CASE REPORT

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Ehlers–Danlos Syndrome (EDS) focusing on oral symptoms: a questionnaire study

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Structured Abstract

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Objectives – To study the prevalence of oral problems reported among a large group of adults with Ehlers–Danlos Syndrome (EDS). Furthermore, to compare proportions of disorders and general psychological well-being with those in a cohort of randomized population-based controls.

Design – A questionnaire study.

Setting and Sample Population – A total of 265 persons with EDS (response rate 77%) and 750 controls (response rate 63%) in a population-based cohort. Sixty persons were excluded from the EDS group (support members, children, undiagnosed EDS) leaving a final study group of 144 adults. The final control group consisted of 331 persons since many had sent back unanswered questionnaires.

Experimental Variables – Questions concerning general and oral symptoms, VAS scales for masticatory muscle pain ratings and General Health Questionnaire (GHQ12) questions were included.

Outcome Measure – Proportions of affirmative answers in EDS group and controls were compared. Mean values for ratings on VAS scales. Proportions of GHQ12 scores with a threshold score of four or more.

Results – The proportions of affirmative answers for persons with EDS concerning general health problems, oral problems and masticatory muscle symptoms were significantly higher compared with controls. In the EDS group those who had daily pain in the masticatory muscles had significantly higher mean values on the VAS scales compared with those who had pain a few days per month. A GHQ12 score of four or more was significantly more common in the EDS group than in the controls, suggesting that a decline in psychological well-being was also more common in this group.

Conclusion – It is important that dental practitioners should be aware of the oral problems associated with EDS and the impact the disease has on quality of life.

Key words: chronic pain; connective tissue; Ehlers–Danlos; General Health Questionnaire; masticatory muscle pain; oral; temporomandibular disorders; temporomandibular joints

Introduction

The connective tissue disorder Ehlers–Danlos Syndrome (EDS) primarily affects the skin, joints, ligaments and sometimes the blood vessels (1, 2). The disease is relatively rare with a prevalence of 1 per 5000 (2). The symptoms vary from mild to severe and are potentially disabling (2). The variability of the disease has led to different classification systems (3, 4). The classical types (EDS I gravis, EDS II mitis) and the hyper mobile type (EDS III) are found in 90% of the cases. The vascular type (EDS IV) is found in 3–10% and the periodontal type (EDS VIII) is rare (2, 3, 5, 6).

Studies on temporomandibular joint (TMJ) and/or masticatory muscle disorders (TMD) in EDS have mainly focused on the hypermobility of the TMJs (7–9). General muscle fatigue and chronic pain are commonly reported among persons with EDS (10).

There are also oral problems in EDS such as hard tissue defects of the teeth, high cusps and fissures on the crowns, stunned or dilacerated roots of the teeth, pulp stones, a high incidence of fractures of the teeth, periodontal diseases and fragile and sensitive mucous membranes (11–15). These factors are likely to complicate dental treatment. Tooth movement in response to orthodontics can also be hazardous because of a collagen cross-linkage defect (14). Unfavorable rapid movements of teeth, increased tooth mobility, a risk of root resorption and relapse after orthodontic treatment have been reported (14, 16). Previously published controlled studies of oral symptoms in a large group of persons with EDS have not been found in the literature.

Many persons with EDS have no faith in the health care system. They may even fail to seek professional help when needed (10). Many persons with EDS experience similar problems regarding dental treatment and the disease is unknown to many dentists (oral communication). Fear of problems related to the disease and the chronic pain affect daily life (10).

The aim of the study was to establish the prevalence of oral problems reported among a group of adults with EDS and to compare the proportions of disorders with those in a cohort of randomized population-based controls. The present general psychological well-being in both groups was assessed and compared (GHQ12).

Material and methods

In January 2002 the Swedish EDS Association had 265 members living in Sweden with an updated address. They all received the questionnaire and the response rate was 77% (205 answers). Two reminders had been sent out. Sixty-one persons were excluded. Exclusion criteria set were: answers from children aged below 18 years, support members and members with suspected but not medically confirmed EDS and members who did not want to participate. The study base then consisted of 144 adults (126 women, 18 men) with a diagnosed EDS.

