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Clinical heterogeneity in patients with the hypermobility type of Ehlers-Danlos Syndrome

Inge De Wandele [a,1,*], Lies Rombaut [a,1], Fransiska Malfait [b], Tine De Backer [c], Anne De Paepe [b], Patrick Calders [a]

[a] Department of Rehabilitation Sciences and Physiotherapy, Ghent University – Artevelde University College, Ghent, Belgium
[b] Centre for Medical Genetics, Ghent University Hospital, Ghent, Belgium
[c] Heymans Institute of Pharmacology, Ghent University, Ghent, Belgium

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ABSTRACT

EDS-HT is a connective tissue disorder characterized by large inter-individual differences in the clinical presentation, complicating diagnosis and treatment. We aim to describe the clinical heterogeneity and to investigate whether differences in the symptom profile are also reflected as disparity in functional impairment and pain experience. In this study, 78 patients were asked to describe their symptoms due to EDS-HT. Next, a hierarchical cluster analysis was performed using the Jaccard measure of similarity to assess whether subgroups could be distinguished based on the symptoms reported. This analysis yielded 3 clusters of participants with distinct complaint profiles. The key differences were found in the domain of non-musculoskeletal complaints, which was significantly larger in cluster 2. Furthermore, cluster 2 was characterized by a worse physical and psychosocial health, a higher pain severity and a larger pain interference in daily life. The results emphasize that non-musculoskeletal symptoms are an important complication of EDS-HT, as the number of these complaints was found to be a significant predictor for both functional health status (SIP) and pain experience (MPI). In conclusion, this study confirms that EDS-HT is a heterogeneous entity and encourages the clinician to be more aware of the large variety of EDS-HT symptoms, in order to improve disease recognition and to establish more tailored treatment strategies.

1. Introduction

The Ehlers-Danlos syndrome (EDS) comprises a heterogeneous group of heritable connective tissue disorders, characterized by an abnormal biosynthesis or secretion of fibrillar collagens (Beighton, De Paepe, Steinmann, Tsipouras, & Wenstrup, 1998). The three main clinical manifestations of EDS are joint hypermobility, skin laxity and tissue fragility (Beighton et al., 1998). Patients are currently classified according to the Villefranche criteria into six major types (Beighton et al., 1998) of which the hypermobility type (EDS-HT) is most prevalent (Levy, 2004). In this type, joint hypermobility and recurrent joint dislocations are typically present from childhood on, which in combination with muscle hypotonia may cause

* Corresponding author at: Ghent University, Dept. of Rehabilitation Sciences and Physiotherapy, De Pintelaan 185, 1B3 9000 Ghent, Belgium. Tel.: +32 9 332 04 26; fax: +32 9 332 38 11.
E-mail address: Inge.dewandele@ugent.be (I. De Wandele).
[1] Inge De Wandele and Lies Rombaut equally contributed to this article.

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a delay in motor development. Later in life, hypermobility often leads to chronic widespread pain and severe physical disability (Castori et al., 2010).

Although at first glance EDS-HT may appear to be a chronic musculoskeletal disorder, it is also associated with 'non'-musculoskeletal problems such as fatigue, orthostatic intolerance and gastrointestinal complaints (Castori et al., 2010; Rowe et al., 1999; Voermans, Knoop, Bleijenberg, & van Engelen, 2010a; Voermans et al., 2010b). These systemic complaints have not been extensively studied and often receive little attention in clinical practice (Grahame, 2008). However, because EDS-HT is a connective tissue disorder rather than a musculoskeletal disorder, the clinician should be aware that patients may present with a large variety of symptoms ranging from the musculoskeletal system to far beyond (Castori et al., 2010; Grahame, 2008; Maeland, Assmus, & Berglund, 2011). This variability in the clinical picture likely contributes to the difficult recognition and diagnosis of the condition. The lack of a correct diagnosis has been shown to severely affect the functionality and quality of life of the patients, usually in terms of excessive financial and time expense, superfluous investigations, wrong therapies, delay of appropriate treatment, and worsening of the disease state (Castori et al., 2010).

Therefore, detailed information on the clinical variability in EDS-HT may be of help in the recognition of the disorder in primary care. This need has been clearly expressed by an expert group meeting in Helsinki, which requested the identification of the range of clinical symptoms associated with EDS-HT and asked for the definition of subsets of patients (Remvig et al., 2011). According to these experts, the current diagnostic criteria insufficiently address the variability seen among patients and lack information regarding features that have recently been recognized.

