Fatigue Is a Frequent and Clinically Relevant Problem in Ehlers-Danlos Syndrome

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Objectives: Ehlers-Danlos Syndrome (EDS) is a clinically and genetically heterogeneous group of inherited connective tissue disorders characterized by joint hypermobility, skin hyperextensibility, and tissue fragility. Fatigue and musculoskeletal pain are associated features but have never been studied systematically. We used a multidimensional assessment method to measure fatigue, its clinical relevance, and possible determinants.

Methods: A questionnaire study was performed among 273 EDS patients. The following dimensions were assessed: fatigue severity, functional impairment in daily life, physical activity, psychological distress, sleep disturbances, concentration problems, social functioning, self-efficacy concerning fatigue, causal attribution of fatigue, pain, and disease-related factors.

Results: More than three-quarters of EDS patients suffer from severe fatigue. Patients who are severely fatigued are more impaired than nonseverely fatigued patients and report a higher level of psychological distress. The 5 possible determinants involved in fatigue are sleep disturbances, concentration problems, social functioning, self-efficacy concerning fatigue, and pain severity.

Conclusions: This is the first study of fatigue and its possible determinants in EDS and shows that fatigue is a frequent and clinically significant problem in EDS. The 5 possible determinants of fatigue could form a starting point for the development of an effective cognitive behavioral intervention for fatigue in EDS.

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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 (1-3). The hypermobility type is the most common type of EDS, followed by the classical type (4). Diagnostic criteria include joint hypermobility, skin hyperextensibility, and tissue fragility, resulting in easy bruising and abnormal scarring (1). Chronic joint/limb pain is 1 of the minor diagnostic criteria in the hypermobility type, and fatigue is acknowledged as an associated feature in the classic type (1). Both symptoms generally receive little medical attention, although patients' reports suggest that these symptoms contribute significantly to the burden of disease in EDS (5).

Fatigue can be defined as an overwhelming sense of tiredness, lack of energy, and feeling of exhaustion and is not the same as muscle weakness (6,7). Fatigue is a common symptom in various chronic diseases and was found to be a major determinant of disability, which significantly influences the quality of life (7-12). The frequency of fatigue in EDS, its clinical relevance, and its associations with possible determinants have not yet been inves-

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tigated together. We therefore performed an extensive questionnaire study on fatigue in EDS and used a multidimensional assessment method to measure fatigue, its clinical relevance, and possible determinants in EDS. Questionnaire studies, due to their relatively unbiased and potential broad-ranged character, may shed light on the patients' perspective of fatigue and pain in EDS. This method has been used in several other chronic disorders and may identify possible determinants of fatigue in EDS, which can serve as a starting point for effective behavioral interventions (6,13).

METHODS

Patients

A cross-sectional design was used to assess fatigue in patients with EDS. We asked 500 members of the Dutch patient organization of EDS (VED: www.ved.nl) to participate, and 19 additional patients were recruited from the outpatient departments of the Radboud University Nijmegen Medical Centre; these latter patients were also included in a clinical study on neuromuscular features in EDS (14). Three hundred twenty-seven questionnaires were returned (63% response rate). The intention of the study was described as "to learn more about various complaints in Ehlers-Danlos syndrome" to prevent a selection bias for fatigued patients. Written information on this purpose was provided to all patients, and all patients gave informed consent. The study was approved by the local ethics committee.

Assessment

All patients were sent a booklet with (1) various questions on EDS type; clinical features of EDS (1); presence of muscle symptoms (14); previous surgery and comorbidity; use of medication (based on a questionnaire assessing volumes of medical consumption in the previous 6 months) (15); 3 most important complaints in order of priority; and (2) 7 validated questionnaires (see below).

Fatigue Severity

The Checklist Individual Strength (CIS) measures 4 aspects of fatigue. We used the subscales fatigue severity (8 items, score range from 8 to 56) and concentration problems (5 items, score range from 5 to 35) (6). High scores indicate more severe problems in the domain that is measured. A CIS-fatigue score of 35 or more was used to identify severe fatigue; this score is higher than the mean plus 2 standard deviations (SD) of a healthy control group (6,16).

Dimensions of Fatigue

The multidimensional assessment method measures the following dimensions of fatigue: functional impairment in daily life; level of physical activity; psychological distress; sleep disturbances; concentration problems; social functioning and social support; self-efficacy concerning fatigue; causal attribution of fatigue; pain; and disease-related factors.

