Prevalence of fibromyalgia syndrome in chronic urticaria

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Abstract

Background: Fibromyalgia syndrome (FMS) can coexist with many autoimmune, rheumatic and inflammatory disorders. Chronic urticaria (CU) and FMS are different types of diseases but share many clinical and pathological features. This study aims to evaluate these features and to investigate whether patients with CU are also affected by FMS.

Patients and methods: Eighty two patients with CU and 86 healthy controls were enrolled to this study. All patients were assessed for autologous serum skin test (ASST), and urticaria total severity score (TSS). Body mass index was calculated for all the participants. All patients were assessed according to the 1990 American College of Rheumatology (ACR) classification criteria for FMS and asked questions regarding the associated clinical features of FMS.

Results: A total of 50(60.9%) patients with chronic urticaria were found to have widespread pain. A total of 28 patients met the criteria of FMS with a prevalence rate of 34.1%; of whom, 20(71.4%) were women. FMS associated clinical features were more frequent in patients with CU than in controls. Positive ASST and severe TSS were more frequent in CU patients with FMS than those patients without FMS.

Conclusion: FMS and its associated clinical features are more prevalent in patients with CU than in the general population. Women with CU are more frequently affected by FMS than are men. Awareness of this comorbidity is an essential part in the treatment of CU.

Key words: Autologous serum skin test, Chronic urticaria, fibromyalgia, Urticaria total severity score.

Introduction

Chronic urticaria (CU) is defined as one of the common, distressing skin diseases that adversely affect the patient quality of life (1). It is characterized by the appearance of rapidly evolving, usually itchy wheals that persist for more than six weeks (2). CU occurs as a clinical manifestation of different inflammatory and immunological disorders, or it may be idiopathic (3,4). Although its pathogenesis is not well understood yet, there is evidence that peripheral nerves are implicated in its pathophysiology, and several neuropeptides have been found to be enhanced in CU (5). There is a network that communicates between cutaneous sensory nerves and immune skin cells; when these neuropeptides are released, they will act on the target cells producing erythema, oedema, hyperthermia and pruritus (6). Mast cells, one of the primary effector cells in the pathogenesis and development of urticaria, are located in the upper dermis, where wheal formation and sensory nerve stimulation occur (7). Fibromyalgia syndrome (FMS) is a chronic, generalized pain condition with characteristic tender points on physical examination, often accompanied by a number of somatic, psychological, and emotional symptoms that include fatigue, sleep disturbances, morning stiffness, headache, irritable bowel, cognitive difficulties, anxiety, and depressive disorders (8,9). FMS prevalence rate is 1%-2% in the general population (10). The pathophysiology of FMS is complex and still not fully understood. Previous studies focused on central sensitization, but it is now apparent that the peripheral nerves play a crucial role in the pathogenesis of FMS (11–14). Mechano-insensitive nociceptive C-fibres which are an itch-specific peripheral sensory neuron can reply to histamine ensuing in the launch of neuropeptides, consisting of substance P and calcitonin gene-related peptide (CGRP)(7). A recent study reported that, mast cells have an important role in fibromyalgia (14). Thus, since both cutaneous nerve fibres and mast cells play an important role both in cutaneous inflammation, including CU, and in FMS. The aim of the present study was to investigate the effect of FMS on patients with CU.

Patients and Methods

This was a cross-sectional study carried out in the outpatient departments of Dermatology and Rheumatology in Basra Teaching Hospital from March 2019 to March 2020. A sample of 82 (35 male and 47 female) patients with chronic urticaria, diagnosed by a dermatologist in the dermatology outpatient, and 84 age and sex matched healthy controls recruited from the general population were enrolled for this study. Exclusion criteria were, diabetes mellitus (DM), congestive heart failure, acute or chronic infections, cerebrovascular diseases, major depression, rheumatological diseases, autoimmune thyroiditis, hypothyroidism, hyperthyroidism, history of malignancy, and any other systemic disorders. The age, sex, disease duration, history of widespread pain, and medication history were determined for all patients. Complete blood count (CBC), erythrocyte sedimentation rate (ESR) along with the antistreptolysin-O (ASO), serum glucose, liver function test, stool sample to check for parasites, hepatitis B surface antigen (HBsAg), hepatitis C antibody (HCAb), rheumatoid factor (RF) and complement levels, antinuclear antibody (ANA), thyroid function tests and chest radiograms were done for all of the patients. Autologous serum skin test (ASST) and urticarial total severity score (TSS) (15) were conducted for all patients. A diagnosis of FMS was confirmed according to the two-stage classification process that was proposed by the 1990 ACR classification criteria for FMS (10). Stage 1 was composed of the patients answering the diffuse widespread pain questionnaire. Stage 2 comprised evaluation of all patients and controls complaining of diffuse pain; this evaluation included the assessment of 18 tender points and 4 control non-tender points through digital palpation with an approximate force of 4 kg (the amount of pressure required to blanch a nail). The four control non-tender points are: the middle of the forehead, the volar aspect of the mid forearm, the thumb nail, and the muscles of the anterior thigh. To meet the diagnostic criteria, musculoskeletal pain had to have been present for at least 3 months, and pain must have been present in 11 or more out of 18 specific tender points on digital palpation. All participants were also asked about the following FMS associated clinical features: morning stiffness, sleep disturbance, fatigue, headache, anxiety, depression, and irritable bowel. Depression and anxiety were assessed by the Hospital Anxiety and Depression Scale (HADS) (16) which consists of 14 items divided into two subscales of seven items each. The subscale value ranges from 0-21 for either anxiety or depression.

