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Research Article

Relationship Between Chronic Spontaneous Urticaria and Fibromyalgia Syndrome

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Abstract

Aim: Autoimmunity, peripheral nerve dysfunction, and neurogenic inflammation are common mechanisms in chronic spontaneous urticaria (CSU) and fibromyalgia syndrome (FMS). We aimed to detect the prevalence of FMS in patients with CSU and to determine whether this prevalence was affected by the severity of urticaria, and dermatology life quality.

Material and Methods: Fifty-three patients with CSU and 49 controls were enrolled in this prospective, controlled, cross-sectional study. The severity of CSU was assessed using Urticaria Activity Scores (UAS), and Dermatology Life Quality Index (DLQI) scores were recorded. The 2016 fibromyalgia diagnostic criteria were used for the diagnosis of FMS, and FMS-related functional disability was assessed using the Fibromyalgia Impact Questionnaire (FIQ).

Results: Fibromiyalgia prevalence and the FIQ scores were higher in the CSU group than in the control (p=0.033 and p=0.004, respectively). There was no statistically significant difference between the urticaria durations and UAS of CSU with and without FMS (p>0.05), but DLQI scores were statistically significantly higher in CSU with FMS (p=0.007). A statistically significant moderate positive correlation was present between DLQI and FIQ, Widespread Pain Index, and Symptom Severity Scale scores (r=0.500, r=0.408, r=0.469, r=0.507, respectively).

Conclusions: The prevalence of FMS and the disability due to FMS was increased in CSU. Furthermore, the FMS prevalence was not affected by the duration and severity of urticaria; however, it was associated with decreased quality of life.

Keywords: Fibromyalgia syndrome, chronic urticaria, quality of life

INTRODUCTION

Chronic spontaneous urticaria (CSU) is a skin disorder characterized by itchy wheals and/or angioedema for 6 weeks or more in the absence of identifiable physical or other stimuli and accounts for half to three-quarters of all cases of chronic urticaria. It is most common between the ages of 20 and 40, with a higher incidence in women. Although CSU etiopathogenesis is not yet clear, immunological and inflammatory mechanisms have been shown to play a considerable role (1). Chronic spontaneous urticaria has been associated with various autoimmune and chronic inflammatory diseases such as autoimmune thyroiditis and connective tissue diseases (2). Depression, anxiety, and psychological stress play a role in the CSU etiology and might lead to exacerbations (3). Peripheral nerves have been shown to contribute to the pathophysiology of chronic urticaria, and some neuropeptides exacerbate the disease (4). It has been shown that there is a network that communicates between cutaneous sensory nerve fibers and immune system cells in the skin. The neuropeptides secreted from the nerve endings affect the target cells and are responsible for erythema, edema, temperature increase, and itching. Mast cells, one of the most crucial cells involved in the pathogenesis of chronic urticaria, play a critical role in this

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neuroimmune bond (5).

Fibromyalgia syndrome (FMS) is a chronic pain syndrome characterized by widespread and chronic musculoskeletal pain, accompanied by sleep disturbance, fatigue, morning stiffness, and cognitive disorders. Its prevalence varies from 0.2–6.6%, with a more common incidence in women (6). Fibromyalgia syndrome has been shown to coexist with diseases wherein emotional factors play a role in the etiology, such as dysmenorrhea, depression, migraine, and irritable bowel syndrome, and chronic inflammatory and autoimmune diseases, such as psoriasis and systemic lupus erythematosus (7-9). Although the pathophysiology of FMS has not been fully elucidated, it is thought that the disease may be associated with changes and dysfunction in peripheral cutaneous nerve fibers. In addition, neurogenic inflammation is higher in skin biopsy samples obtained from FMS patients than in those from non-FMS individuals (10). Again, previous studies have reported that mast cells play a significant role in FMS development (11). No routine blood test or imaging technique is recommended for diagnosing FMS. The 1990 FMS diagnostic criteria of the American College of Rheumatology (ACR), based on tender point examination, have been used in FMS diagnosis for many years. However, since these criteria are difficult to apply in clinical practice and do not include symptoms such as fatigue, sleep disturbance, and cognitive impairment, these criteria have been revised over the years, which led to the emergence of ACR 2010, 2013, and 2016 diagnostic criteria (12).