In addition, investigating clinical variability and identifying subsets of patients in the EDS-HT population may also aid in establishing a more tailored treatment program. Current treatment is often experienced as insufficient and unsatisfactory (Rombaut et al., 2011a). One possible reason may be that treatment for EDS-HT is still poorly defined, and consequently is rather general and vague (Rombaut et al., 2011a). Identification of subsets of patients may lead to the development of more specified treatment strategies for each subgroup. Second, treatment may also be experienced as insufficient because nowadays it is mostly aimed at controlling the typical musculoskeletal symptoms (Rombaut et al., 2011a). The non-musculoskeletal complications of EDS-HT are often overlooked and remain untreated, as they are less obvious compared to the overt joint hypermobility. Consequently, identification of the full range of symptoms may lead to more integrated treatment strategies.

Therefore, the main objective of the present study is to describe the clinical heterogeneity in EDS-HT, with special attention for the presence of non-musculoskeletal symptoms, and to investigate whether subgroups with distinct symptom profiles can be identified in a large patient sample. The secondary objective is to assess whether the subgroup differences are also reflected as disparity in impairment, pain experience, and medication use.

2. Methods

2.1. Participants

Seventy-eight patients, 70 women and 8 men (mean age 40.3 ± 12.6), participated in the study. Patient selection was performed at the Center for Medical Genetics of the Ghent University Hospital. The participants were diagnosed with EDS-HT according to the Revised Villefranche criteria. All patients fulfilled the presence of the 2 major criteria, including generalized joint hypermobility and skin hyperextensibility or skin fragility, and the presence of at least two minor criteria, including recurrent joint dislocations, and/or chronic musculoskeletal pain, and/or a positive family history (Beighton et al., 1998). Before participating in the study, the medical health records of the participants were screened by the treating practitioner (author F.M.) in order to avoid co- and multimorbidity. Patients with another disease in addition to EDS (*e.g.* diabetes, multiple sclerosis, *etc.*) were excluded from the study. Also, pregnant women were not included in the study group. After a routine follow-up consultation at the Center for Medical Genetics, 80 consecutive eligible patients received written information about the purpose of the study. Those who agreed to participate ($n = 78$) 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.

2.2. Evaluation

2.2.1. General characteristics

Demographic data regarding gender, age, civil state, employment status, educational level and number of children were collected.

2.2.2. Symptom profile

Information regarding EDS symptoms was collected using a self-reported questionnaire enquiring about symptoms experienced on a regular basis due to EDS (Rombaut, Malfait, Cools, De Paepe, & Calders, 2010). Afterwards, similar symptoms were combined for analysis, in accordance with the method used by Hakim and Grahame (2004). For instance, 'feeling lightheaded after standing-up' or 'feeling faint after standing-up' were considered synonymous with presyncope and were not treated as mutually exclusive. Three researchers, of which 2 physiotherapists (authors I.DW. and L.R.) and one clinician (author F.M.) independently labeled the complaints of each patient. Afterwards, their results were compared and discussed.

2.2.3. Functional impairment in daily life

Functional impairment in daily life was estimated using the Sickness Impact Profile (SIP) (Bergner, Bobbitt, Carter, & Gilson, 1981). The original SIP has a good reproducibility ($r = 0.92$) and internal consistency (chrohnbach's alpha = 0.94). It has been validated in Dutch and in French (respectively for the northern and southern part of Belgium) and measures changes of conduct in everyday activities due to sickness (Chwalow et al., 1992; Jacobs, Luttik, Touw-Otten, & de Melker, 1990). It contains 136 statements about health-related dysfunction, that are grouped into twelve subscales: sleep and rest (1), emotional behavior (2), body care and movement (3), home management (4), mobility (5), social interaction (6), ambulation (7), alertness behavior (8), communication (9), work (10), recreation and pastimes (11) and eating (12). Three of these subscales (3, 5, and 7) aggregate into a physical dimension score and four (2, 6, 8, 9) into a psychosocial dimension score. The remaining subscales (1, 4, 10, 11, 12) are independent. A percentage score (0–100) was obtained for every subscale, as well as for the 2 dimensions and for the overall SIP. Higher SIP-scores indicate more disability. A score above ten is arbitrarily considered to indicate a clinically relevant dysfunction, a score between zero and ten indicates a slight dysfunction lacking clinical importance, and a score equal to zero indicates no dysfunction.

2.2.4. Pain experience

To quantify the psychosocial impact of pain, the validated Dutch and French versions of the Multidimensional Pain Inventory (MPI) were used (Kerns, Turk, & Rudy, 1985; Laliberte et al., 2008; Lousberg et al., 1999). The MPI is a psychometrically robust questionnaire with good reproducibility ($r = 0.62$–0.91) and internal consistency ($r = 0.70$–0.90) (Kerns et al., 1985). For the purpose of this study, only the first section of the MPI was administered, which assesses pain experience. This section comprises five subscales: pain severity, pain interference, life control, affective distress and social support. The respondent is asked to answer each question on a Likert scale ranging from 0 to 6, with 0 meaning 'no pain' and 6 meaning 'a lot of pain'. Afterwards, obtained raw scores are converted to standardized *T*-scores with a normative value of 50 and a standard deviation of 10, using the MPI software program (version 2.0). Higher scores on pain severity, pain interference, and affective distress signify more psychosocial impairment. Conversely, a higher score on life control and social support is desirable and indicates less psychosocial impairment.

