ORIGINAL ARTICLE

Medication, Surgery, and Physiotherapy Among Patients With the Hypermobility Type of Ehlers-Danlos Syndrome

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ABSTRACT. Rombaut L, Malfait F, De Wandele I, Cools A, Thijs Y, De Paepe A, Calders P. Medication, surgery, and physiotherapy among patients with the hypermobility type of Ehlers-Danlos syndrome. Arch Phys Med Rehabil 2011;92:1106-12.

Objectives: To describe medication use, surgery, and physiotherapy, and to examine the effect of these treatment modalities on functional impairment and amount of complaints among patients with the hypermobility type of Ehlers-Danlos syndrome (EDS-HT).

Design: Cross-sectional study.

Setting: Physical and rehabilitation medicine department and center for medical genetics.

Participants: Patients with EDS-HT (N=79; 8 men, 71 women) were recruited for this study.

Interventions: Not applicable.

Main Outcome Measures: Patients filled out questionnaires regarding type of complaints, medication use, surgery, physiotherapy, and outcome of treatment. Functional impairment in daily life was measured by the Sickness Impact Profile. Pain severity was assessed with visual analog scales.

Results: Patients reported a large number of complaints, a considerable presence of severe pain, and a clinically significant impact of disease on daily functioning. Most patients (92.4%) used medications, among which analgesics were the most prevalent. Fifty-six patients (70.9%) underwent surgery, including mainly interventions of the extremities and abdomen. Forty-one patients (51.9%) are currently enrolled in a physical therapy program, mainly comprising neuromuscular exercises, massage, and electrotherapy. Patients with a high consumption of analgesics, who visited the physiotherapist, or who underwent surgery had a higher dysfunction in daily life. Only 33.9% of the patients who underwent surgery and 63.4% of patients in physical therapy reported a positive outcome.

Conclusions: Patients with EDS-HT have numerous complaints and an impaired functional status that strongly determine their high rate of treatment consumption. The outcome of surgical and physiotherapy treatment is disappointing in a large percentage, which illustrates a strong need for evidence-based therapy.

Key Words: Ehlers-Danlos syndrome; Drug therapy; General surgery; Physiotherapy; Rehabilitation.

EHLERS-DANLOS SYNDROME (EDS) is a group of heritable connective tissue disorders characterized by defects in the biosynthesis of fibrillar collagens, the secretion of fibrillar collagens, or both.[1-3] Among all connective tissue disorders, EDS is thought to be the most prevalent (1:5000–1:10,000).[1,3] The 3 prominent features of this disorder are skin laxity, joint hypermobility, and tissue fragility.[4,5] According to the Villefranche criteria, 6 major types are recognized on clinical, genetic, and biochemical grounds.[5,6] However, most patients with EDS have the hypermobility type (EDS-HT), in which generalized severe joint hypermobility, joint dislocations, and chronic pain are important manifestations.[6] Furthermore, fatigue, muscle weakness, and muscle cramps are common associated features.[7-12] Overall, EDS-HT is considered to be a severe, chronic musculoskeletal disorder.

Chronic musculoskeletal disorders require more attention from society and health care systems because they are the most common causes of impairment leading to deterioration in health-related quality of life.[13] Moreover, these conditions inflict an enormous direct (health care utilization) and indirect (loss of productivity) cost on health care systems.[14]

Regarding EDS-HT, many patients are subject to the burden of delayed diagnosis and misdiagnosis, incredibility when seeking health care, and inappropriate treatment.[15-17] Because EDS is a complex disorder that is often not visible externally at first glance, and because knowledge concerning EDS is very limited among health care professionals, this challenging disorder generally receives little attention in clinical practice and research. Consequently, treatment of EDS-HT is currently poorly defined and described.

Levy[18] mentions different types of treatment for EDS, such as physiotherapy (electrotherapy, hydrotherapy, massage, low-resistance muscle-toning exercise, core stability training), medication (mainly pain management, supplementation with magnesium, glucosamine, and chondroitin), surgery (orthopedic, gastrointestinal, and cardiovascular procedures), and psychological treatment (consumer support groups, cognitive-behavioral therapy). However, the description of these treatment modalities is based on theoretic concepts and practical knowledge of other disease states with local or general problems comparable to those of EDS-HT. Currently, objective data on the different types of treatments consumed by patients with EDS-HT and the effect of these treatments are lacking. Therefore, the purpose of this study was to describe medication use,

List of Abbreviations

EDS	Ehlers-Danlos syndrome
EDS-HT	hypermobility type of EDS
NSAIDs	nonsteroidal anti-inflammatory drugs
SIP	Sickness Impact Profile
TENS	transcutaneous electrical nerve stimulation
VAS	visual analog scale
WHO	World Health Organization

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surgical treatment, and physiotherapy, and to examine the effect of these treatment modalities on functional impairment and the amount of complaints in patients with EDS-HT.