The control group was weighted for a similar distribution of gender and age to that reported for the members of the Swedish EDS Association by the chairman. A low response rate was expected, and 750 persons older than 18 years of age were randomized from the SPAR register of the Swedish population. There were 600 women and 150 men.

The control study base then consisted of 736 persons (591 women, 145 men). The response rate for the controls was 63%. Of these, 331 persons (266 women, 65 men) had answered the questions and the other 136 had sent the questionnaire back with only their name, and a few had phoned. Three reminders had been sent out. None of the controls reported a diagnosed EDS. The response rates (%) for the different age groups were displayed in a bar graph to check that the distribution of the original randomized control sample had not changed as a result of the drop-outs. This was also done for the EDS group.

The questionnaire

The questionnaire was first tested on 10 persons with EDS. Of these, seven wanted to participate in the study and they were phoned and interviewed about the questionnaire. They had had no problems in understanding and answering the questions. Each question had answering alternatives of 'yes' or 'no'. Some questions had more specified 'yes' answers to choose among such as 'yes always' and 'yes sometimes'. Only one alternative was to be chosen. The main topics of the questions were:

General health: diseases confirmed by a doctor, type of EDS, hours of work per day, sick leave during the last year, smoking habits, psychological well-being (GHQ12).

Medication: analgesic and/or hypnotic medication.

Pain in: the masticatory muscles, the TMJs, the muscles of the body, the body joints, headache.

Hypermobility: hand wrists, TMJs, tongue.

Skin: delayed wound healing and permanent scars.

Voice: having a hoarse voice without a throat infection, difficulty in shouting and screaming loudly.

Dental treatment questions: experience of tooth extractions and administration of local anesthetics, periodontal diseases, endocarditic prophylaxis during dental treatment, spontaneous fractures of the teeth.

The Visual Analogue Scale (VAS scale) was used to assess pain in the masticatory muscles (17). It consisted of a horizontal line designed as 100 mm long with the text 'no pain' to the left of it and 'very strong pain' to the right. Three separate scales were used for assessment of 'maximal' pain, 'average' pain and for pain 'right now'. The frequency of pain was chosen among the alternatives; 'never or almost never pain', 'monthly pain', 'weekly pain' and 'daily or almost daily pain'. The location of the masticatory muscles was explained in the questionnaire as 'the chewing muscles' that you can feel with your hand against the cheek when biting hard on your teeth. This location corresponds to the location of the masseter muscle.

The General Health Questionnaire (GHQ12) was used to assess the present psychological well-being of the participants in the study (18). The 12 questions asked the informants about their general level of happiness, experience of depressive and anxiety symptoms, self-confidence and sleep disturbances. The scoring method used was to treat each item as a weighted bimodal response scale (19). Each question had four possible responses that either corresponded to a score value of 0 or 1 that indicated non-possession or possession of the a item in the question (19). Every person could then be assigned a summed total score ranging from 0 to 12 (19). The higher the score, the greater was the likelihood that the person had psychological problems or psychiatric disorders. The threshold had been set to score four or more in accordance with published recommendations (18, 19).

The study was approved by the Ethics Committee of the Medical Faculty of Göteborg University.

Statistics

The answers from persons with EDS and controls were compared as the 95% confidence interval for the difference between proportions. The Wilson method was used (20). A significant difference was assumed when the interval did not include zero. JMP and JMP IN® software was used for descriptive data analyses (21). The affirmative answers when graded 'yes always', 'yes sometimes' or 'yes one side' or 'yes both sides', were added for a compressed presentation. A few 'do not know' responses were included as a 'no' answer.

Results

The original sample of randomized controls did not show any major changes due to the drop outs when the response rates for different age groups in the initial total study base and the study base used for the investigation were compared (Fig. 1). The persons with EDS who participated in the present study had a fairly similar distribution to that in the original sample of the 265 members of the Swedish EDS Association (Fig. 2).

