, as described by Weissman-Fogel et al. (2009). The difference between the NRS scores obtained after 1 and 10 stimulations was calculated (Δ NRS10–1).

2.5 | Statistical analysis

Quantitative data were described as mean and standard deviation (min–max) and qualitative data as frequencies (percentages). Chi-squared tests (or Fisher's exact tests if necessary) and Wilcoxon tests were performed for univariate analyses. All statistical tests were bilateral and a *p*-value <.05 was considered significant. Statistics were performed using the R statistical software version 3.3.1.

3 | RESULTS

3.1 | Patient characteristics, clinical data, and psychometric testing

Thirty-seven consecutive patients fulfilling the diagnostic criteria of hEDS from 34 different families were included. Baseline characteristics are summarized in Table 1. Hypermobile EDS was diagnosed at 24 ± 10 years old. Twenty-nine (78%) patients had a family history of hEDS. All patients suffered from chronic pain. The pain duration has been 7 ± 2.1 years. Seventy-five percent described overall pain as gradually increasing, pain appeared at 10 ± 5 years old, became chronic at 20 ± 8 years old. Abdominal pain is present in 55% of cases, headaches in 63%, and insensitivity to local anesthetic was reported in 48% of cases.

Previous orthopedic surgery was performed in 35% (13/37) of patients in following joints: ankle (5/13), knee (4/13), hip (3/13), and shoulder (1/13). Three patients had two or three surgical procedures on the same joint and three patients had surgical procedures on different joints. All surgeries were performed before the hEDS diagnosis. Patients stated that they consult the emergency department 3 (0–7.5) times per year. Diagnostic wandering was reported for 60% of patients. The most frequent diagnoses previously evoked were fibromyalgia (26%), psychological diseases (21%), and inflammatory/degenerative joint diseases (16%).

The impact of pain on quality of life was important with a median BPI score of 61 ± 23 and interfered with all aspects of life (Figure 1). Six patients (15%) were suspected of depression and three patients (7.5%) of anxiety defined by HAD questionnaire. About 36/37 (97%) of patients complained of fatigue with a mean NRS of 7 ± 1 (6.5–8). The fatigue was severe for 28/37 (75%) of them. Only three (8%) patients had normal working or studying activities. More than half had

TABLE 1 Clinical characteristics of patients

<i>Demography</i>	
Sexe (F/M)	36/37 (95%)
Age (years)	26 ± 10 (10–53)
Body mass index (kg/m ²)	23 ± 4 (16–31)
<i>Rheumatology</i>	
Beighton score $\geq 5/9$	37/37 (100%)
Number of painful joints	9 ± 3 (2–20)
Number of dislocation during last month	11 ± 6 (0–300)
Age of first sprain/dislocation (years)	10 ± 5 (2–27)
Scoliosis $\geq 20^\circ$	1/37 (2.7%)
Congenital hip dislocation	8/37 (22%)
Clumsiness	36/37 (97%)
<i>Dermatology</i>	
Unusual soft or velvety skin	12/37 (32%)
Unexplained and pathologic striae	5/37 (13%)
Mild skin hyperextensibility	19/37 (51%)
Abnormal hematoma	30/37 (81%)
Atrophic scarring >1	15/37 (40%)
<i>Echocardiography</i>	
Mitral prolapse	5/24 (20%)
Aortic root dilatation	0/24 (0%)
<i>Other</i>	
Unexplained pelvic floor prolapse	1/37 (2.5%)
Abdominal hernias	6/37 (16%)
Urinary dysfunction	9/19 (47%)
Ogival palate	19/37 (51%)

Note. Data are reported as mean \pm SD (minimum–maximum) or as number (%).

recurrent absenteeism (54%), and about one third had a long sick leave or permanent disability status. Eight patients reported having attempted suicide at a very young age (10, 13, 24, 15, 15, 16, 23, and 25 years old).