Ethical considerations

Informed verbal consent was obtained from all participants prior to their involvement. It was performed in accordance with the standards of the Declaration of Helsinki.

Statistical analysis

SPSS Software version 25.0 was used for data analysis. Percentages and mean was used to present the data in tables. Comparison of study groups was carried out using chi-square test for categorical data, and Student's t-test for continuous data. P-value of < 0.05 was considered statistically significant.

Results

Table 1 shows the demographic distributions of both patients and control groups. From the total 82 patients with chronic urticaria; there were 35(42.6%) males and 47(57.4%) females, and there were 86 (36 male and 50 female) subjects in the control group. Mean age, disease duration and body mass index (BMI) of patients were 30.32±9.8, 5. 5±1.1 and 24.4±4.3 respectively. Mean age and BMI of the control group were 30.31±9.1 and 24.2±4.1, respectively. There were 50(60.9%) patients with widespread pain compared with 10(11.6%) individuals with widespread pain in the control group, which is a statistically significant difference ($P<0.05$), and there were 28 (34.1%) (20 females and 6 males) patients who fulfilled the 1990 ACR criteria for classification of FMS in the

patients group, compared to 2 (2.3%) in the control group which is also a statistically significant difference (P<0.05) as shown in Table 2. FMS associated clinical features were more prevalent in patients with chronic urticaria than in the control group; the difference is statistically significant (all P<0.05) as shown in Table 3. Table 4 shows that, CU patients with FMS had positive ASST and severe TSS compared with CU patients without FMS; also the difference is statistically significant (P<0.05) for both.

Table 1: The demographic distribution of patients and controls

Characteristics	Patients	Controls	P value
Total number (%)	82(100%)	86(100%)	
Men	35(42.6%)	36(41.8%)	>0.05 NS
women	47(57.4%)	50(58.2%)	
Mean age	30.32±9.8	30.31±9.1	>0.05 NS
Disease duration (mean)	5. 5±1.1		
BMI (mean)	24.4±4.3	24.2±4.1	>0.05 NS

Table 2: Frequency of widespread pain and FMS in patients and controls

Characteristics	Patients	Controls	P value
Total No. (%)	82(100)%	86(100%)	
Widespread pain	50(60.9%)	10(11.6%)	<0.05 S
FMS	28(34.1%)	2(3.48%)	<0.05 S
Men	8(28.5%)	1(50.0%)	
Women	20(71.5%)	2(50.0%)	

Table 3: Frequency of FMS associated features in both patients and controls

FMS associated features	Chronic urticaria 82 (100%)	Controls 86(100%)	P value
Morning stiffness	43(52.4%)	5(5.8%)	<0.05 S
Sleep disturbance	51(62.1%)	5(5.8%)	<0.05 S
Fatigue	47(57.3%)	6(6.9%)	<0.05 S
Anxiety	46(56.0%)	4(4.6%)	<0.05 S
Depression	43(52.4%)	4(4.6%)	<0.05 S
Headache	42(51.2%)	6(6.9%)	<0.05 S
Irritable bowel	56(68.3%)	5(5.8%)	<0.05 S

Table 4: association between FMS with ASST and UTSS

Characteristics	Patient with FMS		Patients without FMS		P value
	No.	%	No.	%	
Total	28	100	56	100	
Positive ASST	26	92.8	27	48.2	<0.05 S
Severe TSS	25	89.2	23	41.1	<0.05 S

