

## CLINICAL REPORT

# Chronic Urticaria is Usually Associated with Fibromyalgia Syndrome

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**Although the pathophysiology of chronic urticaria is not fully understood, it is possible that dysfunctioning of peripheral cutaneous nerve fibres may be involved. It has also been suggested that fibromyalgia syndrome, a multi-symptomatic chronic pain condition, may be associated with alterations and dysfunctioning of peripheral cutaneous nerve fibres. The aim of this study was to determine whether patients with chronic urticaria are also affected by fibromyalgia syndrome. A total of 126 patients with chronic urticaria were investigated for fibromyalgia syndrome. An unexpectedly high proportion (over 70%) had fibromyalgia syndrome. The corresponding proportion for 50 control dermatological patients was 16%, which is higher than previously published data for the Italian general population (2.2%). It is possible that dysfunctional cutaneous nerve fibres of patients with fibromyalgia syndrome may release neuropeptides, which, in turn, may induce dermal microvessel dilatation and plasma extravasation. Furthermore, some neuropeptides may favour mast cell degranulation, which stimulates nerve endings, thus providing positive feedback. Chronic urticaria may thus be viewed in many patients, as a consequence of fibromyalgia syndrome. Speculatively, skin neuropathy (fibromyalgia syndrome) may trigger neurogenic skin inflammation (chronic urticaria). *Key words: chronic urticaria; fibromyalgia syndrome; neuropathic pain; neuropeptides; mast cells; skin nerve fibres.***

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Urticaria is considered “chronic” if episodes persist beyond 6 weeks. Chronic urticaria (CU) occurs as a clinical manifestation of immunological and inflammatory mechanisms, or it may be idiopathic (1). Although the pathophysiology of CU is largely unknown, there is evidence that peripheral nerves contribute to the pathophysiology, since certain neuropeptides have been found to be enhanced in CU, and polymodal and chemosensitive small cutaneous nerve fibres have been shown to

participate in skin inflammation (2). In fact, after their release, neuropeptides act on target skin cells, resulting in erythema, oedema, hyperthermia and pruritus, indicating that a communication network exists between cutaneous sensory nerves and immune skin cells during cutaneous inflammation (reviewed in (3)). In particular, a neuroimmune network between cutaneous sensory nerves and target effector skin cells has been suggested to link dysfunctions of peripheral nervous system and pathogenic events in allergic inflammatory skin diseases (4).

Fibromyalgia syndrome (FMS) is a chronic, generalized pain condition with characteristic tender points on physical examination, often accompanied by a number of associated symptoms, such as sleep disturbance, fatigue, headache, irritable bowel syndrome and mood disorders (reviewed in (5–7)). Although the pathophysiology of FMS is complex, it is now apparent that the role of peripheral nerves in FMS is much greater than previously thought (reviewed in (7)). Indeed, FMS is suggested to represent a neuropathic pain syndrome (8, 9), because neuropathic pain was defined as a “pain initiated or caused by a primary lesion or dysfunction of the nervous system” (10), and the main painful condition that may reflect such dysfunction in the nervous system is FMS (9). Notably, FMS was recently proposed to represent a state of dysfunction of descending, anti-nociceptive pathways, because skin biopsies in patients with FMS not only showed specific receptors and characteristic electron microscopic findings, but also an increased axon reflex flare reaction to mechanical and chemical stimuli and a lower threshold of capsaicin-induced flare (7), and these findings suggest increased neurogenic inflammation. Indeed, cutaneous sensory C fibres can initiate neurogenic inflammation (11), and FMS skin is a site of such neurogenic inflammation (12–15).

Thus, since cutaneous nerve fibres can be altered both in cutaneous inflammation, including CU, and in FMS, the aim of the present study was to investigate whether patients with CU are also affected by FMS.

## PATIENTS AND METHODS

A total of 126 patients (40 men, 86 women; mean age 47.2 years, age range 24–68 years), with CU, were consecutively enrolled over a 3-year period from January 2002 to December 2004.