3.2 | Pain characteristics: Experimental findings

Eleven (27%) patients had severe pain (pain intensity $\geq 7/10$) and sixteen (40%) had moderate pain (pain intensity between 3 and 7). Average worst pain was $8.5 \pm 1.2/10$ and lowest pain was $4.7 \pm 2.3/10$. The total QDSA score was 20 ± 9 over a total score of 60. Pain was described as sharp (70%), stabbing (70%), tender (65%), or exhausting (90%). Three different types of body map representation of pain have been reported (Figure 2). Patients with widespread pain had a more length duration of pain and a higher impact on the affective component of pain (Table 2). The worst pain was most often located in the lower limb 15/37 (40%), followed by the upper limb 10/37 (27%) and spine 5/37 (13%; Figure 3). Pain had neuropathic characteristics in the most painful joint in 67% of the patients (25/37) and was severe with a total score of NPSI of 43 ± 12 . Average intensity of neuropathic symptoms

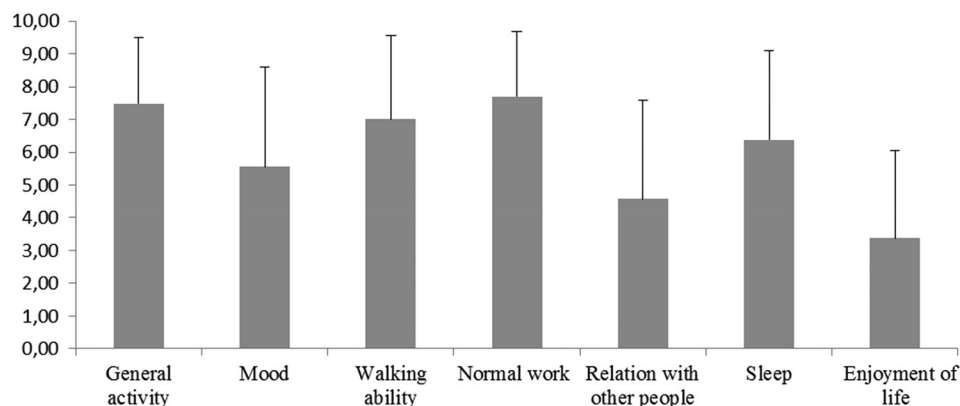


FIGURE 1 Brief pain inventory, interference of pain with daily life. Bar graphs showing the mean and standard deviation of impact of pain in different component of quality of life measured with the BPI questionnaire

was 4.3 ± 3 for burning pain, 5 ± 3.5 for squeezing pain, 5.3 ± 2.8 for pressure pain, 5.2 ± 3.9 for electric shocks, 4.4 ± 3.1 for stabbing pain, 4.5 ± 3.9 for pain evoked by brushing, 2.7 ± 2 for pain evoked by pressure, 1.3 ± 3.2 for pain evoked by cold, 5.0 ± 3.5 for tingling, and 6.7 ± 3.5 for pins and needles.

About a third of patients (11/37) were treated with strong opioid medication, one third (13/37) with antidepressants, and another third 11/37 with gabapentinoids. The combination of two or more of these different classes were reported for 13/37 (35%) patients. Some patients (4/37) reported using cannabis regularly to alleviate pain.

Nineteen patients complained of spontaneous muscular pain. The quadriceps palpation had evoked pain in 73% of them. However, less than a third of the 37 patients examined reported tenderness in the 11 or more of 18 possible "tender points of fibromyalgia." Twenty patients complained of cutaneous hyperesthesia during touching or stroking. Among them, a repetitive caress on the forearm led to pain in 16 of them. In mechanical temporal summation tests with a Von Frey filament, the first stimulation had not induced pain in any of the patients. After 10 consecutive applications, 22 patients among the

35 examined had reported a significant increase of pain (more than 3 points).

Hypoesthesia to thermal stimulation was observed in 9/35 patients (26%) when comparing the most painful joint and contralateral joint. Heat hypoesthesia was the most frequent, one patient had both cold and heat hypoesthesia in the most painful joint. Thermal hyperalgesia was not observed (Table 3).

An asymmetry in the vibratory perception threshold was reported in nine patients among the 28 examined. One patient had an asymmetry of the vibratory perception threshold on the three joints examined (hip, knee, and ankle), a second patient had an asymmetry both on the hip and knee. The other patients had an asymmetry of perception in only one joint (four on the knee and three in the hip).