The mean age was 44 years for both persons with EDS (95% CI 42–46 years) and controls (95% CI 42–45 years). Sixty-four percent of the persons with EDS reported that other family members also had the

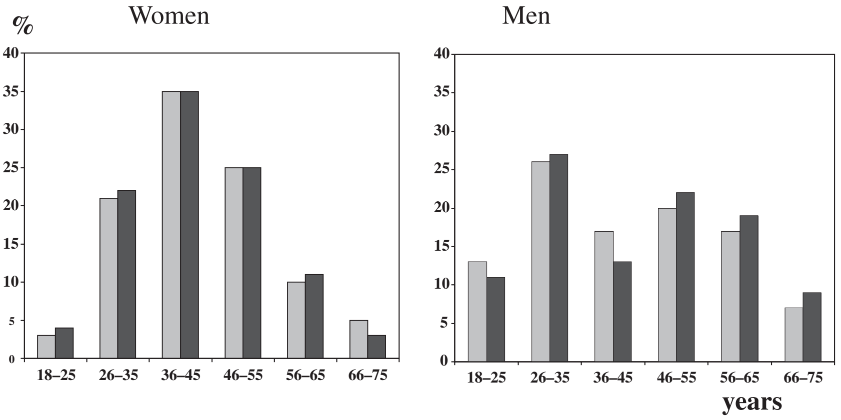

Fig. 1. Frequency of answers (%) in separate age groups for the initial total randomized study base of the controls (grey bars) and the study base used after excluding drop outs (black bars). Men and women are presented separately. The total initial study base consisted of 591 women and 145 men. The study base after excluding drop outs consisted of 266 women and 65 men.

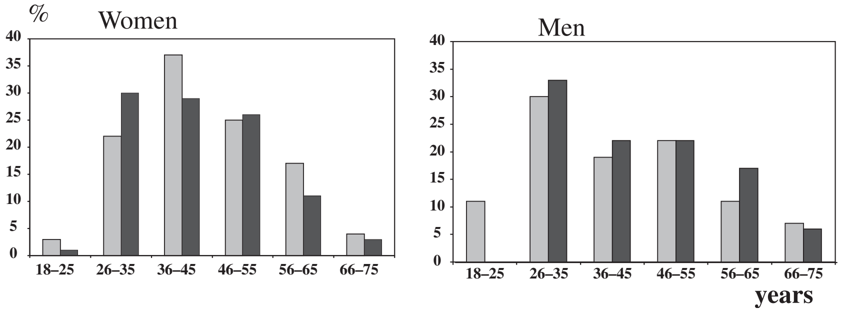

Fig. 2. Frequency of answers (%) in separate age groups for the initial group of members of the Swedish EDS association (grey bars) and the study base used after excluding drop outs (black bars). Men and women are separately presented. The total initial study base consisted of 238 women and 27 men. The study base used after excluding drop outs consisted of 126 women and 18 men.

***Table 1.* The distribution of different types of EDS**

EDS type	Berlin nosology	Number of observations	Proportion
Unknown type		73	0.51
Type I	Gravis	7	0.05
Type II	Mitis	5	0.03
Type III	Hypermobile	45	0.31
Type IV	Arterial-eccymotic	6	0.04
Type VIII	Periodontal	8	0.06
Total		144	1.00

disease. None of the controls knew of any persons with EDS in the family. In the group of persons with EDS the disease was confirmed by a medical doctor when most patients were between 30 and 35 years of age (mean age 32 years; 95% CI 30–35 years). The type of EDS that was most commonly reported by the participants was the type III (hyper mobile) (Table 1). Some persons also reported that they had combinations of different types and were included in the group ‘unknown type’ (Table 1).

Other diseases were slightly more common in the group of EDS compared with the controls. Smoking habits did not differ between the groups (Table 2).

The proportions of affirmative answers for persons with EDS concerning medication, pain, joint hypermobility, tongue hypermobility, delayed wound healing and permanent scars, and voice problems were all significantly increased compared with the controls according to the 95% CI for the difference between proportions (Table 2).

Sixty-two percent of the persons with EDS reported taking sick leave during the last year compared with 36% of the controls. This was in line with the reported number of working hours per week. The persons with EDS worked on average 14 h per week while the controls worked 29 h per week, according to the median values ($p < 0.05$).