### Control group

Fifty patients were enrolled as a control group (15 men, 35 women; mean age 38.8 years, age range 20–63 years). The control group were consecutive dermatopathic patients with various skin diseases other than CU. In order to establish the prevalence of FMS in such a control group, patients were evaluated for FMS using the same criteria and the same examiners as in the CU group.

### Examinations

Patients were asked about personal and family history of atopy, and about specific history of CU, including drugs, feeds, inhalants, insect bites or other possible causative factors. In addition, a questionnaire was administered, directed at CU, in order to identify possible aetiological agents. Haematological and instrumental examinations usually performed for CU were carried out, including physical urticaria tests and an autologous serum test.

All patients were also investigated for FMS. Trained examiners carried out structured visits in which subjects were asked about musculoskeletal symptoms and socio-demographic characteristics, and underwent a standardized physical examination, including analysis of tender points, Fibromyalgia Impact Questionnaire (FIQ), pain location and intensity, and fatigue and sleep complaints. The diagnosis of FMS was made in accordance with the American College of Rheumatology (ACR) 1990 criteria (5).

## RESULTS

Eighty-nine of the 126 patients with CU (70.6%) also had FMS. Compared with the prevalence of FMS in the Italian general population (2.2%) (16), the  $\chi^2$  analysis of such a prevalence of FMS in the CU population gave a statistically highly significant result ( $p < 0.0001$ ).

As far as the control group was concerned, 8 (16%) of the 50 control patients had FMS; only one of these 8 patients was formerly known to be affected with FMS. Although this percentage (16%) in the control group was unexpectedly high compared with the Italian general population (2.2%), when comparing the prevalence of FMS in the CU population (70.6%), there was a highly significant difference ( $p < 0.0001$ ).

The 89 patients with FMS in the CU group comprised 68 women and 21 men. Only 15 of them were aware of having FMS, whereas the remaining 74 were diagnosed with FMS at the time of the present investigation. Intriguingly, in all of these patients with FMS, the symptoms, especially pain and rigidity, had preceded the onset of CU: specifically, FMS had started  $15.4 \pm 7.3$  years (mean  $\pm$  standard deviation (SD)) before the onset of the present investigation, whilst CU had started  $8.3 \pm 2.4$  months before.

Haematological and instrumental examinations gave generally negative results. Eighteen patients, however, showed high anti-streptococcal antibody titres (9 of them had dental granulomas). None of these had FMS. Two patients, who were FMS-free, showed monoclonal gammopathy. Forty-two patients had a positive autologous serum test: 34 of them (80.95%) also had FMS, whereas only 8 were FMS-negative.

Three types of comorbidity were observed: (i) one female patient had Hodgkin's lymphoma; (ii) one male patient had prostate adenocarcinoma; (iii) 27 patients (21.4% of the entire cohort), all females and FMS-positive, had autoimmune thyroiditis: 6 of them also presented type 1 diabetes, one presented vitiligo, and one presented a lupus-like syndrome.

### Data for patients with chronic urticaria/fibromyalgia syndrome

The female:male ratio in the 89 patients with CU/FMS was 3.2:1, compared with 0.9:1 in the 37 FMS-free patients with CU. These data are in agreement with published data showing that FMS patients are mainly female (5), whilst the female:male ratio is approximately 1:1 in CU patients (1). The FMS patients group was younger (mean age 35.8 years, age range 24–46 years) than the CU patients group (mean age 47.2 years, age range 32–68 years).

As for the pain evaluation, structured visits were carried out, in which subjects underwent a standardized physical examination. Examination of tender points was as followed: 51 patients (57.3%), 39 females and 12 males, showed pain at only 11 tender points; 25 patients (28.1%), 16 females and 9 males, showed pain at 11–15 tender points; 13 patients (14.6%), all females, showed pain at 15–18 tender points.

Both FMS criteria were fulfilled (5) in all patients with FMS.