METHODS

Participants

Seventy-nine adult patients with EDS-HT, 8 men and 71 women, participated in the study. Patient selection was performed in the department of Centre for Medical Genetics at the Ghent University Hospital on the basis of the Revised Villefranche Criteria, including the presence of generalized joint hypermobility and/or skin hyperextensibility/fragility, in combination with recurring joint dislocations, and/or chronic musculoskeletal pain, and/or a positive family history.[6] Pregnant women were excluded from the study group. After a routine follow-up physician's visit, every eligible patient received written information about the purpose of the study. Seventy-nine patients consented to participate, and 7 patients declined. The patients who agreed to participate signed an informed consent and received the questionnaires with a stamped return envelope enclosed. All questionnaires were returned complete and were used in the data analysis. The research design was reviewed and approved by the local Ethics Committee of the Ghent University Hospital.

Data Collection

Demographic and clinical data. Background data on age, sex, educational status, living status, and employment status were recorded (table 1). Information regarding EDS symptoms was collected using a self-reported questionnaire enquiring about symptoms experienced on a regular basis. Similar complaints were combined for analysis (table 2).

Medication use, surgery, and physiotherapy. A specific sheet for data collection was developed for the purpose of this study. The first question concerns the presence of medication use (yes or no), surgery (yes or no), and physiotherapy (yes or no).

Regarding medication, the variety of medication use ("Which medication do you regularly use?") was questioned. Homeopathic medication, vitamins, and nutrition supplements were excluded. Afterwards, groups of medication types were made based on the pharmaceutical compendium. In addition, analgesics were categorized in 3 classes according to the 3-step pain-relief ladder of the World Health Organization (WHO).[19] In the lowest step, nonopiates (eg, paracetamol, nonsteroidal anti-inflammatory drugs [NSAIDs] such as ibuprofen) with or without adjuvants (antidepressants, anticonvulsants) are used for mild pain. In the second step, weak opiates (eg, tramadol, codeine, propoxyphene) with or without nonopiates and adjuvants are used for moderate pain. If pain increases in intensity, strong opiates (eg, morphine, fentanyl, oxycodone) are used with or without other pain-relieving products and adjuvants (third step).[20]

Regarding surgery, localization ("Where did you have surgery?"), frequency ("How many times did you have surgery on that location?"), and effect/outcome (positive, neutral, negative) of surgical treatment were questioned.

Regarding physiotherapy, the type of treatment ("What treatment do you receive in the physical therapy program?") was questioned. Afterwards, groups of treatment modalities were made. Also, frequency ("How often do you visit the physiotherapist per week?") and effect/outcome (positive, neutral, negative) of the physical therapy program were evaluated.

A positive effect indicates the patient's perception of physical improvement as a result of the treatment.

Functional impairment in daily life. We used a validated Dutch (for the northern part of Belgium) and French (for the southern part of Belgium) version of the Sickness Impact Profile (SIP) to measure changes of conduct in everyday activities because of sickness.[21-23] The standardized questionnaire consists of 136 items grouped into 12 subscales comprising ambulation, mobility, and body care and movement (the physical dimension); social interaction, communication, alert-

Table 1: Demographic Data of the EDS-HT Group

Variables	EDS-HT Group (N=79)
Age (y)	40±12.7
Sex (F/M)	71 (90)/8 (10)
Educational status	
Primary school	12 (15)
Secondary school	20 (25)
High school	47 (60)
Living status	
Living alone/divorced	29 (37)
Cohabitant/married	50 (63)
Employment status	
Employed	29 (37)
Unemployed (neither paid nor volunteer work)	50 (63)
Sick leave/disability pension	30 (38)

NOTE. Values are mean ± SD or n (%).
Abbreviations: F, female; M, male.