Discussion

In this study, widespread pain was found to be more prevalent in the patients with CU than in the control group in a percentage of 60.9% and 11.6% respectively, whereas the prevalence of FMS among patients with CU was found to be 34.1% which is comparable to a study done by Oktayoğlu et al. (2), who found FMS affected 32.5% of his study group. However, the prevalence rate of FMS in patients with CU in our study was lower than that in a study conducted by Torresani et al. (6) who found, a prevalence rate of FMS in CU was 70.6% and declared that, such a high proportion was unexpected. This high result may be related to the inclusion of patients with DM, thyroid dysfunctions, haematological abnormalities, autoimmune disorders, and other systemic diseases in their study. However, the prevalence rate of FMS in patients with CU in our study was comparable to the prevalence rates of 25% in patients with RA, and 30% in patients with SLE (17,18), and it seems to be low when compared to the prevalence rate of 37.5% and 50% in patients with psoriatic arthritis and Sjogren syndrome respectively (19,20). Women showed higher occurrence of FMS than men, in a ratio of 5:2. This result is comparable with findings of other studies that found a female predominance of FMS in different inflammatory and rheumatic disorders (18,21,22).
The prevalence of FMS in our study population is considered high when compared to the prevalence rate in the general population (23). The coexistence of FMS and inflammatory skin disease has been reported in the literature. In fact, FMS is already known to coexist with psoriasis and systemic lupus erythematosus (18,24). Furthermore, the prevalence of autoimmune diseases is very high, both in the CU (25,26) and FMS (27,28) affected populations although the pathophysiology of FMS is complex and still not fully understood. It is likely that multiple processes contribute to the pathogenesis of FM, which is a pathophysiologically and psychologically heterogeneous syndrome. There is a role of psychosocial factors in the development of FMS which appears to be greater for depression and anxiety, and abnormal responsiveness or function of the nervous system appears to be implicated in irritable bowel syndrome, and tension-type headache (13).

The high prevalence rate of FMS in patients with CU in this study may be explained by the common underlying pathogenesis that involves the implication of the peripheral nerves and different neurotransmitters in the pathogenesis of both CU and FMS; when these neuropeptides are released, they will act on the target cells producing erythema, oedema, hyperthermia and pruritus; nociceptive C-fibres respond to histamine resulting in the release of these neuropeptides, in addition to substance P and calcitonin gene -related peptide (CGRP) which are known to be increased in CU skin, and play an important role in the pathogenesis of both CU and FMS (5,6,11–14). Another explanation for the high prevalence of FMS in CU may be related to the role of mast cells in the pathogenesis of both disorders. Studies reported that, mast cell is one of the primary effector cells in the pathogenesis and development of urticaria, and another recent study conducted by Ang DC et al. (14) reported an increased number of mast cells in all patients with FMS. In addition, SP may stimulate degranulation of mast cells; tryptase release may result in the cleavage of proteinase-activated receptor-2 at the plasma membrane of nerve endings, stimulating the release of CGRP, SP and NKA from nerve endings, thus providing positive FMS/CU feedback (29). Therefore mast cell is considered another common underlying pathway of both CU and FMS, and the use of mast cell stabilizer (ketotifen) may be considered in the treatment of FMS (7,13,14). Morning stiffness, sleep disturbance, fatigue, irritable bowel, headache, anxiety and depression were the most common non-musculoskeletal manifestations recorded in our study group. These FMS associated clinical features were more prevalent in patients with CU compared to the controls. The increased frequency of these symptoms also may be attributed to the common underlying pathogenesis of both CU and FMS. The high frequency of irritable bowel in our study group, may be explained by the common underlying pathogenesis of CC and FMS , which implicates mast cell, because there is evidence that, mast cells play an important role in the pathogenesis of irritable bowel (30,31). Some authors have reported that, patients with this skin disorder usually suffer from both depression and anxiety (32,33), the results of which are comparable to our finding. In this study we demonstrated the association between the status of autologous serum skin test and FMS; Positive ASST was more frequent in CU patients with FMS than those patients without FMS; a result comparable to a study done by Torresani et al (6) who found FMS was associated with positive ASST. Furthermore we found that, FMS was associated with the severity of urticaria total severity score, a result not reported before, therefore, further studies needed to clarify this association. There are remarkable similarities between the CU and FMS that necessitate further clinical and laboratory studies with a larger study population to explain the exact relationship between these two disorders.

Conclusions

FMS and its associated clinical features are more prevalent in patients with CU than in the general population. Women with CU are more frequently affected by FMS than are men. Awareness of this comorbidity and the cooperation between rheumatologist and dermatologist is an essential part in the treatment of CU.

Conflict of interest:
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All authors participated somewhat equally in the preparation and the achievement of this manuscript by completing the questionnaires in the confrontation with the patients, preparing the literatures and writing the manuscript.

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