Neurogenic inflammation is a common pathogenetic factor in both CSU and FMS. Furthermore, the association of both these diseases with autoimmunity, chronic inflammation, and psychological stress is clear (2,3,7-9). Hence, we aimed to investigate FMS prevalence in CSU patients and the relationship of FMS incidence with urticaria activity and dermatology quality of life. Several studies have investigated the relationship between chronic urticaria and FMS. However, unlike these studies, we used the ACR 2016 diagnostic criteria for FMS diagnosis in the current study.

MATERIAL AND METHOD

Ethical Aspects

The present study was conducted according to the Declaration of Helsinki and approved by the Clinical Research and Ethics Committee linked to Hatay Mustafa Kemal University (approval number: 2022/75, date: 22.08.2022).

Study Design

This study was conducted in Dermatology and Physical Therapy and Rehabilitation outpatient clinics of Giresun University Giresun Training and Research Hospital between September 1, 2022 and March 1, 2023. Fifty-three patients diagnosed with CSU and 49 healthy volunteers matched according to age and sex were recruited in this prospective, controlled, cross-sectional study. Patients with a history of malignancy; musculoskeletal, neurological, endocrinological, or rheumatic diseases; severe depression; congestive heart failure; psoriasis; chronic episodic urticaria; or chronic inducible urticaria were excluded from the study.

The urticaria activity score (UAS) was used to determine the disease activity in the CSU group. Urticaria activity score was determined based on the approximate number of urticaria plaques (0=none; 1=mild, ≤20 plaques/24 h; 2=moderate, 21–50 plaques/24 h; and 3=severe, >50 plaques/24 h) and the severity of pruritus (0=none, 1=mild, 2=moderate, and 3=severe) in the previous week from the statements of the patients (1).

Then, all patients were given the dermatology life quality index (DQLI) questionnaire. Dermatology life quality index comprised 10 questions that evaluated the daily activities of a person in the last week, including the way they spend their free time, their relationships, and their feelings. The first and the second questions of the questionnaire are about symptoms and emotions; the third and fourth questions are about daily activities; the fifth and sixth questions are about leisure activities; the seventh question is about work and school; the eighth and ninth questions are about interpersonal relationships; and the tenth question is about treatment. The scoring was as follows: “quite a lot=3 points”, “a lot=2 points”, “mild=1 point”, “none=0 point”, “not related=0 points”, and the total score of the scale, which can vary between 0 and 30, is the sum of the scores of each question. High scores in DLQI indicate low quality of life (13).

Physical examination for FMS diagnosis was performed by experienced physical medicine and rehabilitation specialists. The ACR 2016 diagnostic criteria were used as diagnostic criteria in this study. The scale used in the 2016 ACR diagnostic criteria comprised two parts: the Widespread Pain Index (WPI) and the Symptom Severity Scale (SSS). The sum of WPI and SSS scores gives the Fibromyalgia Score (FS). Widespread Pain Index indicates in how many of the 19 lower regions (left upper, right upper, left lower, right lower, and axial) there was pain in the last week. The total score in WPI can be between 0 and 19. In SSS scale, fatigue, waking up restless, and cognitive symptoms are evaluated from 0–3 points depending on the severity of the symptoms that existed in the last week, and whether there is pain and cramping in the abdomen, depression, and headache in the last 6 months (0–1 points) is questioned. The total score lies between 0 and 12. According to the 2016 diagnostic criteria, FMS is diagnosed in patients and volunteers who experienced generalized pain and other symptoms for three months. Generalized pain was defined as having pain in at least four of the five regions, except for the chin, chest, and abdomen. Moreover, the patients also needed to have WPI≥7 and SSS≥5, or WPI 4–6 and SSS≥9 (12). In addition, a 10-item fibromyalgia impact questionnaire (FIQ) was administered to all participants to determine the FMS-