Table 2: Self-Reported Complaints of the EDS-HT Group

Type of Complaints	EDS-HT Group (N=79)
Pain (joint pain, muscle pain)	79 (100)
Joint problems (dislocation, distortion, pelvic instability, snapping hip, joint lock)	67 (84.8)
Muscle problems (muscle cramps, muscle weakness, muscle stiffness, tendinitis)	51 (64.6)
Skin fragility (easy bruising and rupture, difficult wound healing, papyrus scars)	50 (63.3)
Symptoms suggestive of dysautonomia (dizziness, nausea, feeling faint after standing up, syncope, bloating, vomiting, constipation, heat flushes, urine retention)	46 (58.2)
Fatigue	39 (49.4)
Headaches	29 (36.7)
Neurologic symptoms (paresis, paralysis, paresthesias, sciatica, spasticity)	23 (29.1)
Infections/illness (recurrent infections, repeated colds, recurrent influenza)	22 (27.8)
Cardiorespiratory symptoms (heart palpitations, hypotension/hypertension, breathing difficulties, asthma)	13 (16.5)
Sleeping problems (difficulties falling asleep, difficulties staying asleep, early awakening)	13 (16.5)
Exercise intolerance (bad physical condition, exhaustion after walking a short distance)	12 (15.2)
Inflammation (warm red joints)	12 (15.2)
Cognitive problems (forgetfulness, making mistakes)	8 (10.1)
Logopedic problems (difficulties with swallowing, vocal problems)	6 (7.6)

NOTE. Values are n (%).

ness behavior, and emotional behavior (the psychosocial dimension); and the independent subscales of sleep and rest, eating, work, home management, and recreation and pastimes. A percentage score (0–100) was obtained for each individual subscale, for the 2 dimensions, and for the overall SIP. Higher scores indicate more functional impairment. A score above 10 is arbitrarily considered to indicate a clinically significant dysfunction, a score between 0 and 10 indicates mild dysfunction lacking clinical importance, and a score of 0 indicates no dysfunction.

Pain severity. Pain severity was scored as current pain and average pain over the last week, measured with a visual analog scale (VAS). A score of 0 indicates no pain, and a score of 100 indicates unbearable pain.

Analyses and Statistics

Data were analyzed using the Statistical Package for Social Sciences (SPSS), version 17.0.[a] Descriptive statistics are shown as mean ± SD for continuous data, and percentages or absolute frequencies for categorical data. Because preanalyses revealed that older patients consumed more medication, had more surgery, and had more physiotherapy, age was a covariate in subsequent analyses. Other demographic variables did not significantly correlate with any treatment.

To evaluate the effect of treatment (use of medication, surgery, and physiotherapy) on functional impairment in daily life (SIP scores) and number of complaints, analysis of covariance with Bonferroni procedure was used. $P<.05$ was regarded as statistically significant.

RESULTS

Demographic and Clinical Data

The description of the study population is shown in table 1. Patients in the EDS-HT group had a mean age of 40.0 years, were mostly women (90%), were mainly educated at the level of higher education (60%), and were mainly cohabitant or married (63%). A large number (63%) were unemployed, of which 38% received sick leave benefits or a disability pension.

The mean number of complaints reported in the study group was 5±2.2, ranging from 1 to 13. All patients with EDS-HT reported pain (100%), nearly all had joint problems (84.8%), and 64.6% of the group experienced muscle problems. There was also a high prevalence of nonmusculoskeletal complaints, such as symptoms of skin fragility (63.3%), symptoms suggestive of dysautonomia (58.2%), fatigue (49.4%), headaches (36.7%), neurologic problems (29.1%), and recurrent infections/illness (27.8%) (see table 2).

Medication Use, Surgery, and Physiotherapy

Only 6 patients (4 men, 2 women) did not use any medication (table 3). These patients only had a few complaints, did not experience any clinically significant functional impairment (SIP score between 1.9 and 3.6 out of 100), and had low pain scores (VAS current pain, 0–17/100; VAS average pain last week, 0–33/100). None of them were enrolled in a physical therapy program and only one of them underwent surgery once (at the knee joint).

The other 73 patients with EDS (92.4%) used a variety of drugs, with a mean number of 3±2.4 per patient (range, 1–11). Analgesics were the most prevalent medication type, used by all 73 patients. Within this category, paracetamol and NSAIDs were used by a considerable number of patients (65% and 53%, respectively), whereas opiates were used by more than one third of the patient group, and a few patients reported using other substrates. According to the WHO medication steps, approximately half of the patients were situated in step 1, one quarter in step 2, and only 11.4% in the highest step. Besides pain medication, the use of antidepressants and sedatives was also substantially reported.

The total reported numbers of medicines were consistently higher than the number of patients using that type of medication, indicating that several substrates were combined by the patients.