4 | DISCUSSION

Our cohort study highlights the special features of pain in hEDS patients, meeting the new criteria for hEDS according to the 2017 International Classification (Malfait et al., 2017). Previous studies had

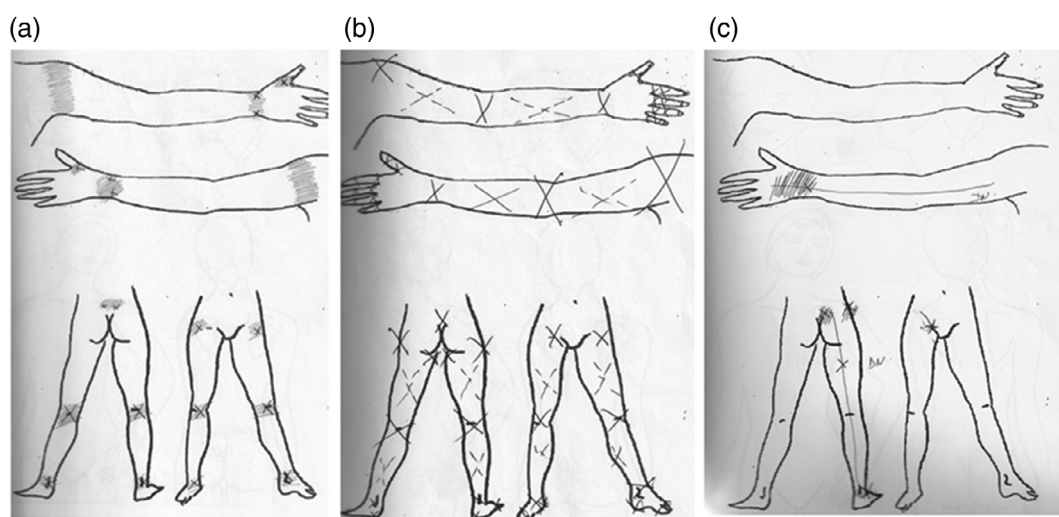
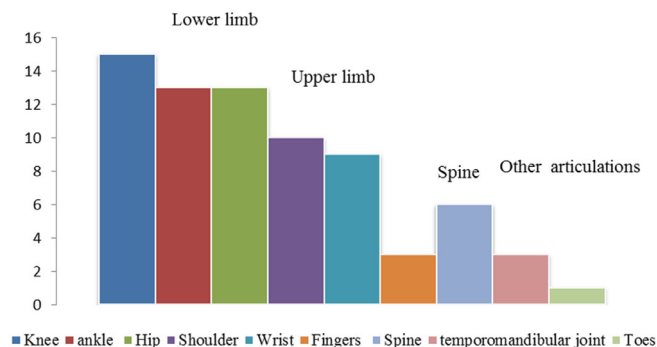


FIGURE 2 Pain drawing assessment. (a) Typical presentation: The most frequent drawing corresponding to 29 patients (78%) was as follows: Pain located in several small and large joints, both in lower and upper limbs, bilaterally. (b) Widespread presentation: Six patients (16%) reported a widespread pain located in joints and also in muscles. (c) Other presentations: Only two patients (6%) had another representation suggesting lomboradiculalgia

TABLE 2 Pain characteristics depending on pain profile (Figure 1)

	Typical presentation	Widespread presentation	p
Number of patients	29	6	
Total duration of chronic pain (years)	6 ± 5	11 ± 7	.05
Worst pain (NRS/10)	8.4 ± 1.2	8.8 ± 0.7	.4
Least pain (NRS/10)	4.5 ± 2.3	4.8 ± 1.6	.7
BPI total (/100)	58.7 ± 21	72.2 ± 21	.1
QDSA total (/60)	19.35 ± 8.2	27.75 ± 7.8	.07
QDSA sensorial (/40)	16.7 ± 6.6	20 ± 5.6	.35
QDSA affective/ (/20)	4.5 ± 2.4	8 ± 2.6	.01

Notes. In this table, pain characteristics of the two most frequent "pain drawing presentation" (i.e., Figure 1) were compared. The total duration of chronic pain and the affective impact were higher in the widespread presentation. Data are reported as mean ± SD (minimum–maximum). $p < .05$ was considered as significant.

**FIGURE 3** Most painful joints reported by patients. On the Y axis: Number of time where joints are cited in the top three most painful [Color figure can be viewed at wileyonlinelibrary.com]

included joint hypermobility syndrome and hEDS patients, considering these as overlapping clinical phenomena.