related effect rate and functional restriction. The first item of the questionnaire includes 11 Likert-type questions evaluating the daily activities of the patients, and the questions are scored from 0–3; the total score is the average of the scores of all 11 questions. In the second item, the patient is questioned about the day they felt good in the last week. In the third item, they are questioned about the day when they could not go to work in the last week. The scores of the first three items are normalized (the score obtained from the first item is multiplied by 3.3, and the scores obtained from the second and the third items are each multiplied by 1.4). The remaining seven questions are related to the severity of symptoms, pain, fatigue, restless sleep, stiffness, anxiety, and depression, and the responses are evaluated on a 10-point scale. A total score of 0–100 is possible from the survey. The average score of a patient diagnosed with FMS is 50, and a higher score means more severe disease (14).

Statistical Analysis

Statistical analyses were performed using the SPSS software version 23. Parametric, nonparametric, and categorical parameters were presented respectively as mean±standard deviation (SD), median (interquartile range (IQR), and numbers (%). The Shapiro-Wilk test was used for testing assumption of normality in numerical variables. Pearson's Chi-square test or Fisher's exact test was used to compare the categorical data. The chi-square and Fisher's exact tests were used to identify the significance of the relationships between categorical variables. To compare the data between two independent groups, Student's t-test was used for variables with a normal distribution and the Mann-Whitney U-test for variables without a normal distribution. The Spearman correlation coefficient was used to evaluate the relationships between quantitative variables. A p-value of <0.05 was considered statistically significant.

RESULTS

Fifty-three CSU patients and 49 healthy controls were included in this study. There was no difference in the demographic characteristics of the two groups (Table 1). The incidence of FMS in the CSU group (n=14, 26.4%) was significantly higher than in the control group (n=4, 8.2%) (p=0.016). Further, 92.8% of the CSU patients diagnosed with FMS were women, while all FMS patients in the control group were women. Among all patients diagnosed with FMS, the female/male ratio was 17/1. The FIQ score was significantly higher in the CSU group than in the control group (p=0.004, Table 1).

Next, we compared the CSU patients with and without FMS (Table 2). The mean age of CSU patients diagnosed with FMS (47.14±8.87 years) was higher than that of the non-FMS CSU group (38.00±13.84 years, p=0.026). There was no significant difference between these two groups in terms of sex, body mass index, duration of urticaria, family history, or status of receiving treatment for urticaria. A significantly higher number of CSU patients with fibromyalgia were in secondary school or below (n=14, 100%) compared to those without fibromyalgia (n=18, 46.2%; p<0.001). While there was no difference between the two groups in terms of urticaria duration and UAS, the DQLI scores were significantly higher in the group with fibromyalgia (10.21±4.74) than in the group without fibromyalgia (6.38±4.25, p=0.007).

The relationships between urticaria duration, UAS and DLQI, FIQ, WPI, SSS scores, and FS are presented in Table 3. Accordingly, a statistically significant moderate positive correlation was present between DLQI and FIQ, WPI, SSS scores, and FS (r=0.500, r=0.408, r=0.469, r=0.507, respectively).

Table 1. Comparison of chronic spontaneous urticaria and control groups according to their demographic characteristics, dermatology life quality index, fibromyalgia impact questionnaire scores, and the presence of the fibromyalgia syndrome

	Urticaria (n=53)	Control (n=49)	p-value
Age (years)	40.42±13.35	40.39±13.29	0.992
Sex			0.463
Female	47 (88.7)	41 (83.7)	
Male	6 (11.3)	8 (16.3)	
BMI (kg/m²)	26.81 (23.87-31.02)	24.61 (22.83-27.99)	0.086
DLQI	7.00 (4.00-10.50)	0.00 (0.00-2.00)	**<0.001**
Diagnosed with FMS	14 (26.4)	4 (8.2)	**0.016**
Female	13 (92.8)	4 (100)	
Male	1 (7.2)	0 (0)	
FIQ score	36.10 (16.88-56.94)	19.01 (9.50-36.83)	**0.004**