2.2.5. Medication use

Patients were asked about their medication use, including type, dose, and frequency using the form developed by Rombaut et al. (2011a) enquiring about medication used on a regular basis. Afterwards, groups of medication types were made based on the pharmaceutical compendium. In addition, analgesics were categorized into 3 classes according to the 3-step pain-relief ladder of the World Health Organization (WHO) (World Health Organization, 2012). The first class is used for mild pain and consists of non-opiates (*e.g.* paracetamol, nonsteroidal anti-inflammatory drugs) with or without adjuvants (*e.g.* antidepressants, anticonvulsants). If pain persist or increases, patients are treated with weak opiates (*e.g.* tramadol, codeine, propoxyphene) often combined with non-opiates and adjuvants (step 2). The third step is used for treating intense or persistent pain, and consists of strong opiates (*e.g.* morphine, fentanyl, oxycodone) with or without other pain-relieving products and adjuvants.

2.3. Statistical analysis

The SPSS statistical package, version 19.0 (SPSS Inc., Chicago, IL) was used for data analysis. Descriptive statistics are shown as mean (SD) for continuous data and as absolute frequencies and percentages for categorical data.

In order to identify subsets of patients with similar symptoms profiles, agglomerative hierarchical cluster analysis was performed using the method of between-groups linkage. The Jaccard measure for binary data was used as the criterion for determining similarity between participants. This measure only considers patients to be similar regarding a certain complaint, if they reported that complaint (Romesburg, 2004). If a specific complaint was not reported, this may have several possible reasons varying from not experiencing the complaint to forgetting to report it whilst experiencing it nonetheless. By consequence, patients may not be regarded as similar based on not reporting a certain complaint.

The number of clusters was decided after analysis of the similarity coefficient. First, all large decreases in the similarity coefficient were determined, which indicate the steps where less similar patients are joined into one group. This procedure showed that both a solution with 72 clusters and a solution with 3 clusters were accurate for describing the data set. Finally, the 3-cluster solution was chosen, as this option preserves enough detail to describe clinical heterogeneity, while it also generalizes enough so that it creates clusters large enough to allow for statistical comparison. Cluster 1, cluster 2 and cluster 3 contained 48, 26 and 4 participants respectively. Cluster 1 and 2 were compared using Chi-square or Fisher's exact tests for categorical data (symptom profile and medication use) and independent sample *t*-tests for continuous numerical data (SIP- and MPI-scores). Because of the small number of participants, cluster 3 could not be included in further statistical analysis. Nonetheless, the data of cluster 3 are presented in the text, figures and tables in order to be complete and to provide an overview of the true clinical variability within this study sample.

Finally, a multiple linear regression analysis was performed (enter method), in order to determine the predictive value of the number of musculoskeletal symptoms and the number of non-musculoskeletal symptoms for functional impairment and for pain experience. The level of statistical significance was set to 0.05.

3. Results

3.1. General characteristics

Table 1 summarizes the general characteristics of the total study sample, as well as per cluster. Patients in cluster 1 and 2 were not significantly different from each other with respect to age, gender, education level, employment status, civil state and number of children. By contrast, cluster 3 contained the youngest individuals and mainly consisted of men.

3.2. Symptom profile

All participants in this study group spontaneously reported musculoskeletal (MSK) complaints, such as pain, articular symptoms and muscle complaints. Ninety five percent of patients also reported having non-musculoskeletal (non-MSK) complaints in addition to their musculoskeletal symptoms. Among the non-MSK complaints especially headaches and fatigue were common, as well as cutaneous problems, gastrointestinal symptoms, orthostatic intolerance and immune deficiency. In general, a median number of 7 symptoms was reported (interquartile range 6), consisting of 4 musculoskeletal (interquartile range 3) and 3 non-musculoskeletal symptoms (interquartile range 5).

Cluster analysis of the total test sample identified 3 subgroups with a distinct symptom profile. These clusters differed with respect to the number of symptoms reported, as well as to the nature of symptoms.

Patients in cluster 2 reported more than twice the number of symptoms compared to cluster 1 (median number, respectively, 13 *vs.* 6). Also, their symptom profile was dominated by non-MSK symptoms (median number of 8.5 non-MSK and 5 MSK symptoms), whereas in cluster 1 the symptom profile contained a rather similar number of MSK and non-MSK symptoms (median number of 2 non-MSK and 3 MSK symptoms).