Fifty-six patients (70.9%) in this study group underwent surgery (see table 3). The mean number of surgical interventions was 2±2.5, ranging from 0 to 15. Thirty-three patients

Table 3: Medication Use, Surgical Treatment, and Physiotherapy Reported by the EDS-HT Group

Variables	EDS-HT Group (N=79)	Total Reported Numbers
Medication	73 (92.4)*	241
Analgesics	73 (100)†	141
Paracetamol	48 (65.6)†	51
NSAIDs (eg, ibuprofen, naproxen, oxicam, diclofenac)	39 (53.4)†	47
Opiates (eg, tramadol, codeine, morphine, fentanyl)	27 (37.0)†	37
Other	6 (8.2)†	6
Antidepressants (eg, amitriptyline, duloxetine, trazadone)	15 (20.5)†	19
Sedatives (benzodiazepines)	15 (20.5)†	18
Cardiovascular medication (α-blockers, diuretics, ACE inhibitors)	11 (15.1)†	18
Pulmonary medication (α-sympathomimetics)	10 (13.,7)†	10
Other	25 (34.,2)†	35
WHO steps‡		
No analgesics	6 (7.6)*	NA
WHO Step 1	43 (54.4)*	NA
WHO Step 2	20 (25.3)*	NA
WHO Step 3	9 (11.4)*	NA
Surgery	56 (70.9)*	175
Upper limb	21 (37.5)†	52
Lower limb	33 (58.9)†	62
Spine	9 (16.1)†	11
Abdominal	20 (35.7)†	33
Eye	5 (8.9)†	11
Other	5 (8.9)†	6
Physiotherapy	41 (51.9)*	
Muscle strength training	27 (65.9)†	NA
Massage	25 (61.0)†	NA
Stabilization training	20 (48.8)†	NA
Electrotherapy	14 (34.1)†	NA
Manual therapy	12 (29.3)†	NA
Aquatic therapy	12 (29.3)†	NA
Heat therapy	6 (14.6)†	NA
Stretching	5 (12.1)†	NA
Other	5 (12.1)†	NA

Abbreviation: ACE, angiotensin-converting enzyme; NA, not applicable.
*Number of patients consuming a therapeutic mode (percentage of total sample).
†Detailed therapeutic information was expressed as number of patients (percentage of sample consuming that therapeutic mode).
‡WHO steps: use of analgesics was categorized according to the 3-step pain-relief ladder of the WHO (see methodology).

underwent 62 operations at the lower limb including, in decreasing order of frequency, the knee, ankle/foot, pelvis, and toe. Twenty-one patients underwent 52 operations at the upper limb, including mainly shoulder and hand/wrist surgery. In addition, 33 operations, of which 15 were appendectomies, were performed at the abdomen of 20 patients. In only 33.9% of cases, patients reported a positive effect of the surgical intervention.

Forty-one patients (51.9%) in this EDS-HT group were currently enrolled in a physical therapy program (see table 3). The mean frequency of visits to the physiotherapist was twice a week (±1.1), with a range from 1 to 5 times a week. The specific treatment they received mainly comprised muscle strength training, massage, joint stabilization training, electrotherapy (eg, transcutaneous electrical nerve stimulation [TENS]), manual therapy consisting of gentle mobilizations within the range of motion and/or manipulations, and aquatic therapy. For most patients (29 of 41 [70.7%]), the physical therapy program consisted of a combination of 3 treatment modalities (range, 2–5 modalities). The combinations observed in this patient group were rather heterogeneous. However, stabilization with muscle strength exercises, and massage combined with electrotherapy were reported by 16 and 12 patients, respectively.

In 63.4% of cases, patients reported a positive effect of the physiotherapeutic treatment they received.

Functional Impairment in Daily Life

The mean overall SIP score for the EDS-HT group was 18.7±11.50, indicating a clinically significant impact of disease on daily functioning (table 4). The scores on the physical as well as the psychosocial dimension of the SIP both contributed to this impairment. The most severe dysfunction was observed in the subscales of work, recreation and pastimes, home management, sleep and rest, and alertness behavior, and the least dysfunction (lacking clinical evidence) in the subscales of eating and communication.

Pain Severity

The mean VAS score was 48.9±24.1 for current pain, and 56.2±20.1 for average pain over the last week, indicating an important presence of severe daily pain.

Table 4: Functional Impairment in the EDS-HT Group

Daily Functioning	SIP Score
Overall functioning	18.7±11.50
Physical functioning	14.3±12.89
Ambulation	18.4±17.20
Body care and movement	13.2±12.21
Mobility	12.6±16.69
Psychosocial functioning	17.5±13.14
Emotional behavior	19.0±17.88
Social interaction	16.7±16.51
Alertness behavior	26.5±23.50
Communication	8.1±10.91
Independent scales	
Sleep and rest	27.8±21.74
Home management	27.4±20.51
Work	46.6±31.59
Recreation and pastimes	33.3±18.66
Eating	3.6±6.17

NOTE. Values are mean ± SD.