BMI: body mass index, DLQI: dermatology life quality index, FMS: fibromyalgia syndrome, FIQ: fibromyalgia impact questionnaire

Table 2. Comparison of patients with and without fibromyalgia syndrome according to the demographic and clinical characteristics in the patients with chronic urticaria

	Fibromyalgia+(n=14)	Fibromyalgia-(n=39)	p-value
Age (years)	47.14±8.87	38.00±13.84	0.026
Sex			1.00
Female	13 (92.9)	34 (87.2)	
Male	1 (7.1%)	5 (12.8)	
Education			**<0.001**
Secondary school and below	14 (100.0)	18 (46.2)	
High school and above	0 (0.0)	21 (53.8)	
BMI (kg/m²)	29.82±3.45	26.71±5.65	0.060
Disease duration (months)	9.50 (5.50-48.00)	24.00 (6.00-48.0)	0.598
Urticaria history in the family			0.649
Yes	2 (14.3)	4 (10.3)	
No	12 (85.7)	35 (89.7)	
Status of treatment			0.182
Receiving	12 (85.7)	25 (65.1)	
Not receiving	2 (14.3)	14 (34.9)	
UAS	22.43±9.44	20.10±12.17	0.520
DLQI	10.21±4.74	6.38±4.25	**0.007**
FIQ score	78.93±15.52	26.56±16.16	**<0.001**
FS (WPI+SSS)	23.00 (17.75-27.25)	4.00 (2.00-7.00)	**<0.001**
WPI score	13.50 (8.00-15.25)	0.00 (0.00-2.00)	**<0.001**
SSS score	12.00 (8.75-12.00)	3.00 (1.00-5.00)	**<0.001**

BMI: body mass index, FIQ: fibromyalgia impact questionnaire, WPI: widespread pain index; SSS: symptom severity scale, FS: fibromyalgia score (WPI+SSS), UAS: urticaria activity score; DLQI: dermatology life quality index

Table 3. Relationship between the duration of urticaria, urticaria activity score, and Dermatology life quality index and fibromyalgia impact questionnaire, widespread pain index, and symptom severity scale scores in patients with chronic urticaria (n=53)

	FIQ score	WPI score	SSS score	FS
Duration of urticaria	0.098	-0.004	0.019	0.048
UAS	0.147	0.081	(0.214)	0.192
DLQI	0.500	0.408**	0.469	0.507**

FIQ: fibromyalgia impact questionnaire, WPI: widespread pain index, SSS: symptom severity scale, FS: fibromyalgia score, UAS: urticaria activity score, DLQI: dermatology life quality index; ** p<0.001

DISCUSSION

In the current study, the FMS incidence in CSU patients (26.4%) was significantly higher than in the control group (8.2%). Similar studies comparing FMS prevalence in patients with chronic urticaria and healthy volunteers have shown that the FMS incidence in the urticaria group varied between 9.7% and 70.6% (15-20). In all these studies, a higher FMS prevalence was observed in the urticaria group than in the control group, and, similar to our study, the difference in FMS prevalence between these two groups was statistically significant (15-19). Torresani et al. compared 126 patients with chronic urticaria with 50 controls and used ACR 1990 criteria for diagnosing FMS. Similar to the current study, Torresani et al. reported a significantly higher FMS prevalence in the chronic urticaria group (70.6% in the chronic urticaria group and 16% in the control group). Based on their findings, the authors suggested that the neuropeptides secreted from