The nature of symptoms is illustrated in more detail in Fig. 1, which shows the prevalence of all reported complaints. The prevalence of musculoskeletal complaints is similar in cluster 1 and 2 (pain: $p = 1.000$; articular complaints: $p = 0.410$; muscle complaints: $p = 0.74$). In both clusters, the most prevalent MSK symptom was pain, followed by articular complaints (*e.g. joint dislocations, subluxations, joint swelling*) and muscle complaints (*e.g. muscle cramps, muscle weakness*).

Interestingly, the prevalence of non-MSK complaints significantly differed between these clusters. Patients in cluster 2 more often reported cutaneous complaints (*e.g. skin fragility, slow wound healing;* $p = 0.036$), immune deficiency (*e.g. recurrent infections, especially airway infections;* $p < 0.001$), swallowing difficulty and dysphonia ($p = 0.018$). Also, they more often reported fatigue ($p < 0.001$) and sleeping problems (*e.g. difficulty falling asleep or staying asleep;* $p = 0.032$), as well as cardiorespiratory complaints (*e.g. palpitations or dyspnea in rest;* $p < 0.001$), exercise intolerance (*e.g. feeling faint or fainting, shortness of breath, or frequently needing rest during physical activity;* $p < 0.001$) and inflammatory signs (*e.g. red and warm joints or tendons and inflamed bursae;* $p = 0.003$). Furthermore, a significant difference could be detected in the prevalence of thermoregulatory problems (*e.g. feeling cold all the time;* $p = 0.020$), orthostatic intolerance (*e.g. feeling faint, dizzy or fainting on standing;* $p < 0.001$), gastrointestinal complaints (*e.g. constipation, diarrhea, slow transit, nausea and vomiting;* $p < 0.001$),

Table 1
General characteristics.

	Total sample 78 (100%)	Cluster 1 48 (100%)	Cluster 2 26 (100%)	Cluster 3 4 (100%)	*p*-Value*
Age (years)					
Mean (SD)	40.3 (12.6)	39.5 (11.63)	43.0 (12.03)	32.25 (23.89)	0.231[a]
Range	18–75	19–64	20–75	18–68	
Gender					
Male	8 (10.3%)	3 (6.3%)	2 (7.7%)	3 (75%)	1.000[b]
Female	70 (89.8%)	45 (93.8%)	24 (92.3%)	1 (25%)	
Education level					
Elementary school	12 (15.4%)	7 (14.6%)	3 (11.5%)	2 (50%)	0.332[b]
Secondary & high school	20 (25.6%)	9 (18.8%)	9 (34.6%)	2 (50%)	
College/university	46 (59%)	32 (66.7%)	14 (53.9%)	0 (0%)	
Civil state					
Living alone/divorced	29 (37.2%)	16 (33.3%)	10 (38.5%)	3 (75%)	0.659[b]
Cohabitant/married	49 (62.8%)	32 (66.7%)	16 (61.5%)	1 (25%)	
Number of children	1.5 (1.77)	1.5 (1.26)	1.7 (2.49)	0.67 (1.16)	0.716[a]
Employment status					
Student/employed	32 (41.0%)	20 (41.7%)	9 (34.6%)	3 (75%)	0.283[b]
Unemployed/old-age retirement	15 (19.2%)	11 (22.9%)	3 (11.5%)	1 (25%)	
Sick leave/disability pension	31 (39.7%)	17 (35.4%)	14 (53.9%)	0 (0%)	

Data are expressed as mean (standard deviation) for continuous variables and as absolute frequency (relative frequency in %) for categorical variables.

* Significance level for comparison between cluster 1 and 2. Due to the small number of participants in cluster 3, this subgroup was not implicated in statistical analysis. Its data are shown for completeness.

[a] Student's *t*-test for independent samples: comparison of continuous variables between cluster 1 and 2.

[b] Chi-square test: comparison of categorical variables between cluster 1 and 2.