Functional Impairment in Daily Life

The Sickness Impact Profile (SIP) is aimed at measuring changes of conduct in everyday activities due to sickness (13,17-19). For functional impairment, we used the subscales household management, work, and recreation and pastimes. Higher scores on this subscale indicate more disabilities in this domain. Physical disabilities were measured with the physical functioning subscale of the Short Form-36 (SF36) (20). Scores range from 0 (maximum physical limitations) to 100 (optimal physical functioning) (21). Additionally, we included the number of hours worked per week (paid and unpaid) as measures of functional ability. Unpaid work was defined as studying, household duties, and volunteer work.

Physical Activity

The level of physical activity was measured with the subscales mobility and ambulation of the SIP.

Psychological Distress

The Beck Depression Inventory was used to measure clinical depression, which was defined as a score of >4 (on a scale of 0 to 21) (22) Psychological distress was measured with the sum score of the subscales anxiety and depression of the Symptom Check List 90 (23). Higher scores indicate a higher level of psychological distress.

Sleep Disturbances

Sleep disturbances were measured with the sleep/rest scale of the SIP (reflecting disturbance of the normal wake and sleep pattern) and the sleep subscale of the Symptom Check List (reflecting quality of nocturnal sleep). Higher scores indicate more sleep disturbances. To differentiate between daytime and nighttime sleeping problems, we split the SIP sleep and rest subscales into items focusing on daytime sleeping and the items focusing on nighttime sleep disturbances. Furthermore, we asked for the duration of nighttime and daytime sleep (hours) and occurrence of good quality of nighttime sleep (%).

Concentration Problems

Perceived concentration problems were measured with the concentration subscale of the CIS. Furthermore, we used the alertness behavior subscale of the SIP. Higher scores indicate more concentration problems.

Social Functioning

Social functioning and social support were measured with the social interaction subscale of the SIP and the social

functioning subscale of SF36. Higher scores indicate more impairment.

Self-efficacy Concerning Fatigue

Self-efficacy, a sense of control over fatigue symptoms, was measured with the Self-Efficacy Scale. The Self-Efficacy Scale consisted of 7 questions that measured sense of control with respect to fatigue. The total score ranges from 7 to 28, and a higher score reflects a higher sense of control (24).

Causal Attribution of Fatigue

Patients were asked for their causal attribution of fatigue with the following options: EDS itself; too many activities, not enough leisure time; sleep disturbances; personal reasons; worrying thoughts; depressive thoughts; and a positive family history of fatigue. Patients could choose 1 or more attributions.

Pain

The visual analog scale (VAS) scores for the current and the most severe pain (subscale of the McGill Pain Questionnaire) were measured (25). Pain was further assessed by the following 3 questions of the McGill Questionnaire: whether pain occurred (yes or no), whether it occurred at least 12 hours each day (% yes), and whether analgesics were used (% yes). Furthermore, we asked whether myalgia was present (% yes).

Disease-related Factors

Disease-related factors questioned were hypermobility, joint dislocations, skin hyperextensibility, and easy bruising (1). We added questions about muscle hypotonia, myalgia, and muscle weakness since we recently showed considerable neuromuscular involvement in various types of EDS (14).

Impact of Fatigue and Impact of Pain

The pain subscale of the SF36 was used to assess the impact of pain; it measures the magnitude of pain and its resulting self-reported functional limitations due to pain. Scores range from 0 to 100 (0 = no pain and no impairment due to pain; 100 = maximal pain and maximal impairment due to pain). We used the same items and scores again, replacing the word pain by fatigue, to compare the impact of fatigue (magnitude of fatigue and self-reported functional limitations due to fatigue) with the impact of pain.

Statistics

SPSS for Windows (version 16.0) was used to carry out data analysis, and we used descriptive statistics to depict the sample. We defined 2 groups of patients: severely fatigued patients (CIS fatigue $\geq$35) versus nonseverely fatigued patients (CIS fatigue $<$35) (6,16). We tested the differences in scores on the various measures between the nonseverely and severely fatigued patients with the χ^2 or Fisher's exact test (dichotomous variables), Student's *t*-test (variables at least interval level), or a Mann-Whitney *U* test (ordinal variables). Correlations were calculated with the Pearson coefficient (*r*). Probability (*P*) values smaller than 0.05 were regarded as statistically significant. For each dimension, we selected the measure with the strongest and statistically significant correlation with the CIS fatigue score for subsequent multiple linear regression analysis, in which we determined the contribution of various measures to the level of fatigue (backward method; *P* in = 0.01; *P* out = 0.05). The measures that resulted from this regression analysis were considered to be possible determinants of fatigue.