### Data for control group/patients with fibromyalgia syndrome

The characteristics of the 8 control patients with FMS were as follows: 2 females, aged 56 and 75 years, with prurigo nodularis; 2 females, aged 26 and 34 years, with generalized itch; 2 females, aged 25 and 27 years, with acne vulgaris; one male, aged 42 years, with lichen planus; and one male, aged 29 years, with seborrhoeic keratoses.

## DISCUSSION

The present study shows that an overwhelming subpopulation (over 70%) of patients with CU also has FMS. Such a high proportion was unexpected, because the general prevalence of FMS is only 2.2% in the entire Italian population (16).

Similarly, an unexpectedly high subpopulation of control patients with skin diseases other than CU also had FMS. There are at least two hypothetical explanations for this result. First, only 50 consecutive patients affected with various skin diseases were considered, and such a low number might not reflect the entire dermatopathic patient population. Secondly, not only CU,

but also other skin diseases, especially inflammatory ones, may be associated with neurogenic inflammation. This hypothesis is currently being investigated in our laboratory.

A high proportion of both CU patients (74 out of 89) and control patients (7 out of 8) did not previously know they also had FMS. In our opinion, such a fact may be associated with an underestimation of FMS by physicians, which has a number of possible explanations. First, they may not know of the existence of FMS. Secondly, they may know about FMS, but believe that it should not be considered as a real nosocomial entity. Thirdly, they may accept the reality of FMS, but believe that FMS is a psychosomatic disorder rather than a physical disease. The comorbidity of FMS and inflammatory skin disease is perhaps not so surprising. In fact, FMS is already known to be relevant within patients affected with psoriasis or systemic lupus erythematosus (17, 18). Furthermore, the prevalence of autoimmune diseases is very high, both in the CU-affected (19, 20) and the FMS-affected (13, 21) populations.

A putative common pathophysiological pathway explaining the clinical association of CU and FMS is not known at present. It is tempting to hypothesize, however, that such an association might be ascribed to cutaneous neurogenic mechanisms generating skin inflammation. First, cutaneous nerve fibres are altered in patients with FMS; in turn, altered FMS nerves may release the calcitonin gene-related peptide (CGRP) and substance P (SP), which are known to be increased in CU skin, together with neurokinin A (NKA); CGRP may interact with the CGRP1-receptor to induce arteriolar dilatation; SP and NKA may interact with the NKA1-receptor on endothelial cells of post-capillary venules to cause plasma extravasation; in addition, SP may stimulate degranulation of mast cells; tryptase released from degranulated mast cells may cleave proteinase-activated receptor-2 at the plasma membrane of nerve endings, which stimulates the release of CGRP, SP and NKA from nerve endings, thus providing a positive FMS/CU feedback (22).

Support for such a hypothesis comes from the following six observations:

- a series of electron-microscopically identifiable alterations were noted affecting the cutaneous nerve fibres in patients with FMS (23);
- nerves with fine unmyelinated (C-) or myelinated (A $\delta$ -) fibres innervating the skin respond to a range of physiological and pathological, both external and endogenous, stimuli, rapidly releasing active neuropeptides into the cutaneous microenvironment, thus triggering cutaneous inflammation (2);
- direct contacts may exist between cutaneous nerve fibres and mast cells, as judged by electron microscopy (24), and adhesion between such cells is guaranteed by the "synaptic cell adhesion molecule" (SynCAM) (25), namely, SynCAM expressed by the

nerve directly binds SynCAM expressed by the mast cell;

- inflamed nerves are responsible for mast cell activation (26, 27);
- neuropeptides may both trigger release from mast cells of mediators relevant for skin inflammation, such as histamine, tryptase, chymase, tumour necrosis factor-alpha (TNF- $\alpha$ ) (28), and favour the development of CU (29);
- mast cells are, on the other hand, the key cells supporting neuropathic pain (7, 13), and FMS is, as mentioned above, a neuropathic pain syndrome (8, 9).

In conclusion, most patients with CU also have FMS, and such an association might be viewed as a type of neuropathic skin inflammation.

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