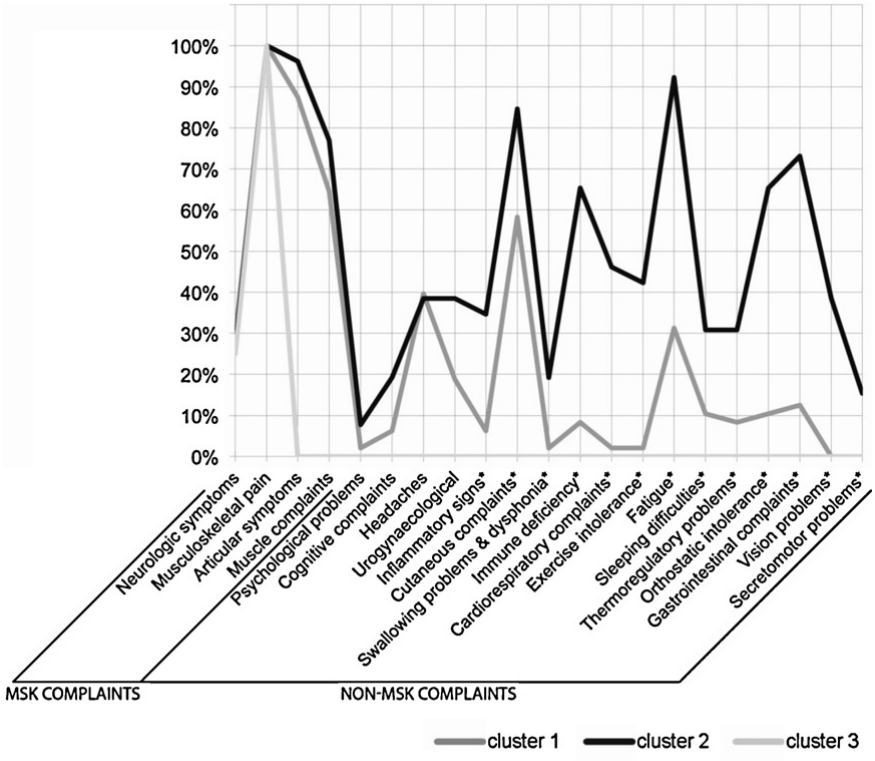


Fig. 1. The symptom profile per cluster.

secretomotor problems (*e.g. sweating too much or too little;* $p = 0.013$) and vision problems (*e.g. blurred vision, sensitivity to light, difficulty focusing;* $p < 0.001$).

The top 3 of most frequently reported non-MSK complaints in cluster 1 consisted of cutaneous signs, followed by headaches and fatigue, whereas in cluster 2 the most frequently reported non-MSK complaints were fatigue, cutaneous signs and gastrointestinal complaints.

In contrast to cluster 1 and 2, cluster 3 reported very few complaints, with a median number of only 1 MSK complaint without any non-MSK symptoms. Fig. 1 shows that patients in this group mainly complained of musculoskeletal pain.

3.3. Functional impairment in daily life

The SIP scores of the total test sample indicate that the participants in this study had severe physical and psychosocial impairment (SIP scores of, respectively, 13.9 (12.43) and 17.2 (12.79)). They experienced the largest restrictions due to their illness in their work and leisure time activities (Fig. 2).

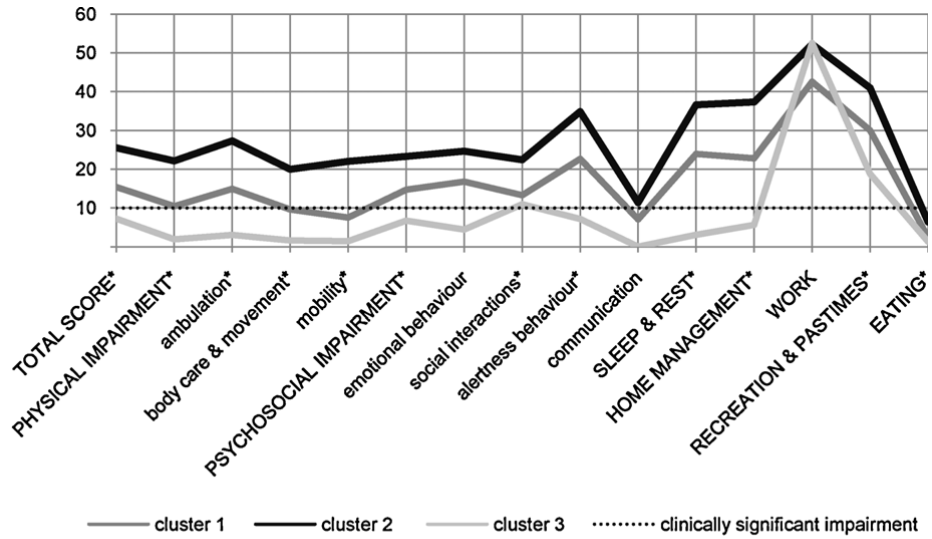
Furthermore, the level of functional impairment varied within the total sample (Fig. 2). Compared to cluster 1, patients in cluster 2 had a significantly higher degree of impairment, physically as well as psychosocially ($p < 0.001$; $p = 0.005$). The greater physical impairment was due to larger restrictions in each of the physical subscales (ambulation: $p = 0.003$, body care and movement: $p = 0.001$, mobility: $p = 0.001$). The greater psychosocial impairment in cluster 2 was mainly due to larger restrictions in the subscales of social interaction and alertness behavior ($p = 0.038$; $p = 0.029$). In addition, cluster 2 is also characterized by more severe dysfunction in the independent subscales of home management, recreation and pastimes, eating, and sleep and rest ($p = 0.002$; $p = 0.012$; $p = 0.034$; $p = 0.010$) compared to cluster 1.

By contrast, patients in cluster 3 generally showed smaller levels of impairment. They only experienced clinically significant restrictions in social interactions, work, and recreational activities.