RESULTS

Excluded were patients who were younger than 16 years ($n = 16$), patients in whom EDS had not been diagnosed ($n = 30$), and patients who had incompletely filled out the CIS fatigue severity scale ($n = 8$). Hence, 273 patients were included; in 53 of them the specific type of EDS was not (yet) known, although EDS was diagnosed by a medical specialist. In all other patients the EDS type was classified according to the diagnostic criteria (1). Demographic characteristics of the patients are summarized in Table 1.

Table 1 Demographics of Ehlers-Danlos Syndrome Patients, Age and Sex Distribution of EDS Patients, and Distinction Between Nonseverely and Severely Fatigued Patients

Ehlers-Danlos Syndrome (EDS) Type	Number of Patients	Mean Age range (y)	Female n (%)	EDS Nonseverely Fatigued n (%)	EDS Severely Fatigued n (%)	Stat. Sign.[a] of Difference *P*
Classic (C)	45	43.1 (16 to 68)	35 (78)	14 (31)	31 (69)	C vs H 0.032
Hypermobility (H)	162	38.8 (16 to 74)	152 (94)	26 (16)	136 (84)	
Vascular (V)	11	33.6 (19 to 61)	9 (82)	5 (45)	6 (55)	
Kyphoscoliotic (K)	2	21.0 (16 to 26)	0 (0)	2 (100)	0 (0)	
Other/Type unknown	53	46.2 (19 to 89)	48 (91)	15 (28)	38 (72)	
Total	273	40.7 (16 to 89)	244 (89)	62 (23)	211 (77)	

[a]Fisher's exact test.

Three Most Important Symptoms

Two hundred sixty-four patients completed the questionnaire on most important complaints. The mean number of self-reported complaints was 5.6 (SD 2.5), and 204 patients reported at least 4 complaints. Musculoskeletal pain, hypermobility/dislocations, and fatigue were most frequently reported spontaneously: 99% of the patients reported musculoskeletal pain as 1 of their 3 most important complaints; 63% reported hypermobility/dislocations; and 57% reported fatigue. In contrast, dermal features (skin hyperextensibility, easy bruising, abnormal scar formation) were far less often reported, although they are part of the diagnostic criteria (1).

Fatigue Severity and Dimensions

The mean CIS fatigue score was 41.7 (SD 11.3). The majority of patients (77%) were severely fatigued (CIS fatigue $\geq$35). Severe fatigue was more common in the hypermobility type than in the classic type ($P = 0.032$) (Table 1). Age, sex, and level of education did not differ between severely and nonseverely fatigued patients. Table 2 shows the differences between nonseverely and severely fatigued patients on the various dimensions. In all dimensions, being severely fatigued was associated with more problems or limitations.

Previous Surgery, Comorbidity, and Use of Medication

Previous surgery of any kind was reported by 247 (90%) patients. Patients who had surgery had higher CIS fatigue score than those who did not (mean (SD): 42.4 (11.0) versus 34.5 (11.9); $P = 0.001$). One hundred seventeen (43%) patients reported any kind of comorbidity, and this group had higher mean CIS fatigue score than those without self-reported comorbidity (mean (SD): 43.9 (9.3) versus 40.0 (12.4); $P = 0.003$). Among the patients with comorbidity, anemia was mentioned by 3 patients, and hypothyroidism was mentioned by 2. Analgesics with possible sedative side effects were used by 62 patients, and these patients had a higher CIS fatigue score than those not using these medications (46.7 (SD7.9) versus 40.1 (SD11.8); $P < 0.001$). Antidepressive drugs with possible sedative (side-) effects were used by 38 patients, and the CIS fatigue scores were similar in both groups (44.1 (SD 10.5) versus 41.7 (SD 11.0); $P = 0.24$). Use of benzodiazepines was reported by 39 patients, and these patients had a higher CIS fatigue score than those not using them (46.5 (SD 9.4) versus 40.8 (SD 11.4); $P = 0.003$). Use of β-blockers was reported by 6 patients, and they had similar scores to those not using them (39.2 (SD 6.6) versus 41.8 (SD 11.4); $P = 0.59$). Table 3 summarizes the (categories of) diagnoses reported as comorbidity and the self-reported medications with possible sedative (side-) effects.