Effect of Treatment on Functional Impairment and Complaints

Regarding analgesic use, the results revealed that the number of complaints was significantly higher in patients who used strong opiate medication (step 3) compared with patients who used no medication (step 0) ($P=.013$). Further, significant differences in SIP scores regarding overall, physical, and psychosocial impairment were found between the groups of medication (table 5). Overall, the results denote that patients with a stronger analgesic consumption experienced higher dysfunction in daily life.

In addition, function, specifically on the physical level, was significantly more impaired in patients who underwent surgery in comparison with the patients who did not have any surgery ($P=.044$ overall SIP score, $P=.003$ physical SIP score). The number of complaints did not differ between both groups (see table 5).

Patients with EDS-HT who reported to be enrolled in a physical therapy program had significantly higher scores regarding overall ($P=.002$), physical ($P=.002$), and psychosocial ($P=.015$) impairment, and had significantly more complaints ($P=.022$) than the patients with EDS-HT who did not visit the physiotherapist (see table 5).

DISCUSSION

In this cohort of patients with EDS-HT, important musculoskeletal and nonmusculoskeletal complaints, marked functional impairment, and severe pain are present. Patients with EDS-HT are consuming a large amount of medication, and frequently undergoing surgery and receiving physiotherapy, although the outcome of physiotherapy and certainly surgery is often disappointing.

The results of this study confirm that EDS-HT is a severe, chronic musculoskeletal disorder. Pain, joint problems, and muscle problems are omnipresent, but also a large number of nonmusculoskeletal problems are reported. These results are in accordance with those of previous studies in patients with EDS.[8-10,12,24-26] This high number of complaints results in a high consumption of medication, surgery, and physiotherapy.

Almost every patient with EDS-HT used several types of medication, mainly analgesics. The high level of analgesic consumption is a consequence of the high prevalence of pain in this population.[25-27] According to the pain-relief ladder of the WHO, our population was situated mainly in step 1 and 2, which is said to reflect mild to moderate pain associated with the use of nonopiates, weak opiates, or both, either in combination with or not in combination with adjuvants.[20] However, the pain severity scores reported by these patients indicate that their pain intensity is severe rather than mild to moderate. The pain often reaches a level and an intensity that is not reconcilable with normal daily life functioning. As such, analgesic medication is often perceived as insufficient and unsatisfactory in this patient group. The basis for this resistance to pain control is unknown, but suggests a possible defect in pain processing (central sensitization). Besides, patients carry the risk of serious side effects, in particular constipation and gastrointestinal bleeding, when taking opiates and NSAIDs, respectively.

Moreover, the patient group reported a high consumption of antidepressants. A plausible explanation can be found in several observations of increased rates of anxiety, depression, anger, and interpersonal concerns in patients with EDS.[16,28] Another explanation may be that tricyclic antidepressants, especially amitriptyline, have been found useful in the treatment of neuropathic pain, which probably also occurs in this popu-

Table 5: Effect of Treatment (Medication, Surgery, Physiotherapy) on Functional Impairment and Complaints

Variables	Physiotherapy			Surgery			WHO-Medication Steps				
	Yes (n=41)	No (n=38)	*P*	Yes (n=56)	No (n=23)	*P*	0 (n=6)	1 (n=43)	2 (n=20)	3 (n=9)	*P*
Functional impairment (SIP)											
Total score	23.1±10.62	14.0±10.67	.002*	20.6±12.19	14.2±8.29	.044*	4.1±2.10†‡	17.0±9.57§	21.5±10.25	30.8±13.81	<.001*
Physical score	19.2±13.54	9.0±9.75	.002*	17.2±13.32	7.3±8.40	.003*	2.7±4.03†	11.1±10.13§‖	19.9±13.81	25.4±15.07	<.001*
Psychosocial score	21.5±11.89	13.3±13.27	.015*	18.7±13.91	14.7±10.79	.300	3.2±4.02†	17.6±12.71	16.3±11.27¶	29.3±13.82	.003*
Number of complaints	5±1.8	4±2.3	.022*	4±2.1	4±2.3	.440	3±1.2°	5±2.3	5±1.6	6±1.9	.023*

NOTE. Values are mean ± SD or as otherwise indicated. WHO medication steps: use of analgesics was categorized according to the 3-step pain-relief ladder of the WHO (see methodology). Analysis of covariance adjusted for age was performed. (n = number of patients).

*Significant between-group difference, $P<.05$.
†Significant between step 0 and 3 difference, $P<.05$.
‡Significant between step 0 and 2 difference, $P<.05$.
§Significant between step 1 and 3 difference, $P<.05$.
‖Significant between step 1 and 2 difference, $P<.05$.
¶Significant between step 2 and 3 difference, $P<.05$.

lation.[20,29] Beneficial effects have been reported in studies of chronic musculoskeletal pain problems, such as fibromyalgia and low back pain.[30] Future research is needed to establish the appropriate pharmacologic pain treatment (concerning product, dose, and combinations) in EDS-HT.