Almost half of the persons with EDS reported pain in the masticatory muscles. The pain was chronic with a median duration of 10 years. Of these, 27% reported daily pain, 22% had pain a couple of days per week, and 51% had pain a few days per month. Those who reported daily pain rated the pain significantly higher on the three different VAS scales for ‘maximal pain’,

***Table 2*. Questions concerning general health, medication, pain, hypermobility, skin and voice problems. 95% CI for the difference between proportions of affirmative answers in the EDS group and the control group**

Questions	EDS proportion yes answers	Controls proportion yes answers	Difference between proportions	95% CI for the difference between proportions
Other diseases confirmed by a medical doctor	0.51, n = 140	0.34, n = 327	0.17	0.07–0.27
Regular medication	0.67, n = 143	0.32, n = 330	0.35	0.25–0.43
Analgesic medication	0.74, n = 143	0.30, n = 315	0.44	0.35–0.52
Hypnotic medication	0.23, n = 143	0.04, n = 324	0.19	0.12–0.27
Daily smoking last month	0.25, n = 144	0.21, n = 328	0.04	(−0.04)–0.12 (NS)
Sick leave last year	0.62, n = 128	0.36, n = 324	0.26	0.16–0.36
Pain in the masticatory muscles	0.49, n = 138	0.06, n = 325	0.43	0.34–0.51
General muscular pain	0.83, n = 142	0.38, n = 331	0.45	0.37–0.53
General pain in body joints	0.89, n = 141	0.26, n = 319	0.63	0.54–0.69
TMJ problems right now	0.45, n = 144	0.07, n = 328	0.38	0.30–0.47
Hyper mobility of the tongue	0.21, n = 141	0.09, n = 330	0.12	0.05–0.20
TMJ hyper mobility	0.67, n = 141	0.04, n = 330	0.63	0.55–0.71
Hand wrist hyper mobility	0.82, n = 144	0.05, n = 330	0.77	0.69–0.83
Headache during the last month	0.78, n = 142	0.59, n = 330	0.19	0.09–0.27
Delayed wound healing and permanent scars	0.29, n = 137	0.06, n = 308	0.23	0.16–0.32
Marked visible scars after wound healing	0.82, n = 140	0.12, n = 328	0.70	0.62–0.77
Voice problems	0.36, n = 141	0.13, n = 322	0.23	0.15–0.32
Voice problems when shouting and screaming loudly	0.43, n = 141	0.11, n = 330	0.32	0.23–0.41
Hoarse voice without a throat infection	0.43, n = 140	0.13, n = 331	0.30	0.21–0.39

n, total number of answers in the EDS group and the control group, respectively.
NS, no significant difference.
TMJ, temporomandibular joints.

'average pain' and pain 'right now' compared with those who reported masticatory muscle pain during a couple of days per month ($p < 0.05$) (Fig. 3). Significantly higher 'maximal', 'average' and 'right now' pain ratings were also found for pain during a couple of days per week compared with pain during a couple of days per month ($p < 0.05$) (Fig. 3). Only 6% of the controls reported pain from masticatory muscles and were not further analyzed.

Ninety-one percent among persons with EDS and 96% among the controls answered that they only had their 'own teeth', but by definition these included fixed prostheses and implants. The answers to the questions on dental treatment indicated that significantly more persons with EDS compared with controls were aware of problems with periodontal disease, spontaneous fractures of the teeth and complicated tooth extractions (Table 3). They needed extra administration of local anesthetics. More often in the EDS group than in controls, the injections were reported to be painful and not always sufficient. Endocarditic prophylaxis had been used in 11% of the persons with EDS (Table 3).

The GHQ12 scores showed that 52 of 143 respondents with EDS (36%) and 45 of 331 controls (14%) had a score of four or more, indicating a decline in psychological well-being. The difference between their proportions was significant (95% CI 0.14–0.32).