the dysfunctional nerve fibers in FMS patients cause vasodilation and extravasation in the dermal vessels. These neuropeptides stimulate the nerve endings and trigger mast cell degranulation, leading to a higher release of neuropeptides. Moreover, FMS triggers cutaneous neurogenic inflammation, leading to chronic urticaria (15). In addition, the FMS incidence observed by Torresani et al. in the chronic urticaria group (70.6%) was much higher than that observed in the CSU group of our study (26.4%). The higher FMS incidence in the former study might be attributed to the inclusion of patients with autoimmune diseases, such as autoimmune thyroiditis, type 1 diabetes mellitus, and vitiligo, by Torresani et al. In another study, Hapa et al. compared 50 patients with chronic urticaria with 48 controls. They found that 26% of the urticaria patients and 20.8% of the individuals in the control group had FMS, suggesting no significant difference between the two groups (20). While the FMS prevalence in their urticaria group was similar to that observed in our chronic urticaria group, Hapa et al. reported a much higher FMS prevalence in the control group than that observed in our control group. According to Hapa et al., such high FMS prevalence in the control group might be attributed to the selection of the female sex in the control group in the foreground. In our study, although the number of women in the control group was high in order to obtain a sex-matched group to the patient group, no such results were obtained. Hence, we postulate that this discrepancy in the FMS prevalence in the control groups of the two studies might be attributed to the inclusion of individuals with other dermatological diseases in the control group by Hapa et al.

On comparing CSU patients with FMS with those without FMS, we found that the mean age of the patients with FMS was significantly higher. This finding was consistent with the previous findings that FMS was less common at a young age and that its prevalence increased with age (21-23). Many studies have reported low education levels and low socioeconomic status as risk factors for FMS and other chronic pain syndromes (22-24). Corroborating these findings, our results also showed that the education level of patients with FMS was lower than those without FMS.

Similarly, Hapa et al. found no relationship between urticaria duration and UAS and FMS prevalence (20). Contrarily, Koca et al. reported that UAS was significantly higher in urticaria patients with FMS. They also reported a positive correlation between the UAS and FIQ scores. They did not use the DLQI questionnaire but administered the Pittsburgh Sleep Quality Index and Beck Depression Scale to the patients. They reported a positive correlation between the UAS and the scores of these scales. Based on their findings, Koca et al. stated that as the severity of urticaria increases, FMS prevalence, anxiety, and depression increase in the patients. Thus, common pathogenetic mechanisms involved in both diseases warrant further elucidation (18). Yener et al., unlike our study, reported a positive correlation between both urticaria duration and UAS; and DLQI score, FMS prevalence, FMS duration, and the number of sensitive points. They attributed the relationship between chronic urticaria and FMS to underlying common etiopathogeneses, such as autoimmunity and cutaneous neurogenic inflammation (19). In our study, no significant difference was observed in urticaria duration, urticaria treatment status, or UAS between the CSU patients with and without FMS. Yet, the DLQI score was significantly higher in CSU patients diagnosed with FMS. Moreover, we found that the duration of urticaria and UAS did not correlate well with FIQ, WPI, and SSS scores. Nevertheless, these scores positively correlated with DLQI. Hence, FMS incidence was not related to the severity and activity of urticaria but was associated with the psychosocial impact rate of urticaria. Accordingly, we predict that rather than the common pathophysiologic pathway, the relationship between the two diseases may be due to emotional and psychosocial factors, which play a critical role in both.

CONCLUSION

In this study, FMS prevalence and the impact rate of fibromyalgia were found to be higher in CSU patients. This prevalence was not affected by the duration or severity of urticaria. However, it was associated with a drop in the quality of life. Outcomes of our study support that CSU with FMS possesses more restrictions in their daily life than CSU alone, and the association of two diseases might be due to common psychosocial factors. However, there is a need for extensive studies involving more patients to support this hypothesis.

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Conflict of Interest: *The authors have no conflicts of interest to declare.*

Ethical approval: *The present study was conducted according to the Declaration of Helsinki and approved by the Clinical Research and Ethics Committee linked to Hatay Mustafa Kemal University (approval number: 2022/75, date: 22.08.2022).*

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