Original Article

Pain in Ehlers-Danlos Syndrome Is Common, Severe, and Associated with Functional Impairment

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Abstract

Objectives. The Ehlers-Danlos Syndrome (EDS) is a clinically and genetically heterogeneous group of heritable connective tissue disorders characterized by joint hypermobility, skin hyperextensibility, and tissue fragility. Musculoskeletal pain is mentioned in the diagnostic criteria and described as early in onset, chronic, and debilitating. However, systematic research on pain in EDS is scarce. Therefore, we investigated prevalence and impact of pain and associated features in a large group of EDS patients.

Methods. We performed a study among members of the Dutch EDS patient organization ($n = 273$) and included the McGill Pain Questionnaire to investigate various aspects of pain, the Sickness Impact Profile to study functional impairment, the Symptom Checklist subscale sleep to evaluate sleep disturbances, and the Checklist Individual Strength subscale fatigue to determine fatigue severity.

Results. The results of this study show that 1) chronic pain in EDS is highly prevalent and associated with regular use of analgesics; 2) pain is more prevalent and more severe in the hypermobility type than in the classic type; 3) pain severity is correlated with hypermobility, dislocations, and previous surgery; 4) pain is correlated with low nocturnal sleep quality; and 5) pain contributes to functional impairment in daily life, independently of the level of fatigue.

Conclusion. From this large cohort of EDS patients, we conclude that pain is common and severe in EDS. Pain is related to hypermobility, dislocations, and previous surgery and associated with moderate to severe impairment in daily functioning. Therefore, treatment of pain should be a prominent aspect of symptomatic management of EDS. J Pain Symptom Manage 2010;■:■—■.

The authors declare no conflicts of interest.

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Key Words
Ehlers-Danlos syndrome, pain, inherited connective tissue disorder, collagen, tenascin-X, questionnaire, functional impairment

Introduction

The Ehlers-Danlos Syndrome (EDS) is a clinically and genetically heterogeneous group of inherited connective tissue disorders, caused by mutations in genes encoding various types of collagen or collagen-modifying enzymes (collagen I, III, and V; tenascin-X (TNX); or lysyl hydroxylase-1). The collagen in connective tissue increases its elasticity and thus helps tissues to resist deformation. In the skin, muscles, ligaments, blood vessels, and visceral organs, collagen plays a very significant role. Reduced elasticity secondary to abnormal collagen in EDS results in joint hypermobility, skin hyperextensibility, tissue fragility, and possibly to ruptures of visceral organs and blood vessels.

The revised classification of EDS in six major types is based on clinical and biochemical features.[1] The hypermobility type is the most common type, followed by the classical type; together these types account for 90% of cases.[2] The vascular, kyphoscoliotic, arthrochalasia, and dermatosparaxis types are rare, as is the TNX deficient type, which was described more recently.[3,4] Musculoskeletal pain is mentioned in the diagnostic criteria of the hypermobility type and described as early in onset, chronic, and possibly debilitating.[1,5] This latter aspect is clearly illustrated by patients' report of pain in EDS.[6]

Systematic research on pain in EDS is restricted to a questionnaire study on 51 patients, which showed that moderate-to-severe pain is common in EDS.[5] Pain was often chronic and multifocal and suggested to have several causes; secondary to frequent dislocations, resulting from repeated soft tissue injury, or related to multiple operations with peripheral nerve injury.[5] This multifactorial basis was assumed to cause a variable course of pain in EDS:[5] pain related to repeated soft tissue injury or multiple operations with peripheral nerve injury was thought to cause a constant level of pain, whereas hypermobility and dislocations may lead to additional peaks of pain.[5] Differences between EDS types could not be tested because of the small sample size.[5] Other studies on general symptoms in EDS also reported high prevalence of pain but did not focus on specific pain characteristics.[7–10]