Regression Analysis

The measures with the highest correlation coefficient for each dimension were selected to be included in multiple regression analysis; these measures are asterisked in Table 2. Regression analysis with CIS fatigue as the dependent variable resulted in a model with 5 possible determinants (asterisked in Table 4): disturbances in sleep and wake pattern (SIP sleep and rest), concentration problems (CIS concentration), social functioning (SF36 social functioning), self-efficacy concerning fatigue (Self-Efficacy Scale 28), and pain (most severe pain: VAS). Together, these possible determinants predicted 38% of the fatigue severity (Table 4).

Impact of Fatigue and Impact of Pain

Pain severity (most severe pain (VAS)) was higher in the severely fatigued than in nonseverely fatigued patients ($P = 0.001$). In contrast, fatigue more frequently had a larger impact on daily functioning than pain ($P < 0.001$): in 40% of the EDS patients fatigue had a larger impact than pain (SF36 fatigue $>$ SF36 pain); for 34% of the patients the impact of pain was equivalent to that due to fatigue (SF36 pain = SF36 fatigue); and 26% reported a larger impact of pain symptoms than of fatigue (SF36 fatigue $<$ SF36 pain).

DISCUSSION

This is the first in-depth questionnaire study of fatigue in EDS and shows that fatigue is a frequent and clinically relevant problem in EDS: 77% of EDS patients suffer from severe fatigue; and patients who are severely fatigued are more impaired and report a higher level of psychological distress. Patients with the hypermobility type EDS are most often severely fatigued. Furthermore, severe fatigue in EDS is related to sleep disturbances, concentration problems, social functioning, self-efficacy concerning fatigue, and pain.

The 77% prevalence of severe fatigue and the mean CIS fatigue score of 41.7 is high in comparison with the general population. In a Dutch study of chronic fatigue in disease-free breast cancer patients, a control group of 78 healthy women (mean age, 48.1 (SD 6.2) years) had a mean CIS fatigue score of 19.4 (SD 11.0), and 11% of the women had a CIS fatigue score of 35 or more (12). Another study reported a mean CIS fatigue score of 17.3 (SD 10.1) in a group of 53 healthy Dutch controls with predominantly female subjects (26). The prevalence of severe fatigue in this EDS population was also high in comparison with rheumatoid arthritis, another chronic disorder with extensive articular involvement and high prevalence of pain. A recent study among 150 rheumatoid arthritis patients reported a mean CIS fatigue of 34.2 (SD 10.2), with 52% of the patients being severely fatigued (11).

Many EDS patients in this study reported previous surgery and 1 or more comorbidities. Patients with previ-