Further, sedatives were used by 1 of 5 patients, which can be explained by the presence of sleeping problems in EDS-HT (20%).[7] In contrast, it is unknown whether the use of cardiovascular and pulmonary medication is related to the presence of EDS.

Also, nonpharmacologic treatments comprise an important portion of the treatment consumption in patients with EDS-HT. The results of this study reveal a high prevalence of surgery, mainly involving the upper and lower extremities. This is plausible because EDS-HT is a musculoskeletal disorder with a high rate of (sub)luxations and joint pain. Instability of almost every joint has been reported, with the highest incidence in the shoulder, wrist and fingers (upper extremity), knee, hip and ankle (lower extremity), and jaw.[10,31,32] This is consistent with the most prevalent localizations for surgery in the study group. Also, a high number of abdominal surgical interventions (n=33) were reported. Some studies point towards the presence of structural anomalies, such as diverticula, bowel perforations, bowel dilatations, and megacolon.[33,34]

The effect of the surgical intervention was only favorable in a limited percentage of patients (33.9%). In fact, the results are often disappointing to both the patient and the surgeon.[35] According to Grahame,[35] 3 basic problems arise. First, tissues are less robust in patients with EDS-HT, making them less amenable to surgical procedures. Second, blood vessel fragility can cause technical problems in wound closure and homeostasis during surgery. Third, healing is often delayed and may remain incomplete. As a consequence, adapted techniques and detailed information about the consequences of EDS-HT are required to improve surgical results.

Physiotherapy in its various modalities forms a mainstay of treatment for several chronic musculoskeletal disorders. In this study, muscle strength training, joint stabilization training, massage, electrotherapy, manual therapy, and aquatic therapy are frequently reported treatment modes.

Low-dose muscle strength exercises and joint stabilization exercises, including proprioceptive enhancement and reeducation of muscle control, are likely appropriate treatment modalities in hypermobile patients because the proprioceptive and muscular system play important roles in joint stability.[36] Moreover, proprioception and quantitative muscle function have been shown to be defective in patients with EDS-HT.[8,37,38] Muscle strength training, as part of physical fitness, could also be a relevant treatment modality to recondition patients with EDS-HT, who have a decreased level of physical activity and who are easily fatigued.[9,10] A proper medium for achieving physical goals, with simultaneously psychological and social benefits, is aquatic therapy.[39]

Further, massage and electrotherapy were frequently reported. In most cases, massage is applied to reduce pain and stress. This technique is widely used in patients with chronic low back and neck pain, knee osteoarthritis, fibromyalgia, myofascial pain syndrome, and migraine headache.[40] Also electrotherapy, especially TENS, has been used in several chronic widespread pain conditions since the 1960s, in which it is proposed to have an adjuvant role to reduce localized musculoskeletal pain.[41,42] In addition, hands-on therapeutic techniques are able to resolve localized musculoskeletal pain problems. Effectiveness is proven in chronic fatigue syndrome, a condition displaying several clinical similarities with EDS-HT

regarding joint and muscle pain, fatigue, and functional impairment.[43]

Unfortunately, until now, proven physiotherapeutic treatment techniques are absent in EDS-HT. In spite of this, 63.4% of the patients reported a positive effect after physical therapy. This could be because physiotherapists apply treatment principles based on clinical experience gained in other populations or based on theoretic concepts. Nevertheless, in almost 40% of the cases, therapy seems ineffective, which is reflected by the patient as a neutral or even a negative outcome. Consequently, further research to establish a high-quality, evidence-based physical therapy for this specific population is urgently needed.

Regarding the effect of the treatments on functionality and number of complaints, we show that the patients with EDS-HT who consumed medication, surgery, or physiotherapy had more complaints and were more impaired in daily life than patients without treatment. The SIP scores in our study are in agreement with previous results of clinically relevant dysfunction in patients with EDS.[9,10,24] These results reflect that the treatments consumed by most of our patients with EDS-HT are not sufficiently effective. To tackle this problem, evidence-based interventions in different therapeutic fields are needed.[44]

Study Limitations

The present results must be viewed within the limitations of the study. We chose to use a self-report method concerning treatment questioning. This reveals a lot of information, but not always correctly described, which can make categorization difficult, even with error. On the other hand, this is the first study that makes an inventory of different treatment modalities in a population of patients with EDS-HT and that reveals relations with complaints and functional disability.