3.4. Pain experience

The MPI results of the total study population demonstrated an important impact of pain on daily life activities in patients with EDS-HT (mean score for pain severity: 41.2 (9.54); interference of pain with daily life: 45.9 (9.96); perceived life control: 49.8 (8.75); affective distress: 41.5 (9.08) and social support 42.2 (11.20)).

Pain experience also clearly differed between the clusters (Fig. 3). Both pain severity and interference of pain with daily life were significantly higher in cluster 2 compared to cluster 1 ($p = 0.016$; $p = 0.017$).



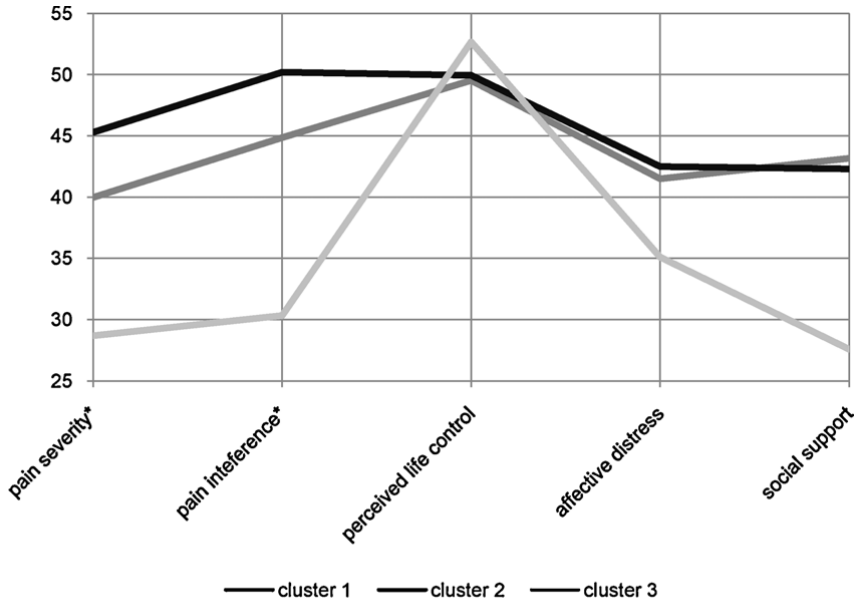
Mean SIP-scores for each cluster.
*** Items with a significantly greater impairment in cluster 2 compared to cluster 1.**

Fig. 2. Functional impairment assessed by the Sickness Impact Profile.

Cluster 3 was characterized by relatively low levels of pain severity, and a smaller interference of pain with daily life. Participants within cluster 3 experienced a slightly higher degree of control over pain and life events, and less affective distress and less social support in coping with pain.

3.5. Multiple regression analysis

The number of non-MSK complaints was a significant predictor for total functional impairment ($p = 0.021$; beta = 0.313); physical impairment ($p = 0.019$; beta = 0.322) and pain interference in daily life ($p = 0.047$, beta = 0.275). The number of MSK complaints did not significantly influence functional impairment or pain experience.



Mean MPI scores for each cluster.
*** Items that score significantly higher in cluster 2 compared to cluster 1.**

Fig. 3. Pain experience assessed by the MPI.

Table 2
Medication use.

	Cluster 1	Cluster 2	Cluster 3	*p*-Value*
Medication use	44 (91.7%)	26 (100%)	2 (50%)	0.291
Analgesics	43 (89.6%)	25 (96.2%)	2 (50%)	0.416
Paracetamol	32 (66.7%)	18 (69.2%)	1 (25%)	0.822
NSAID (e.g. ibuprofen, naproxen, oxicam, diclofenac)	24 (50%)	8 (30.8%)	1 (25%)	0.111
Opiates (e.g. tramadol, codeine, morphine, fentanyl)	12 (25%)	13 (50%)	0 (0%)	**.030***
Other analgesics	2 (4.2%)	0 (0%)	0 (0%)	0.538
Antidepressants e.g. Amitriptyline, duloxetine, trazadone)	11 (22.9%)	4 (15.4%)	0 (0%)	0.442
Sedatives (benzodiazepines)	1 (2.1%)	3 (11.5%)	0 (0%)	0.121
Cardiovascular medication (α-blockers, β-blockers, diuretics, ACE-inhibitors)	6 (12.5%)	7 (26.9%)	0 (0%)	0.199
Pulmonary medication (β-sympathomimetics, mucolytics)	4 (8.3%)	4 (15.4%)	0 (0%)	0.440
Gastrointestinal medication	9 (18.8%)	9 (34.6%)	0 (0%)	0.129
Other (e.g. Homeopathic medicines, nutrition supplements)	10 (20.8%)	8 (30.8%)	0 (0%)	0.342
WHO Pain relief ladder				
No pain medication	4 (8.33%)	0 (0.00%)	2 (50%)	0.291
Step 1 WHO	30 (62.5%)	12 (46.2%)	2 (50%)	0.175
Step 2 WHO	12 (25%)	8 (308%)	0 (0%)	0.594
Step 3 WHO	2 (4.2%)	6 (23.1%)	0 (0%)	**0.019***

Medication used on a regular basis in each cluster.
* $p < 0.05$: Significance level for comparison between cluster 1 and 2. Due to the small number of participants in cluster 3, it was not implicated in statistical analysis.