Pain was found to be a prominent symptom in our questionnaire study on fatigue in EDS,[11] and myalgia was frequently reported in our study on neuromuscular features in EDS.[12] Furthermore, the previous study on pain in EDS was restricted in size and focus.[5] Therefore, we investigated prevalence, characteristics, and impact of pain in a large group of EDS patients. Our aims were to 1) determine pain prevalence, pain characteristics, and use of analgesics to replicate the findings of previous studies; 2) investigate whether differences in pain prevalence and impact of pain occur between the two most common types of EDS (hypermobility and the classic type); 3) explore the relation between pain and disease-related factors. Because sleep disturbances are common in EDS,[13] we also wanted to 4) investigate the relationship of pain with sleep disturbances. Finally, we meant to 5) assess the contribution of pain to functional impairment in daily life. Because previous research has shown that pain and fatigue are associated,[14] we controlled for the contribution of fatigue when determining the relationship between pain and level of disabilities. This study thus may contribute to a better recognition and understanding of pain in EDS, which is a necessary starting point for treatment protocols for pain in EDS.

Methods

Patients

We used a cross-sectional design to assess fatigue and pain in patients with EDS. In total, 519 patients were asked to participate (500 questionnaires were sent to members of the Dutch patient organization of EDS [Vereniging van Ehlers-Danlos patienten (VED): www.ehlers-danlos.nl], and 19 patients were

recruited from the outpatient departments of internal medicine, dermatology, and human genetics of the Radboud University Nijmegen Medical Center). These 19 patients also were included in our clinical study on neuromuscular features in EDS.[12] Three hundred twenty-seven questionnaires were returned (63% response rate). Questionnaires were provided on paper, patients were asked to fill them out by themselves, and return them by mail. We excluded patients who were younger than 16 years, in whom EDS had not (yet) been diagnosed, and who had incompletely filled out the Checklist Individual Strength (CIS) questionnaire.

Written information about the purpose of the study was provided, and all patients gave informed consent. To prevent a selection bias for patients, the purpose of the study was described as "to learn more about various complaints in Ehlers-Danlos syndrome." The study was approved by the local ethics committee.

Prevalence of Pain, Pain Characteristics, and Use of Analgesics

We used the McGill Pain Questionnaire because it provides qualitative and quantitative data on various aspects of pain in a standardized way.[15] The first question concerns occurrence of pain. If no pain is reported, the subsequent questions on this questionnaire do not have to be filled out, and patients are referred to the next questionnaire in the booklet. Therefore, only the patients who reported having pain were included for the subsequent subgroup analyses of pain severity, pain characteristics, use of analgesics, differences between two EDS types, relation of pain with disease-related factors and sleep disturbances, and impact of pain (Fig. 1). For the multiple regression analysis, we used all 273 patients (see Fig. 1 and section Statistical Analysis below).

The subsequent questions of the McGill Pain Questionnaire focus on pain severity, changes in pain over time, and specific characteristics of the pain. The pain severity is scored as current pain, most severe pain, and least severe pain, measured with a visual analog scale (VAS); a score of 0 indicates no pain, and a score of 100 indicates unbearable pain. Pain on the day of completing the questionnaire is scored as none—mild—moderate—

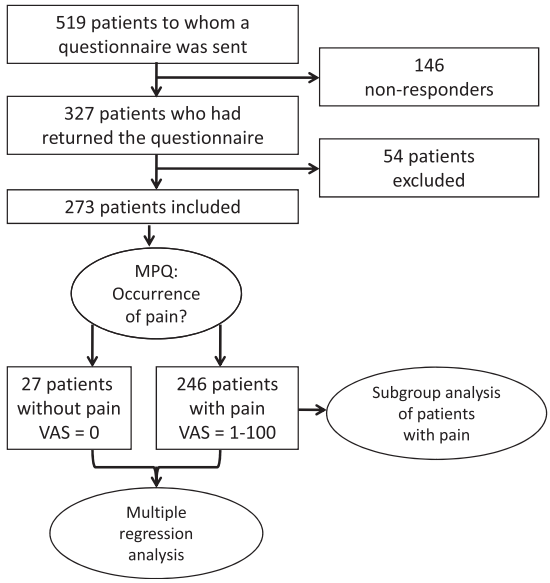

Fig. 1. Inclusion and exclusion of EDS patients in this study. MPQ = McGill Pain Questionnaire.

severe. Pain characteristics are assessed with the use of a list of adjectives reflecting pain quality and intensity, of which patients have to select the most appropriate ones. Use of analgesics is qualitatively assessed with the McGill Pain Questionnaire. Additionally, we used the items on a health care use questionnaire that assessed doses of (non)prescribed medication to screen whether patients exceeded the maximally allowed doses.[16]

In our study on neuromuscular features in EDS, muscle weakness and myalgia were frequently reported by EDS patients (65% and 73%, respectively).[12] Therefore, we also asked patients whether they experienced myalgia, how often this occurred, and which parts of the body were involved.