The first episode of pain in hEDS is most often consecutive to a sprain or dislocation. Then joint events multiply during adolescence and chronic pain becomes one of the predominant symptoms, often described as diffuse (Castori et al., 2013; Sacheti et al., 1997; Voermans, Knoop, van de Kamp, et al., 2010), leading to disabilities and reduced activity. Sacheti found a 100% incidence of pain in hEDS patients (Sacheti et al., 1997) whereas other authors found a slightly

lower incidence (90% in various EDS; Voermans, Knoop, Bleijenberg, & van Engelen, 2010). Our study underlines a diagnosis delay in hEDS despite an old painful joint instability, evolving since childhood. The pain, initially localized, gradually spreads to all joints and becomes permanent. Three quarters of the patients described a very progressive entry into chronic pain in frequency, intensity, and duration. When they visit the pain center for the first time, their chronic pain has been evolving for years with frequent visits to the emergency department. As reported in literature, besides musculoskeletal pain, patients often suffered from headaches, gastro-intestinal, genito-urinary, and pelvic pain (Castori et al., 2012, 2013; Syx, De Wandele, Rombaut, & Malfait, 2017; Tinkle et al., 2017).

Patients frequently experienced misdiagnosis and medical wandering. They shared some symptoms with fibromyalgia (10), and this diagnosis was frequently wrongly made because of widespread pain and major asthenia. But hEDS patients have joint hypermobility and recurrent joint dislocations since childhood, which help physicians to distinguish those diagnoses. Other doctors do not believe patients about their invisible pain (Syx et al., 2017) and misdiagnose them as having a psychological disease.

The pain history is also marked by the frequency of surgeries performed on one-third of the patients because of joint instability, before the diagnosis of hEDS has been made. This figure is worrisome because the anesthetic and surgical management of these patients should ideally be adapted to their pathology to avoid complications (risk of failure of the surgery, bleeding, poor wound healing, infection; Fogel, 2013).

Nociceptive pain is directly due to joint instability leading to repetitive joint dislocations and sprains. Muscle cramps, periarticular inflammation, entesopathies can also increase nociceptive pain (Rombaut, De Paepe, Malfait, Cools, & Calders, 2010). In our study, the pain was present in small and large joints, as already shown (6), predominating in the "supporting" joints of the lower limbs, whereas other studies reported comparable pain in lower and superior limbs (Voermans, Knoop, Bleijenberg, et al., 2010). Common additional complaints included burning sensations, generalized hyperalgesia, allodynia, and hypersensitivity to a various stimuli, as previously reported (Syx et al., 2017).

Among relevant data we found, a significant increase of pain after 10 consecutive applications of Von Frey filament, thermal hypoesthesia, heat hypoesthesia, and asymmetry in vibratory perception threshold. One limit of our cohort is the absence of a control group.

TABLE 3 Thermal quantitative sensory testing

Thermal quantitative sensory testing	Most painful joint	Contralateral side	Difference of threshold more than 2 SD between the two joints
Heat detection threshold (degree)	33 ± 2.8	35 ± 1.7*	9/35 (25%)
Cold detection threshold (degree)	28 ± 1.75	30 ± 2	1/35 (3%)
Hot pain threshold a (degree)	42 ± 3.2	41.6 ± 2.9	1/35 (3%)
Cold pain threshold (degree)	13 ± 8.3	15 ± 9.4	0/35 (0%)

Notes. Comparison of detection and pain thermal threshold between most painful joint and contralateral side. Data are reported as mean ± SD (minimum–maximum) or as number (%).

* $p < .05$.