3.6. Medication use

The majority of the patients (92.3%) used medication on a regular basis. The average patient used 3.3 (2.42) different medicines. Analgesics were the most frequently used medication type (by 89.7%), mainly in the form of paracetamol-based substances and NSAIDs (65.4% and 42.3% of the study sample, respectively). Besides analgesics, patients also reported the use of medication aimed at treating the non-musculoskeletal complications of EDS-HT, but to a much lesser extent. Gastrointestinal medication and food supplements or homeopathic medicines were most frequently reported (by 23.1% of the participants), followed by antidepressants, cardiovascular medicines, pulmonary medicines and sedatives (19.2%, 16.7%, 10.3% and 5.1%, respectively).

Table 2 indicates that the medication use was largely comparable in cluster 1 and 2. The only significant difference between both clusters was found in the use of opiate analgesics, which more often occurred in cluster 2 ($p = 0.030$). In addition, patients in cluster 2 were more often treated according to the third WHO step ($p = 0.019$).

In contrast to cluster 1 and 2, cluster 3 is characterized by a relatively low prevalence of medication use. Analgesics are only used by half of these patients, and all of them are paracetamol-based substances or NSAIDs situated in the first WHO step. Besides analgesics, participants in cluster 3 did not use any other type of medication.

4. Discussion

This study aimed to describe the clinical heterogeneity of EDS-HT and to investigate whether subgroups could be identified based on the symptom profile. As expected, all patients reported MSK symptoms, with dominance of pain, joint dislocations, and muscle symptoms. Furthermore and of importance, the majority also reported non-MSK symptoms, among which headaches, fatigue, cutaneous problems, gastrointestinal symptoms, orthostatic intolerance and immune deficiency. This high prevalence of non-MSK symptoms in EDS-HT is in accordance with the results of Maeland et al. (2011) and Castori et al. (2010).

Within the present study sample, three homogeneous clusters could be distinguished, each showing a distinct symptom profile. After exclusion of cluster 3 due to the low number of patients, cluster 1 and cluster 2 showed significant differences not only with respect to the number of symptoms reported, but also with respect to the type of symptoms reported. Comparing both symptom profiles, the key differences could be found in the domain of non-musculoskeletal complaints, which was significantly larger in cluster 2. This resulted in notable differences between the two clusters in functional health status and pain experience, with a larger functional impairment and more severe pain in cluster 2.

A first possible explanation for the clinical variability found in this study may be genetic heterogeneity. To date, the genetic defects underlying EDS-HT are barely defined and remain largely elusive (Levy, 2004). However, new insights have been gained recently. For instance, haploinsufficiency of tenascin-X (TNX) due to mutations in the TNX-B gene has been identified in a small subset (5%) of patients with EDS-HT (Zweers et al., 2003). As tenascin-X is a large glycoprotein situated in the extracellular matrix, the molecular background of EDS-HT probably extends beyond the genes coding for the collagen

structure. For the vast majority of patients affected with EDS-HT; however, no molecular defects have yet been discovered. Most likely, EDS-HT has a multigenetic and multifactorial background (Zweers et al., 2003). The clinical differences between patients diagnosed with the same type may possibly be a reflection of this genetic heterogeneity.

Second, part of the non-musculoskeletal complaints that characterize cluster 2 and add to the clinical variability may result from deconditioning. In the second cluster, a larger number of cardiorespiratory problems, exercise intolerance and fatigue was reported. Due to severe musculoskeletal pain and articular problems, patients with EDS often are less physically active, leading to a lower physical fitness level (Rombaut et al., 2010). This can result in a variety of problems at the cardiorespiratory and musculoskeletal level leading to earlier peripheral fatigue.

Third, the higher prevalence of non-MSK symptoms in cluster 2 may be partly due to a more frequent use of opioids in this group. Although opioid analgesics primarily act on the central nervous system, they also have a profound inhibitory action on the intestinal tract. This is mainly due to the presence of opioid receptors, whose activation by exogenous opioids in particular disrupts gastrointestinal motility and secretion. Decreased gastric, biliary and pancreatic secretions and inhibition of peristalsis lead to constipation and gastroparesis (Panchal, Muller-Schwefe, & Wurzelmann, 2007). Nausea and vomiting probably caused by stimulation of the chemoreceptor trigger zone also often occur. Furthermore, peripheral vasodilation, reduced peripheral resistance and the inhibition of baroreceptors caused by opioids may result in orthostatic hypotension and fainting (Holaday, 1983; Smith & Bruckenthal, 2010).