The Relationship of Pain with Disease-Related Factors

We asked patients about the previous or current presence (yes or no) of joint hypermobility, dislocations, dermal features (velvety skin; hyperextensible skin; easy bruising; presence of varices; thin, translucent skin; molluscoid pseudotumors; impaired wound healing; scars that are thin, wide and discolored and/or have an atrophic papyraceous appearance; and presence of striae), muscle weakness, and about previously performed operations (with explanations of medical terms).

The Relationship of Pain with Sleep Disturbances

The McGill Pain Questionnaire includes items on waking up during the night because of pain and on the duration of being awake at night. Sleeping problems were further measured with the sleep subscale of the Symptom Checklist (SCL-90). This scale consists of three items that focus on the quality of sleep (difficulty falling asleep, early awakening, and sleep disturbances during the night), which must be rated on a five-point scale.[17] A total score is obtained by adding the item scores; scores can range from 3 (not bothered by sleep problems) to 15 (high level of distress because of sleep problems).

Contribution of Pain and Fatigue to Functional Impairment in Daily Life

We used the McGill Pain Questionnaire items on functional limitations because of pain. These functional consequences of the pain are scored in the following order: none—mild—moderate—severe, and concern limitations in daily activities, both work and leisure activities, appetite, and lack of energy. Physical disabilities were measured with the physical functioning subscale of the Short Form-36 (SF-36).[18] Scores range from 0 (maximum physical limitations) to 100 (optimal physical functioning).[19] Additionally, the Sickness Impact Profile (SIP) was used to assess functional disability. The SIP is a standardized list of statements aimed at measuring changes of conduct in everyday activities because of sickness. We used eight SIP categories: sleep and rest, home management, ambulation, social interaction, mobility, alertness behavior, work, and recreation and pastimes. Higher scores mean more functional disability.[20–23] We used the SIP sum score to assess the level of overall disabilities.[19]

The CIS subscale fatigue severity consists of eight items. Each item was scored on a seven-point Likert scale (scores range from 8 to 56). High scores indicated high levels of fatigue. The CIS has good reliability and validity.[24]

Statistical Analysis

Data analysis was carried out using SPSS 16.0 for Windows (SPSS Inc., Chicago, IL). Descriptive statistics were used to describe the sample. For the analyses of pain characteristics and impact of pain, only patients who reported having pain on the first question of McGill Pain Questionnaire were included. Differences in prevalence and severity of pain between the classic and hypermobility types were tested with the independent t-test for continuous variables and with a chi-squared or Fisher's exact test for dichotomous variables. Correlations were calculated with the Pearson's or Spearman's coefficient. Multiple regression analysis was performed (enter method; P in $= 0.05$; P out $= 0.1$), with functional impairment (SIP sum score) as the dependent variable. For this analysis, we used the data of all patients and designated "no pain" as a VAS score of 0 (Fig. 1). Pain severity (VAS of most severe pain; VAS of current pain) and fatigue (CIS fatigue) were defined as predictors. In all analyses, probability (P) values smaller than 0.05 were regarded as statistically significant.