Table 2 Differences Between Nonseverely and Severely Fatigued Patients

	EDS Nonseverely Fatigued Mean (SD)/%	EDS Severely Fatigued Mean (SD)/%	Sign. Testing[a]	Pearson Correlation (unless otherwise specified)	
				Correlation Coefficient r	Stat. Sign. of Correlation α
1. Functional impairment in daily life					
SF36 physical functioning*	61 (27)	37 (23)	<0.001	−0.498	0.000
SIP work problems	96 (145)	198 (163)	<0.001	0.343	0.000
SIP household management	119 (131)	195 (116)	<0.001	0.341	0.000
SIP recreation and pastime	58 (63)	123 (76.4)	<0.001	0.403	0.000
Weekly worked hours (paid)	14 (19)	5 (14)	0.001	−0.332	0.000
Weekly worked hours (unpaid)	8 (17)	7 (19)	n.s.	−0.022	n.s.
2. Physical activity					
SIP mobility*	39 (68)	94 (114)	<0.001	0.344	0.000
SIP ambulation	83 (102)	156 (120)	<0.001	0.319	0.000
3. Psychological distress					
% BDI PC >4	3	20	0.010[b]	0.337[d]	0.000
SCL psychological distress*	33 (7)	42 (16)	<0.001	0.420	0.000
4. Sleep disturbances					
SIP sleep and rest—Daytime sleep	30 (34)	68 (59)	<0.001	0.409	0.000
SIP sleep and rest—Nighttime sleep	11 (24)	31 (31)	<0.001	0.338	0.000
SIP sleep and rest	42 (44)	100 (70)	<0.001	0.478	0.000
SCL sleep disturbances*	4 (2)	7 (3)	<0.001	0.462	0.000
Duration nighttime sleep (h)	8 (1)	7 (2)	n.s.	−0.078	n.s.
Duration daytime sleep (h)	0.3 (0.7)	0.9 (1)	<0.001	0.264	0.000
% Good quality of nighttime sleep	61	32	<0.001[b]	−0.290[d]	0.000
5. Concentration problems					
CIS concentration*	11 (7)	16 (9)	<0.001	0.359	0.000
SIP alertness behavior	62 (80)	153 (158)	<0.001	0.357	0.000
6. Social functioning and social support					
SIP social interaction	82 (116)	190 (180)	<0.001	0.404	0.000
SF36 social functioning*	80 (21)	54 (23)	<0.001	−0.557	0.000
7. Self-efficacy concerning fatigue					
SES28*	21 (4)	18 (4)	<0.001	−0.403	0.000
8. Causal attribution of fatigue					
% Ehlers-Danlos syndrome	82	94	0.010[c]	0.186[d]	0.003
% Too many activities	27	13	0.012[b]	−0.155[d]	0.012
% Not enough leisure time	6	6	n.s.[c]	−0.059[d]	n.s.
% Sleep disturbances*	19	37	0.013[b]	0.232[d]	0.000
% Personal reasons	2	7	n.s.[c]	0.001[d]	n.s.
% Worrying thoughts	17	19	n.s.[b]	0.059[d]	n.s.
% Depressive thoughts	6	10	n.s.[c]	0.119[d]	n.s.
% Family history of fatigue	6	4	n.s.[c]	−0.030	n.s.
9. Pain					
% Occurrence of pain	69	96	0.001[b]	0.387[d]	0.000
% Daily pain duration >12 h	20	54	0.001[b]	0.210[d]	0.002
% Use of analgesics	56	86	0.001[b]	0.180[d]	0.000
% Occurrence of frequent or continuous myalgia	65	87	<0.001	0.380[d]	0.000
Current pain: VAS	4 (3)	5 (2)	0.002	0.373	0.000
Most severe pain: VAS*	5 (4)	8 (2)	0.001	0.540	0.000
10. Disease-related factors					
% Hypermobility	91	95	n.s.[c]	0.104[d]	n.s.
% Dislocations	76	78	n.s.[b]	0.049[d]	n.s.
% Skin hyperextensibility	57	48	n.s.[b]	−0.080[d]	n.s.
% Easy bruising	89	83	n.s.[b]	−0.064[d]	n.s.
% Muscle weakness	61	80	0.0039[b]	0.167[d]	0.006

Table 2 Differences Between Nonseverely and Severely Fatigued Patients (continued)

	EDS Nonseverely Fatigued Mean (SD)/%	EDS Severely Fatigued Mean (SD)/%	Sign. Testing[a]	Pearson Correlation (unless otherwise specified)	
				Correlation Coefficient r	Stat. Sign. of Correlation α
% Muscle hypotonia*	43	56	n.s.[b]	0.209[d]	0.001

SF36, Short Form 36; SIP, Sickness Impact Profile; SCL, Symptoms Check List; BDI, Beck Depression Inventory; CIS, Checklist Individual Strength; SES28, Self-Efficacy Scale; SD, standard deviation.

Differences between nonseverely and severely fatigued patients on 10 dimensions, each of which is assessed by 1 or more measures (left columns). Correlation of each of these measures with the CIS fatigue score is given in the right columns. The measure with the highest correlation coefficient of each dimension is asterisked. These measures are used in the multiple regression analysis.

[a]Independent t-test unless otherwise specified.

[b]χ^2 test.

[c]Fisher's exact test.

[d]Spearmans's ρ; nonparametric correlation.

ous surgery or comorbidity had higher mean CIS fatigue scores than those without, although in both groups this was above 35. However, anemia and hypothyroidism, disorders known to cause fatigue, were very rare. Furthermore, the prevalence of medication use with possible sedative side effects is high in this population. The mean CIS fatigue score in patients using analgesics with possible sedative side effects or benzodiazepines was higher than in the other EDS patients. Most likely, use of this medication contributes to the high prevalence of severe fatigue in this population. The limitation of these data is that it is based on self-reports, and this may not be very accurate. Furthermore, it is difficult to evaluate the individual contribution of these factors to fatigue, since they are probably interrelated, and dependent on the severity of EDS.