Discussion

Before the start of the study a check was made to see that the questionnaire was easily understood. Most participants in both groups answered the majority of the questions, and no particular pattern was found among the questions left unanswered. The answers and telephone calls from the members of the EDS Association showed that it was a very heterogeneous group. The group included support members and healthy parents with diseased children. Even hospital

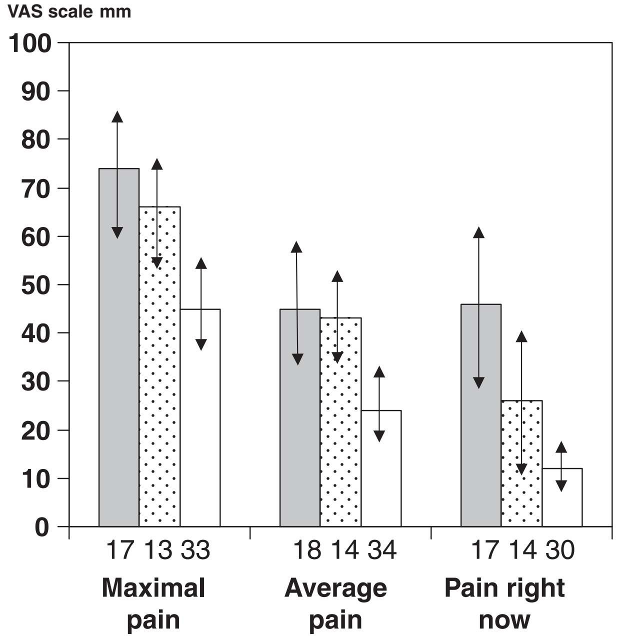

Fig. 3. Masticatory muscle pain ratings for persons with EDS. Mean values in millimetres (mm) on three different VAS scales for separate ratings of maximal pain, average pain and pain 'right now' are presented. Mean rating values for the chosen answer 'daily pain' (grey bars), 'pain during a couple of days per week' (dotted bars) or 'pain during a couple of days per month' (white bars) are presented. The number of answers is presented below the bars. The 95% CI is given on top of each bar.

personnel and one journalist were members out of sympathy for those who had the disease. Many completed questionnaires unfortunately had to be excluded due to the above mentioned factors.

Half the persons with EDS did not know their type of EDS diagnosis. The most common known diagnosis was the hypermobility type III (31%). It was not possible to analyze different diagnoses separately. This was not believed to be crucial in a screening of symptoms of EDS. The connective tissue defect is a basic factor in the disease, and some persons also had combinations of different types of EDS.

Many questions concerned symptoms known from previous studies to be characteristic of the EDS disease. It was still remarkable that the proportions of affirmative answers were so high compared with controls. Musculoskeletal symptoms are also reported to be common in the general population (22) but the proportion of affirmative answers concerning pain in body muscles (83%) and body joints (89%) was nevertheless higher in persons with EDS. In a previous questionnaire study with 77 members of the Swedish EDS Association, the most frequent symptoms were related to joint problems (75%), to pain (71%), and to skin/tissue (52%) (16). Verbraecken et al. reported pain and back complaints in 77% of a group of persons with EDS (23). A comparison of women with EDS and fibromyalgia showed that the former rated their functional health status with the Sickness Impact Profile (SIP) as worse than fibromyalgia (24). On the other hand women with EDS reported a better functional health status than those with rheumatoid arthritis (24). Sacheti et al. reported that pain in EDS was common and progressed over time (25). In the present study, the mean age of the adults was 44 years, and it seemed as if pain was a problem mainly in terms of general pain but temporomandibular pain was also found.

The pain ratings on the VAS scale that were marked by the persons with EDS supported the affirmative answers regarding severe pain in the masticatory muscles at times. Daily pain was rated significantly higher than monthly pain. Daily masticatory muscle pain points towards acute muscular problems and would benefit from temporomandibular disorders (TMD) treatment. It is interesting that jaw pain also has been significantly related to shoulder and neck pain in persons with TMD (26). It is possible that there is a similar relationship for persons with EDS and TMD disorders.

The increased intake of analgesic was probably mostly related to body pain since it was more common than pain in masticatory muscles. The intake of hypnotic medication could be related to both pain and psychological stress. The significantly increased use of analgesic and hypnotic medication among persons with EDS compared with controls could be a confounder in assessment of pain in the masticatory muscles. It is likely that the pain ratings on the VAS scales were underestimated.

Hypermobility of the tongue has been described as a characteristic of EDS (15). Approximately 50% of those with the syndrome were reported to be able to touch the end of their nose with their tongue (Gorlin's sign) compared with 8–10% of the population (27). In the present study, 10% of the controls and 21% of the persons with EDS reported that they were able to do this after trying the procedure. This value is a remarkably lower than the one reported by Gorlin (27).