CONCLUSIONS

This study reveals that patients with EDS-HT have a significant number of musculoskeletal and nonmusculoskeletal complaints. These complaints, resulting in substantial functional impairment, trigger a substantial use of treatment, which is insufficient in a considerable percentage of patients. The study highlights the need for effective evidenced-based treatment strategies in this challenging but very rewarding group of patients. In the light of our findings, further research should focus on the contributing pain mechanisms and sources of pain to gain better pain management, on adapted techniques for surgery, and on the effectiveness of physiotherapeutic approaches in patients with EDS-HT.

References

1. Beighton P, De Paepe A, Hall JG, et al. Molecular nosology of heritable disorders of connective tissue. Am J Med Genet 1992; 42:431-48.
2. Steinmann B, Royce PM, Superti-Furga A. The Ehlers-Danlos syndrome. In: Royce P, Steinmann B, editors. Connective tissue and its heritable disorders: molecular, genetic and medical aspects. New York: Wiley-Liss; 1993. p 351-407.
3. Grahame R. Heritable disorders of connective tissue. Best Pract Res Clin Rheumatol 2000;14:345-61.
4. Beighton P. Ehlers-Danlos syndrome. Ann Rheum Dis 1970;29: 332-3.
5. Beighton P, De Paepe A, Danks D, et al. International nosology of heritable disorders of connective tissue, Berlin, 1986. Am J Med Genet 1988;29:581-94.
6. Beighton P, De Paepe A, Steinmann B, Tsipouras P, Wenstrup RJ. Ehlers-Danlos syndromes: revised nosology, Villefranche, 1997. Ehlers-Danlos National Foundation (USA) and Ehlers-Danlos Support Group (UK). Am J Med Genet 1998;77:31-7.
7. Verbraecken J, Declerck A, Van de Heyning P, De Backer W, Wouters EF. Evaluation for sleep apnea in patients with Ehlers-Danlos syndrome and Marfan: a questionnaire study. Clin Genet 2001;60:360-5.
8. Voermans NC, van Alfen N, Pillen S, et al. Neuromuscular involvement in various types of Ehlers-Danlos syndrome. Ann Neurol 2009;65:687-97.
9. Voermans NC, Knoop H, van de Kamp N, Hamel BC, Bleijenberg G, van Engelen BG. Fatigue is a frequent and clinically relevant problem in Ehlers-Danlos syndrome. Semin Arthritis Rheum 2010;40:267-74.
10. Rombaut L, Malfait F, Cools A, De Paepe A, Calders P. Musculoskeletal complaints, physical activity and health-related quality of life among patients with the Ehlers-Danlos syndrome hypermobility type. Disabil Rehabil 2010;32:1339-45.
11. Voermans N, Knoop H. Both pain and fatigue are important possible determinants of disability in patients with the Ehlers-Danlos syndrome hypermobility type. Disabil Rehabil 2010 Nov 15. [PubMed Epub ahead of print].
12. Maeland S, Assmus J, Berglund B. Subjective health complaints in individuals with Ehlers-Danlos syndrome: a questionnaire study. Int J Nurs Stud 2010; Nov 20. [PubMed Epub ahead of print].
13. Smolen JS. Combating the burden of musculoskeletal conditions. Ann Rheum Dis 2004;63:329.
14. Woolf AD. The bone and joint decade. Strategies to reduce the burden of disease: the Bone and Joint Monitor Project. J Rheumatol 2003;30(Suppl 67):6-9.
15. Castori M, Camerota F, Celletti C, et al. Natural history and manifestations of the hypermobility type Ehlers-Danlos syndrome: a pilot study on 21 patients. Am J Med Genet A 2010; 152A:556-64.
16. Berglund B, Nordström G, Lützén K. Living a restricted life with Ehlers-Danlos syndrome (EDS). Int J Nurs Stud 2000;37:111-8.
17. Berglund B, Mattiasson AC, Randers I. Dignity not fully upheld when seeking health care: experiences expressed by individuals suffering from Ehlers-Danlos Syndrome. Disabil Rehabil 2010; 32:1-7.
18. Levy HP. Ehlers-Danlos syndrome, hypermobility type. 2004 Oct 22. In: Pagon RA, Bird TC, Dolan CR, Stephens K, editors. GeneReviews. Seattle: University of Washington, Seattle; 1993. Available at: http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=eds3. Accessed April 27, 2010.
19. World Health Organization. WHO's pain ladder. Available at: http://www.who.int/cancer/palliative/painladder/en/. Accessed April 28, 2011.
20. Bergman S. Management of musculoskeletal pain. Best Pract Res Clin Rheumatol 2007;21:153-66.
21. Bergner M, Bobbitt RA, Carter WB, Gilson BS. The Sickness Impact Profile: development and final revision of a health status measure. Med Care 1981;19:787-805.
22. Jacobs HM, Luttik A, Touw-Otten FW, de Melker RA. The Sickness Impact Profile; results of an evaluation study of the Dutch version. Ned Tijdschr Geneeskd 1990;134:1950-4. [Dutch].
23. Chwalow AJ, Lurie A, Bean K, et al. A French version of the Sickness Impact Profile (SIP): stages in the cross cultural validation of a generic quality of life scale. Fundam Clin Pharmacol 1992;6:319-26.
24. Berglund B, Nordström G. Symptoms and functional health status of individuals with Ehlers-Danlos syndrome (EDS). J Clin Rheumatol 2001;7:308-14.
25. Sacheti A, Szemere J, Bernstein B, Tafas T, Schechter N, Tsipouras P. Chronic pain is a manifestation of the Ehlers-Danlos syndrome. J Pain Symptom Manage 1997;14:88-93.