A last possible explanation for the clinical variability, to our opinion, may be related to the presence of dysautonomia. The larger number of gastrointestinal complaints, orthostatic intolerance, secretomotor and thermoregulatory problems in cluster 2 may be suggestive of a dysfunction of the autonomic nervous system. A recent study in the joint hypermobility syndrome, which is clinically indistinguishable from EDS-HT (Tinkle et al., 2009), has demonstrated that dysautonomia is a possible complication in hypermobile individuals (Gazit, Nahir, Grahame, & Jacob, 2003). Dysautonomia has previously been related to fatigue, cardiorespiratory complaints such as palpitations and dyspnea, which may explain the higher prevalence of such associated complaints in cluster 2 (Friedman & Irwin, 1997; Gazit et al., 2003; Rowe et al., 1999; van, Boer, Mulder, van Montfrans, & Wieling, 2008).

Further, the differences in number and type of symptoms between the clusters resulted in notable differences in functional impairment and pain experience.

Previous research has indicated that musculoskeletal complaints as such, and pain in particular, are associated with functional impairment in EDS-HT (Rombaut et al., 2011b; Voermans et al., 2010a). However, non-musculoskeletal symptoms, as reported in this study, may also importantly contribute to the functional impairment experienced by patients. Fatigue for instance, is known to be associated with a lower quality of life, greater functional impairment, more psychological distress and more intense pain in EDS (Voermans et al., 2010a, 2010b). Consistent with these findings, fatigue was significantly more reported in cluster 2, which also demonstrated the largest physical impairment, worst psychosocial health and highest pain intensity. Likewise, sleeping difficulties, occurring significantly more in cluster 2, are thought to be related to a lowered quality of life and pain in EDS (Verbraecken, Declerck, Van de Heyning, De Backer, & Wouters, 2001; Voermans et al., 2010a, 2010b). Moreover, patients in cluster 2 reported more gastrointestinal complaints, orthostatic intolerance, thermoregulatory problems, inflammatory signs and cardiorespiratory symptoms. In other diseases, these non-MSK complaints have been shown to significantly lower quality of life (Kollensperger et al., 2007; Van Gestel et al., 2011).

In addition to the differences in symptom profile and functional impairment, pain experience also varied between the clusters. The present study showed that these differences in pain experience were reflected in the current analgesic use. The patients in cluster 2 reported the most severe pain and the largest interference of pain with daily life, which was reflected in a greater opioid use. Also, in this cluster more patients were treated according to the third WHO-step, consisting of opiates and adjuvants for intense pain.

Interestingly, except for the previously mentioned difference in analgesic use, the pharmacological treatment did not significantly differ between cluster 1 and 2. Although cluster 2 reported significantly more non-musculoskeletal complaints, medication aimed at treating these systemic complications was not more prevalent in this group. One possible reason may be that non-MSK symptoms are often not recognized as being part of the EDS-HT symptom profile. According to Grahame et al., clinicians indeed appear to be frequently unaware of the recent literature concerning the systemic complications of EDS-HT (Grahame, 2008).

The present results must be viewed within the limitations of the study. First, we chose to use a self-report method for symptom questioning. A limitation of this method is that it may not provide an adequate estimate of the real prevalence of symptoms. Symptoms that are not intensely or not frequently experienced may not have been reported. However, we are convinced that this method most accurately identifies those symptoms that are of importance to the patient. Second, we cannot be certain whether the division into 3 clusters can be generalized to the total population of patients with EDS-HT. Nevertheless, this was not the purpose of the study. The cluster analysis was merely a means to demonstrate that patients with the same type of EDS may thoroughly differ, and to provide insight into the various possible clinical representations of EDS-HT. A disadvantage of cluster analysis is that creating groups within a study sample is a way of generalization and loosing individual data. Therefore, a cluster analysis can never fully describe the variability seen among individuals. Nonetheless, to our knowledge this study is the first that provides an overview of the clinical differences that may occur within a large study sample of patients with the same type of EDS. A last limitation of this study is the cross-sectional design. Future research should include follow-up studies in order to evaluate how non-musculoskeletal complaints arise and to determine which patients are at risk for developing this kind of complaints.

In conclusion, this study demonstrates that EDS-HT is a clinically heterogeneous disorder with respect to the symptom profile, functional health status and pain experience. Our data also stress the importance of detecting the non-MSK complications of EDS-HT, as their presence affects the functional health status and pain experience. The clinician is encouraged to use the current knowledge to be more aware of the large variety of EDS-HT symptoms, in order to improve disease recognition and to establish more tailored and integrated treatment strategies for these patients.

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