Results

Patients

In total, 327 questionnaires were returned. Excluded were patients who were younger than 16 years ($n = 16$), patients in whom EDS had not (yet) been diagnosed ($n = 30$), and patients who had incompletely filled out the CIS questionnaire ($n = 8$). Hence, 273 patients were included. The mean age of EDS patients was 41 years (range 16–89), and 89% of the patients were female. Highest level of education was low in 16% of patients (primary school, low vocational school), middle in 47% (high school, middle vocational school), and high (higher vocational school, university) in 37%. EDS was diagnosed by a medical specialist in all patients. In 53 of them (91% female), the specific type of EDS was not (yet) known; in all other patients, the EDS type was diagnosed based on clinical features and partly supported by biochemical or genetic analysis: 45 EDS patients of the classic type (78% female); 162 of the hypermobility type (94% female); 11 of the vascular type (82% female); and two of the kyphoscoliotic type (0% female).[1] No differences were found in age or gender between the various EDS types or between patients with or without classification. Overall, 237 (87%) patients had undergone surgery at least once;

this included various orthopedic operations (all types) and vascular surgery after ruptured aneurysm or abdominal surgery after ruptured intestines (vascular type).

Prevalence of Pain, Pain Characteristics, and Use of Analgesics

Of the 273 patients included, 246 (90%) reported having pain on the first question of the McGill Pain Questionnaire (Table 1). Female patients reported pain more frequently than male patients: 92% vs. 74% ($P = 0.001$), and patients with the hypermobility type EDS reported pain more frequently than those with the classic and vascular types (98% vs. 76% and 55%, respectively ($P < 0.001$) (Table 1). The findings presented below are the result of the subgroup analyses of these patients with pain ($n = 246$), whereas for the multiple regression analysis, data of all patients were used ($n = 273$).

Reported pain severity (VAS of current pain, least severe pain, and most severe pain) is presented in Table 1. Overall, patients with the hypermobility type had the highest VAS scores for current pain, least severe pain, and most severe pain (Table 1).

Pain was most frequently localized in neck, shoulders, hips, and forearms, and legs (>40% of all patients), which might reflect a pattern of musculoskeletal pain (Fig. 2). In contrast, headache or abdominal pain was reported infrequently. This was supported by the response to the question of presence of myalgia: frequent or continuous myalgia was reported by 87% of patients with pain. It did not occur in a specific distribution; approximately 60% of patients reported myalgia in arms, legs, and/or trunk.

Most patients reported chronic pain (i.e., lasted for more than one year; 92%), gradual increase of pain (84%), and an equal severity of pain (64%). Frequently used adjectives (reported by >40% of the patients) to characterize the pain were cutting, nagging, tiring, troublesome, and sickening. Pain severity changed over time but remained continuously present to some degree in most (85%) patients. Most (95%) patients suffered from pain the day before filling out the questionnaire. In 90% of them, pain occurred for more than four hours, and 72% of them had to rest because of pain the previous day. Of the patients resting, 38% rested

Table 1
Pain severity in various EDS types ($n = 246$)

Clinical Feature	EDS Total	Classic Type	Hypermobility Type	Vascular Type	Kyphoscoliotic Type	Type Unknown	Differences Between Types[a]
Total number of patients	273	45	162	11	2	53	—
Prevalence of pain (% of patients of that type)	246 (90)	34 (76)	159 (98)	6 (55)	1 (50)	46 (87)	Classic < hypermobility: $P < 0.001$ Hypermobility > vascular: $P < 0.001$
Joint hypermobility	230	26	157	4	1	42	Not tested
Dislocations	193	17	137	2	0	37	Not tested
Dermal features	236	34	149	6	1	46	Not tested
Muscle weakness	196	27	125	3	0	41	Not tested
Previous operations	228	33	146	5	1	43	Not tested
Current pain: mean VAS score (SD)	48.0 (22.4)	39.2 (25.4)	49.1 (21.0)	21.2 (12.0)			Classic > vascular: $P = 0.016$ Hypermobility > vascular: $P = 0.001$
Least severe pain: mean VAS score (SD)	21.5 (16.3)	19.6 (17.3)	21.6 (15.5)	6.3 (6.3)			Hypermobility > vascular: $P = 0.018$
Most severe pain: mean VAS score (SD)	82.5 (17.4)	76.0 (19.5)	85.3 (13.5)	67.7 (30.9)			Classic < hypermobility: $P = 0.014$
Use of analgesics: number of patients (% of patients of that type)	216 (88)	27 (82)	145 (91)	4 (67)			Not significant

[a]Fisher's exact test.