The highest proportion of yes answers concerning oral symptoms among the persons with EDS referred to hypermobility of the TMJs (67%). The TMJ problems

***Table 3.* Dental treatment questions. 95% CI for the difference between proportions of affirmative answers in the EDS group and the control group**

Questions: dental treatment questions	EDS proportion yes answers	Controls proportion yes answers	Difference between proportions	95% CI for the difference between proportions
Use of local anesthetics (LA) during dental treatment	0.98, n = 144	0.93, n = 331	0.05	0.00–0.08 (NS)
Effect of LA (last time)	0.62, n = 138 (very good effect and rather good effect)	0.91, n = 304 (very good effect and rather good effect)	−0.29	(−0.38)–(−0.20)
Need of extra injections (last time)	0.41, n = 139	0.10, n = 316	0.31	0.22–0.40
Pain experience during LA administration (last time)	0.66, n = 142 (very painful, rather painful)	0.23, n = 316 (very painful, rather painful)	0.43	0.34–0.52
Experience of a tooth extraction	0.86, n = 144	0.82, n = 330	0.04	(−0.04)–0.11 (NS)
Special problems during the last tooth extraction	0.50, n = 118	0.14, n = 284	0.36	0.26–0.46
Presence of periodontal disease	0.34, n = 140	0.15, n = 331	0.19	0.11–0.28
Endocarditic prophylaxis during dental treatment	0.11, n = 142	0.01, n = 331	0.10	0.05–0.16
Presence of spontaneous fractures of teeth without caries	0.41, n = 139	0.10, n = 327	0.31	0.23–0.40

n, total number of answers in the EDS group and the control group, respectively.
NS, no significant difference.

have already been discussed and were partly based on the same material (7). The data supported the claim stated in literature that persons with EDS are naturally predisposed to TMJ problems (7).

Only six percent among the persons with EDS reported that they had the periodontal type VIII diagnosis, which is known to be rare. It is an atypical form of periodontitis in that it is fast developing and aggravating (11–13). Significantly more persons with EDS (34%) reported that they had a periodontal disease compared with controls (15%). A further clinical study is needed in the future to find whether there is a general predisposition among persons with EDS to develop periodontitis without having the type VIII diagnosis. Dental problems, many as case reports, have previously been reported in the literature (7–16). A quite common dental problem that was reported in the present study was the spontaneous fractures of the teeth. Some of the participants also commented that these fractures cause an extra economic burden.

More than 80% of the participants in both the EDS group and controls had experienced tooth extractions. Tooth extractions were often complicated in terms of 'special problems during the last tooth extraction' in EDS. The injections of local anesthetics (LA) were more frequently reported to be very painful or rather painful among persons with EDS compared with controls. The anesthetic effect was not sufficient despite extra injections. Many participants with EDS also verbally described problems such as complications in healing, postoperative bleeding, and severe pain both during and after the extraction.

A Scottish Health Survey used GHQ12 questions and reported that women were more likely than men to have a high score (19). Overall, 19% of the women compared with 13% of the men had a score of four or more in that study. The difference between men and women was greatest for those aged 16–34 years (19). In the present study, the majority of the participants were women so that no differentiation was made for gender. The control group was weighted for women to avoid gender being a confounding factor when comparing EDS persons and controls. The reported value of a GHQ12 score of four or more for 14% the controls in our study is in line with the Scottish study (19). A previous qualitative study on 11 interviewed members of the Swedish EDS Association identified a main theme that was called 'living a restricted life'. This included fears, pain, stigmatism and limited possibility of self-actualization in daily living and social life (10). The higher proportion of persons with EDS having a GHQ12 score of four or more (36%) confirms the possibility that the psychological effects are related to the disease.

The present questionnaire study showed higher proportions of affirmative answers referring to various oral symptoms in a group of persons with EDS than in a population based randomized control group. It is important that dental practitioners should be aware of the oral problems associated with EDS and the impact that the disease has on quality of life. Only then, will they be able to provide the most appropriate professional help.

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