Table 3 Self-reported Comorbidity and Use of Medications With Possible Sedative Side Effects

Self-reported Comorbidity	Number of EDS Patients
Anemia	3
Hypothyroidism	2
Hypertension	11
Diabetes mellitus	2
Other internal diseases	21
Osteoarthritis	5
Other rheumatologic diseases	25
Chronic obstructive pulmonary disease/ Bronchial asthma	22
Migraine/other headaches	4
Other neurological diseases	5
Depression	2
Burnout	3
Other psychiatric diseases	8
Allergy	14
Dermatological diseases	6
Gynecological diseases	5
Ophthalmological diseases	4
Cardiac disease	6
Self-reported Use of Medication With Possible Sedative Side Effects	**Number of EDS Patients**
One or more analgesics with sedative side effects	62
Tramadol	14
Opiates/other opiate agonists	39
Codeine	22
Anti-epileptic drugs	3
Baclofen	2
One or more anti-depressive drugs with possible sedative side effects	38
One or more benzodiazepines	39
One or more β-blockers	6

We found that pain is another common and clinically relevant symptom in EDS, which is in accord with the results of a previous study on pain in EDS (27). In fact, pain was more often spontaneously reported than fatigue, whereas fatigue had a larger impact than pain on daily functioning. Hence, our study shows that both pain and fatigue contribute to the burden of disease in EDS. Therefore, fatigue and pain should preferably be evaluated collectively and addressed simultaneously in symptomatic treatment. Pain and fatigue are mentioned as associated features in the diagnostic criteria (1) but generally receive little attention in medical practice and in the literature. The finding that these symptoms are very often spontaneously reported as the most important complaint, that they are severe, and that they have a large impact, emphasizes the importance of questionnaire studies.

We identified 5 possible determinants of fatigue in EDS: sleep disturbances, concentration problems, social functioning, self-efficacy concerning fatigue, and pain. Since we used cross-sectional data, we were only able to show that these factors are possible determinants. However, a strong association of these possible determinants with severe fatigue is suggested by this study. More precisely, sleep disturbances (28), low self-efficacy concerning fatigue, and pain most likely contribute to persistence of severe fatigue. Sleep problems in EDS were previously found to consist predominantly of difficulties initiating and maintaining sleep (29). We added the finding that a significant number of patients rest and sleep during the day, which was associated with fatigue severity. Concentration problems may be a result of fatigue, whereas social

Table 4 Multiple Regression Analysis of Possible Determinants of Fatigue

Independent Variables		Dependent Variable CIS Fatigue	
Dimension	Possible Determinant	Beta	*P* Value
1. Functional impairment in daily life	SF36 physical functioning		
2. Physical activity	SIP mobility		
3. Psychological distress	SCL negative affectivity		
4. Sleep disturbances*	SIP sleep and rest	0.136	0.028
5. Concentration problems*	CIS concentration	0.148	0.007
6. Social functioning and social support*	SF36 social functioning	−0.229	<0.001
7. Self-efficacy concerning fatigue*	SES28	−0.240	<0.001
8. Causal attribution of fatigue	Sleep disturbances		
9. Pain*	Most severe pain: VAS	0.220	<0.001
10. Disease-related factors	Muscle hypotonia		

SF36, Short Form 36; SIP, Sickness Impact Profile; SCL, Symptoms Check List; BDI, Beck Depression Inventory; CIS, Checklist Individual Strength; SES28, Self-Efficacy Scale; SD, standard deviation.

Backward; P in = 0.01; P out = 0.05; Adjusted R^2 = 0.382.

Results of multiple linear regression analysis, in which we determined the contribution of 1 measure of each dimension to the level of fatigue. This analysis resulted in a model with 5 possible determinants, which are asterisked. This model predicted 38% of the fatigue severity score of the CIS.

impairment might be either a perpetuating factor or a consequence of fatigue (12,30). A follow-up study may help determine whether these factors are the cause or consequence of fatigue.

A limitation of this study is the ascertainment bias introduced by addressing members of a patient support group, and only using the questionnaires that were returned. Both patients who are not severely impacted by the disease and busy with their work and family and patients who are severely affected with major impairment might not get involved in a patient support group and tend not to complete questionnaires. However, recruitment of consecutive EDS patients at an outpatient department is complicated, since the care for EDS patients is multidisciplinary, and most hospitals do not have a specialized EDS center. Furthermore, we were unable to perform a nonresponders analysis, since the patient support group took care of the mailing of the questionnaires and did not send us the names and addresses of their members for privacy reasons.

The results of our study can serve as a starting point for symptomatic treatment approaches. A cognitive behavioral intervention focusing on pain, sleep disturbances, the reaction of others to the symptoms and self-efficacy concerning fatigue could help reduce fatigue and fatigue-related disabilities. Positive results of this approach can be expected from recent findings in other chronic diseases with a high frequency of severe fatigue (31-33). Furthermore, medical interventions should address pain and evaluate medication use, and irregular sleeping patterns should be analyzed for treatable causes.

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