However, the abnormalities in the quantitative sensory testing seem sufficiently obvious to enlighten the heterogeneity of the clinical symptoms of hEDS. Indeed, the presence of neuropathic pain has been reported several times among hEDS patients (Camerota, Celletti, Castori, Grammatico, & Padua, 2011; Cazzato et al., 2016; Rombaut et al., 2015), although it was not confirmed in another study that was rather in favor of hyperalgesia (Di Stefano et al., 2016). Neuropathic pain was present in 60% of the patients in a study (Camerota et al., 2011). Our data confirm neuropathic pain using the validated DN4 questionnaire in the most painful joint in 75% of the cases and suspect lesions of small nerve fibers with warm thermal hypoesthesia in one of four patients. Previous studies already found a decreased intra-epidermal nerve fiber density in EDS skin biopsies, providing evidence for small fiber neuropathy (Cazzato et al., 2016; Pascarella et al., 2016). Patients with hEDS have defects in different components of the extracellular matrix, which could impact the central and peripheral nervous system (Syx et al., 2017) and contribute to increase the vulnerability of peripheral nerves to stretching or pressure (Voermans & Knoop, 2011). Besides these nociceptive and neuropathic components, central sensitization has been described in patients with hEDS (Di Stefano et al., 2016; Rombaut et al., 2015; Scheper et al., 2017; Syx et al., 2017). A study (Scheper et al., 2017) found that generalized hyperalgesia is already present in childhood and suggested an involvement of the central nervous system in the development of chronic pain. Some authors (Rombaut et al., 2015) provided evidence for the presence of hyperalgesia even in asymptomatic areas and for a nervous system sensitization phase, which is responsible for the onset of chronicity. Our results suggest the presence of central sensitization with the presence of an increased wind-up ratio, in 37% of patients. This mechanical sensitization, previously described as a central sensitization (Di Stefano et al., 2016), could share similar mechanisms with those underlying dysfunctional pain syndrome like fibromyalgia. Widespread pain is more common in patients with a long history of pain, 11 years versus 6 years. This could be explained by long-term changes in the nervous system (development of synaptic plasticity in the peripheral and central nervous system neurons), observed in cases of intense and repeated pain (Woolf, 2007) but could be a consequence of the continuous stimulation of peripheral nociceptors by mediators released from the aberrant Extracellular Matrix (ECM) (Kawasaki et al., 2008; Syx et al., 2017; Tajerian & Clark, 2015). Diffuse hyperalgesia is therefore clearly one more step in the evolution of hEDS. Proprioception helps to protect the joints from hyperextending and damaging the ligaments, reducing joint instability and the risk of injury (Celletti et al., 2011; Clayton, Cressman, & Henriques, 2013; Hall, Ferrell, Sturrock, Hamblen, & Baxendale, 1995). The excessive joint mobility in hEDS may damage joint's proprioceptive receptors and generate chronic pain. Proprioceptive acuity could have effects on the trajectory of pain (Felson et al., 2009). In this study, we have found an asymmetry of proprioception, which reinforces the idea that joint complications could be correlated with the lack of proprioception. Physical exercises to enhance proprioception could reduce pain (Ferrell et al., 2004). Wearing somatosensory compressive garments could also help (Dupuy et al., 2017).

Our study, as others, shows how pain interferes with socialization and activities of daily life (Voermans, Knoop, van de Kamp, et al., 2010). We found a link between diffuse hyperalgesia and decrease of the quality of life, as already reported (Cazzato et al., 2016). Severe fatigue was a predominant symptom in almost all patients, confirming previous findings (Castori et al., 2013; Celletti et al., 2011). Severe kinesiphobia was spontaneously mentioned in three patients, as reported in the literature with a correlation to pain and fatigue (Hall et al., 1995). The percentage of depressed patients remained low. This result contrasts with the high rate of suicide attempts (22%) at a very young age. This alarming rate, not reported in literature, is probably a reflection of the extreme distress that patients face before the diagnosis is made. Pain in hEDS is considered to be a multifactorial perception dependent on biological, psychological, and environmental substrates (Rombaut et al., 2015). Currently, no specific treatment is available for hEDS. The treatment is only symptomatic, relying essentially on analgesics, orthotics, physical medicine, and rehabilitation, with multidisciplinary and personalized care (Syx et al., 2017). Our experience shows that it is essential to raise awareness among pain specialists of the necessity of early detection of hEDS, in collaboration with EDS reference centers, using the 2017 new diagnostic criteria, to distinguish hEDS from other dysfunctional pains. Pain killers have to be adapted to the type of pain. Strong opioid could be used against acute pain, but with caution and for a limited time to avoid misuse and addiction. The use of specific treatments for neuropathic pain should be offered if necessary (Finnerup et al., 2015). Clinicians should use a validated questionnaire to detect neuropathic pain, and search for loss of sensitivity and diffuse hyperalgesia with an interview and clinical exam. A careful assessment of the impact of pain on the quality of life and on the suicide risk should be mandatory.

5 | CONCLUSION

Patients with hEDS suffer from intense and recurrent pain, evolving toward chronic pain. Pains in hEDS are nociceptive, neuropathic, or more frequently mixed. Diffuse hyperalgesia is not rare. Unfortunately, hEDS diagnosis is often delayed due to the small number of doctors evoking this diagnosis and the lack of genetic testing. The use of the revised 2017 International Classification criteria should clarify some diagnoses, allowing to adapt medical care. Due to the phenotypical variability, an individual pain management seems necessary.