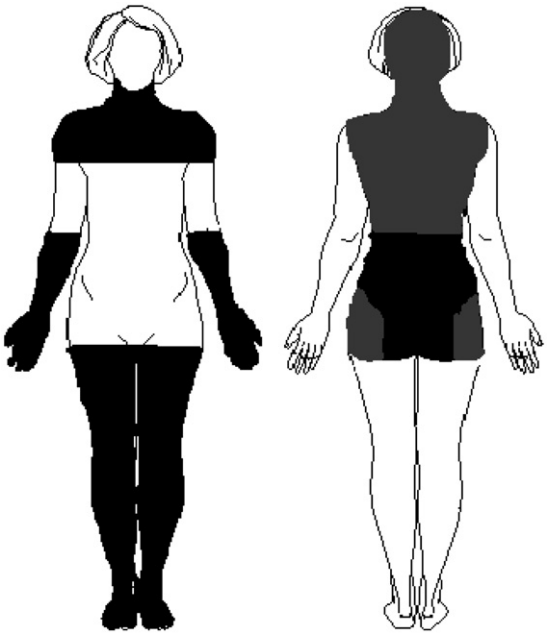

Fig. 2. Pain occurred in the highlighted regions at least 40% (gray) and respectively 50% (dark gray) of EDS patients; pain was most frequently localized in neck, shoulders, hips, and forearms, and legs, which might reflect a pattern of musculoskeletal pain.

for at least four hours that day. Most (89%) patients suffered from pain on the day of questionnaire completion, and in 53% of the patients, this pain severity was moderate to severe.

One or more analgesics were used by 89% of the EDS patients with pain, paracetamol (acetaminophen) was used by 59%, paracetamol with codeine by 21%, acetylsalicylic acid by 4%, other nonsteroidal anti-inflammatory drugs by 67%, tramadol by 23%, and antineuropathic pain drugs by 11% of the patients (Table 2). Reported doses did not exceed the maximally allowed prescriptions.

The Relationship of Pain with Disease-Related Factors

Joint hypermobility was reported by 230 (93%)of the 246 patients with pain. Dislocations occurred in 193 (78%) patients, and dermal features were reported by 236 (96%) patients with pain. Previous surgery was reported by 227 (92%) of these patients and muscle weakness by 196 (80%) (Table 1).

Most severe pain (VAS) was significantly correlated with previous surgery (0.213; $P < 0.01$), hypermobility (0.175; $P < 0.001$), and dislocations (0.183; $P < 0.001$). Current pain (VAS) was significantly correlated with dislocations (0.153; $P < 0.05$). Neither most severe pain nor current pain (VAS) was significantly correlated with dermal features or muscle weakness.

The Relationship of Pain with Sleep Disturbances

Half of the patients with pain ($n = 246$) were awake during the night because of pain (50%); and of these patients, 93% was awake at least two hours. The mean SCL sleep subscale score was 6.7 (standard deviation [SD] 3.3; range 3−15). Pain severity was significantly correlated with SCL sleep subscale score ($r = 0.31$; $P < 0.001$ for most severe pain and $r = 0.29$; $P < 0.001$ for current pain $P < 0.001$).

Contribution of Pain Symptoms to the Functional Impairment in Daily Life

Based on the results of the McGill Pain Questionnaire, 87% of the patients with pain ($n = 246$) was impaired in performing their daily activities, and in 55% of them, this consisted of moderate-to-severe impairment. Appetite was reduced in 32% of patients. Furthermore, patients had moderate-to-severe impairment because of pain based on the SF-36: mean SF-36 subscore pain was 42.4 (range 0−100; SD 20.2). Pain severity was significantly

Table 2
Use of Analgesics in EDS Patients Reporting Pain ($n = 246$)

Drug	% of Patients with Pain Using Analgesics ($n = 246$)
Paracetamol (acetaminophen)	
Paracetamol	59
Paracetamol with codeine	21
Nonsteroidal anti-inflammatory drugs	
Acetylsalicylic acid	4
Ibuprofen	31
Naproxen	14
Diclofenac	16
Opioids	
Tramadol	23
Neuropathic Pain Drugs	
Amitriptyline	7
Carbamazepine	1
Gabapentin	3
Other	
Various	33

Note: Several patients used more than one analgesic.

correlated with the total SIP score ($r = 0.45$; $P < 0.001$ for most severe pain and $r = 0.43$, $P < 0.001$ for current pain). The mean total SIP score was 1157 (SD 660; range 0–2865) reflecting severe impairment in daily functioning.