26. Voermans NC, Knoop H, Bleijenberg G, van Engelen BG. Pain in Ehlers-Danlos syndrome is common, severe, and associated with functional impairment. J Pain Symptom Manage 2010;40:370-8.
27. Lang LJ, Pierer M, Stein C, Baerwald C. Opioids in rheumatic diseases. Ann N Y Acad Sci 2010;1193:111-6.
28. Lumley MA, Jordan M, Rubenstein R, Tsipouras P, Evans MI. Psychosocial functioning in the Ehlers-Danlos syndrome. Am J Med Genet 1994;53:149-52.
29. Saarto T, Wiffen PJ. Antidepressants for neuropathic pain: a Cochrane review. J Neurol Neurosurg Psychiatry 2010;81:1372-3.
30. Maizels M, McCarberg B. Antidepressants and antiepileptic drugs for chronic non-cancer pain. Am Fam Physician 2005;71:483-90.
31. Stanitski DF, Nadjarian R, Stanitski CL, Bawle E, Tsipouras P. Orthopaedic manifestations of Ehlers-Danlos syndrome. Clin Orthop Relat Res 2000;376:213-21.
32. Rose PS, Johnson CA, Hungerford DS, McFarland EG. Total knee arthroplasty in Ehlers-Danlos syndrome. J Arthroplasty 2004;19: 190-6.
33. Mohammed SD, Lunniss PJ, Zarate N, et al. Joint hypermobility and rectal evacuatory dysfunction: an etiological link in abnormal connective tissue? Neurogastroenterol Motil 2010;22:1085-e283.
34. Zarate N, Farmer AD, Grahame R, et al. Unexplained gastrointestinal symptoms and joint hypermobility: is connective tissue the missing link? Neurogastroenterol Motil 2010;22:252-e78.
35. Grahame R. Overall management of the joint hypermobility syndrome. In: Keer R, Grahame R, editors. Hypermobility syndrome. Recognition and management for physiotherapists. Philadelphia: Butterworth-Heinemann; 2003. p 27-33.
36. Riemann BL, Lephart SM. The sensorimotor system, part I: the physiologic basis of functional joint stability. J Athl Train 2002; 37:71-9.
37. Rombaut L, Malfait F, Cools A, De Paepe A, Calders P. Joint position sense and vibratory perception sense in patients with the Ehlers-Danlos syndrome type III (hypermobility type). Clin Rheumatol 2010;29:289-95.
38. Voermans NC, Altenburg TM, Hamel BC, de Haan A, van Engelen BG. Reduced quantitative muscle function in tenascin-X deficient Ehlers-Danlos patients. Neuromuscul Disord 2007;17: 597-602.
39. Skinner AT, Thomson AM. Duffield's exercise in water. 3rd ed. London: Baillière Tindall; 1993.
40. Bronfort G, Haas M, Evans R, Leininger B, Triano J. Effectiveness of manual therapies: the UK evidence report. Chiropr Osteopat 2010;18:3.
41. Osiri M, Welch V, Brosseau L, et al. Transcutaneous electrical nerve stimulation for knee osteoarthritis. Cochrane Database Syst Rev. 2009;(4):CD002823.
42. Offenbächer M, Stucki G. Physical therapy in the treatment of fibromyalgia. Scand J Rheumatol 2000;113:78-85.
43. Nijs J, Meeus M, De Meirleir K. Chronic musculoskeletal pain in chronic fatigue syndrome: recent developments and therapeutic implications. Man Ther 2006;11:187-91.
44. Grahame R. Time to take hypermobility seriously. Rheumatology 2001;40:485-91.

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