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CONFLICT OF INTEREST

None.

ORCID

Karelle Bénistan  <https://orcid.org/0000-0002-2193-457X>

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APPENDIX



The International Consortium
on Ehlers-Danlos Syndromes
& Related Disorders
In Association with The Ehlers-Danlos Society

Diagnostic Criteria for Hypermobile

Ehlers-Danlos Syndrome (hEDS)

This diagnostic checklist is for doctors across
all disciplines to be able to diagnose EDS



Distributed by

The
Ehlers
Danlos
Society.

Patient name: _____ DOB: _____ DOV: _____ Evaluator: _____

The clinical diagnosis of hypermobile EDS needs the simultaneous presence of all criteria, 1 and 2 and 3.

CRITERION 1 – Generalized Joint Hypermobility

One of the following selected:

- ☐ ≥ 6 pre-pubertal children and adolescents
- ☐ ≥ 5 pubertal men and women to age 50
- ☐ ≥ 4 men and women over the age of 50

Beighton Score: _____/9



If Beighton Score is one point below age- and sex-specific cut off, two or more of the following must also be selected to meet criterion:

- ☐ Can you now (or could you ever) place your hands flat on the floor without bending your knees?
- ☐ Can you now (or could you ever) bend your thumb to touch your forearm?
- ☐ As a child, did you amuse your friends by contorting your body into strange shapes or could you do the splits?
- ☐ As a child or teenager, did your shoulder or kneecap dislocate on more than one occasion?
- ☐ Do you consider yourself "double jointed"?

CRITERION 2 – Two or more of the following features (A, B, or C) must be present

Feature A (five must be present)

- ☐ Unusually soft or velvety skin
- ☐ Mild skin hyperextensibility
- ☐ Unexplained striae distensae or rubae at the back, groins, thighs, breasts and/or abdomen in adolescents, men or pre-pubertal women without a history of significant gain or loss of body fat or weight
- ☐ Bilateral piezogenic papules of the heel
- ☐ Recurrent or multiple abdominal hernia(s)
- ☐ Atrophic scarring involving at least two sites and without the formation of truly papyraceous and/or hemosideric scars as seen in classical EDS
- ☐ Pelvic floor, rectal, and/or uterine prolapse in children, men or nulliparous women without a history of morbid obesity or other known predisposing medical condition
- ☐ Dental crowding and high or narrow palate
- ☐ Arachnodactyly, as defined in one or more of the following:
 - (i) positive wrist sign (Walker sign) on both sides, (ii) positive thumb sign (Steinberg sign) on both sides
- ☐ Arm span-to-height ratio ≥ 1.05
- ☐ Mitral valve prolapse (MVP) mild or greater based on strict echocardiographic criteria
- ☐ Aortic root dilatation with Z-score $> +2$

Feature A total: _____/12

Feature B

- ☐ Positive family history; one or more first-degree relatives independently meeting the current criteria for hEDS

Feature C (must have at least one)

- ☐ Musculoskeletal pain in two or more limbs, recurring daily for at least 3 months
- ☐ Chronic, widespread pain for ≥ 3 months
- ☐ Recurrent joint dislocations or frank joint instability, in the absence of trauma

CRITERION 3 – All of the following prerequisites MUST be met

1. Absence of unusual skin fragility, which should prompt consideration of other types of EDS
2. Exclusion of other heritable and acquired connective tissue disorders, including autoimmune rheumatologic conditions. In patients with an acquired CTD (e.g. Lupus, Rheumatoid Arthritis, etc.), additional diagnosis of hEDS requires meeting both Features A and B of Criterion 2. Feature C of Criterion 2 (chronic pain and/or instability) cannot be counted toward a diagnosis of hEDS in this situation.
3. Exclusion of alternative diagnoses that may also include joint hypermobility by means of hypotonia and/or connective tissue laxity. Alternative diagnoses and diagnostic categories include, but are not limited to, neuromuscular disorders (e.g. Bethlem myopathy), other hereditary disorders of the connective tissue (e.g. other types of EDS, Loeys-Dietz syndrome, Marfan syndrome), and skeletal dysplasias (e.g. osteogenesis imperfecta). Exclusion of these considerations may be based upon history, physical examination, and/or molecular genetic testing, as indicated.

Diagnosis: _____