Multiple regression analysis of data of all patients ($n = 273$) resulted in a model in which pain severity (most severe pain [VAS]) and fatigue severity predicted 31% of functional impairment (Table 3). The predictive value of the model with current pain rather than most severe pain as independent variable had a similar predictive value (28%; data not shown).

Table 3
Results of Multiple Regression Analysis of Pain and Fatigue, with Functional Impairment as Dependent Variable in all EDS patients ($n = 273$)

Dependent Variable: Functional Impairment (SIP Sum Score) in All EDS Patients			
Independent Variables		Beta	*P*
Pain	Most severe pain (VAS)	0.241	<0.001
Fatigue	CIS fatigue	0.392	<0.001
Enter: P in = 0.05; P out = 0.1; adjusted $R^2 = 0.309$			

Discussion

This study in a large group of EDS patients shows that 1) chronic pain is highly prevalent in EDS and is associated with regular use of analgesics; 2) pain is more prevalent and more severe in patients with the hypermobility type than in those with the classic type and vascular type; 3) pain severity is related to hypermobility, dislocations, and previous operations but not to other disease-related factors; 4) pain is related to sleep disturbances; and 5) pain is related to functional impairment in daily life, independent of the level of fatigue.

Previous studies also reported high prevalence of pain in EDS but were limited in size and scope.[5,7,8] Results of our study confirm the high prevalence of pain and add the finding that pain is most common and most severe in patients with the hypermobility type of EDS. Furthermore, this study shows that myalgia is reported by most patients, and that pain is predominantly localized in neck, shoulders, hips, and legs but not in the head or abdomen. Most severe pain is correlated to hypermobility, dislocations, and previous surgery. Together, these findings may indicate that pain in EDS has a compound origin: a constant level of pain may originate in the musculoskeletal system,[1] and additional peaks of severe pain may be related to recurrent (sub)luxations and/or dislocations.[5]

The results of this study further show that pain severity in EDS is related to sleep disturbances. Pain has previously been reported as one of the causes of low sleep quality in EDS, causing difficulties in initiating and maintaining sleep.[13] Also in other chronic diseases, pain severity was found to be related to sleep disturbances. However, recent data seem more consistent with poor sleep leading to an increasing pain severity than pain predicting poor sleep.[25]

Furthermore, pain severity in EDS was found to be independently related to functional impairment. This relationship between pain severity and disability also has been found in other populations with chronic pain, for example, in patients with chronic lower back pain or fibromyalgia.[25]

This study has not focused on the psychological variables that are known to influence pain, such as catastrophizing and fear of exercise-related pain.[14] These and other factors should be addressed in future studies on pain in EDS because they may be a starting point for treatment of chronic pain in EDS.[26,27] Based on

experience with chronic pain in other diseases, cognitive behavioral interventions in EDS might reduce pain and pain-related disability.[26] In addition, symptomatic treatment of pain in EDS can be directed at prevention of dislocations and optimizing medical treatment of pain. Patients' reports of severe pain in EDS stress the importance of development of multidisciplinary treatment protocols.[6]

A possible limitation of our study is the selection bias occurring with the recruitment of members of the Dutch EDS Foundation. The previous questionnaire study on 51 patients, which showed that moderate-to-severe pain is common in EDS, also relied on members of a national EDS foundation.[5] Patients who are most severely affected might be more likely to join a patient support group. EDS patients with only mild symptoms might not even be diagnosed and not seek medical attention. This selection bias has to be taken into account when interpreting the results of this study.

This limitation notwithstanding, our findings suggest that pain is a very common and severe symptom in this group of EDS patients. It is related to dislocations, sleep disturbances, and moderate-to-severe impairment in daily functioning. Therefore, treatment of pain should be a prominent aspect of clinical management of EDS, and multidisciplinary protocols should be developed.

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