Pain in Sjögren's syndrome

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SUMMARY

Sjögren's syndrome (SjS) is an autoimmune disease that affects the salivary and lacrimal glands, but it can also have extra-glandular manifestations. Although pain has not yet been fully studied and characterized, it is a symptom that can be often found in patients with SjS, who mainly complain of neuropathic pain, followed by nociceptive pain. The latter when combined with widespread dysfunctional symptoms is defined fibromyalgia. The aim of this work is to analyze the scientific literature on the presence of pain in patients with primary Sjögren's syndrome.

Key words: *Pain, Sjögren syndrome, Therapy.*

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INTRODUCTION

Sjögren's syndrome (SjS) is a systemic autoimmune disease that affects the exocrine glands, in particular the salivary and lacrimal glands (*sicca syndrome*), but it can also have extra-glandular manifestations. The SjS has a prevalence between 0.2 and 3% in the general population, with a male:female ratio of 1:9 (1). Along with the typical manifestations of the disease, including oral and ocular dryness, many patients with SjS have peripheral neuropathy and other neurological disorders (2-4). Another complication associated with SjS that occurs in a variable percentage of patients (4-5%), is the B-cell lymphoma (1, 5, 6).

The diagnostic criteria of SjS (7) focus on the relevance of oral and ocular symptoms, the involvement of the salivary glands investigated by means of a biopsy and a sialography (lymphocytic infiltration) and the presence of autoantibodies to Ro-SSA and/or La-SSB.

Pain does not currently fall under the classification criteria of the disease. However, since it is frequently reported by patients, the aim of this paper is to review the literature on this symptom which is widespread and often debilitates SjS patients and has also important implications in the choice of therapy.

Neuropathic pain in Sjögren's syndrome

Only a limited number of studies of pain in SjS can be found in the literature.

Neuropathic pain seems to be very frequent and significant in SjS (8) but in the literature we found very discordant data concerning frequency, which ranges from less than 2 (9) to over 60% (10). These discrepancies can be attributed to several factors, such as differences in the diagnostic criteria, the design and the methodology of the studies, which are mostly retrospective and with a limited sample of patients, and the differences in the definition of peripheral neuropathy, which does not always include clinical and electrophysiological objective tests. An interesting review based on a large cohort of patients, published by Pavlakis et al. (11), studied the neuropathic manifestations in SjS. The authors underlined that only 15 out of 509 SjS patients met the diagnostic criteria for small fiber peripheral neuropathy as well as axonal polyneuropathy. The skin biopsies of patients with small fiber neuropathy showed a characteristic hypodensity of fibers and a significant reduction in the number of small fibers. However, the pathogenesis of this neuropathy is still unclear. Infiltrates of T cells, a common finding in the salivary glands of SjS patients, were also associated with vasculitis (12). Although vasculitis is a rare event in SjS (13), the inflammatory

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infiltration of the vessel walls leads to the destruction of the endothelial cells, which appears to correlate with the presence of mononeuropathy and polyneuropathy (14, 15). In a paper published by Ramos-Casals et al. (16), 16% of 558 patients with SjS showed a cutaneous involvement, which in 58% of these cases was of vasculitic origin. Although the pathogenic role of T cells in the development of neuropathy remains still unclear, it appears to be related to the production of interleukins (IL), in particular IL-6 and IL8, as highlighted by a recent work that evaluated the high presence of these cytokines in skin biopsies of patients with small fiber neuropathy (17). Another suggested pathogenic mechanism of neuropathy in SjS seems to be related to B lymphocytes. In particular some autoantibodies are thought to be related to neuropathy, such as antibodies *versus* GW/P (18), α-fodrin (19) and anti-muscarinic acetylcholine type III receptor (20). These antibodies, however, are nonspecific, and the correlation with neuropathies is not always confirmed.

In a recent paper published by Segal et al. (21), the authors evaluated the presence of neuropathic pain, comorbidity, and quality of life (QoL) in 108 patients with SjS. In particular, they assessed the influence of seropositivity (anti Ro/SSA La/SSB) on the clinical features, the outcome of the disease and the prevalence of neuropathic and chronic pain. The authors also evaluated the presence of psychiatric comorbidity in these patients. The results show that pain is a symptom reported by both groups of patients, namely 65% in the seropositive group and 75% in the seronegative group. A significant difference was identified in the intensity of pain, which was found to be higher in the group of seronegative patients. Although other symptoms, such as fatigue, anxiety and depression were not statistically significant in the groups of seropositive and seronegative patients, they affect a high percentage of patients. This study also shows that pain and the impairment of physical skills were more severe in seronegative patients and confirms that chronic pain affects a high percentage of patients. However, the presence of neuropathic pain can often be underestimated, as it is mainly assessed by patient's interviews, using verbal descriptors, thus potentially leading to incorrect evaluations. From an analysis of the literature, it emerged that a high percentage of SjS patients are also affected by a comorbidity, *i.e.* fibromyalgia (FM) (22, 23), which could explain the high percentage of chronic pain in these patients (24).

Widespread pain in Sjögren's syndrome

Widespread pain is a symptom reported by 72% of SjS patients (25). In addition, several studies report a high incidence of fibromyalgia in SjS, as shown in (25-27). An interesting work published by Iannuccelli et al. (28) wonders whether pain in SjS is a result of inflammation or comorbid fibromyalgia. In a cohort of 50 SjS patients, the authors evaluated the presence of extremely debilitating symptoms, such as fatigue, widespread pain, QoL by administering the health assessment questionnaire, and the fibromyalgia impact questionnaire (FIQ). Anxiety and depression were assessed on the basis of the Zung anxiety and depression scales. The presence of FM was assessed also by examining the tender points. The most interesting result is the high percentage of SjS patients who report fatigue (88%) and pain (90%), even though visual analogue scores, pain and fatigue were not statistically significant with respect to the patients with systemic lupus erythematosus (SLE). However the presence of fibro-

Table I - Percentage of fibromyalgia on Sjögren's syndrome.

Author	Year of publication	Number of patients	Percentage of FM
Ostuni et al. (26)	2002	100	22%
Dohrenbusch et al. (25)	1996	38	44%
Bonafede et al. (27)	1995	72	11%

FM, fibromyalgia.

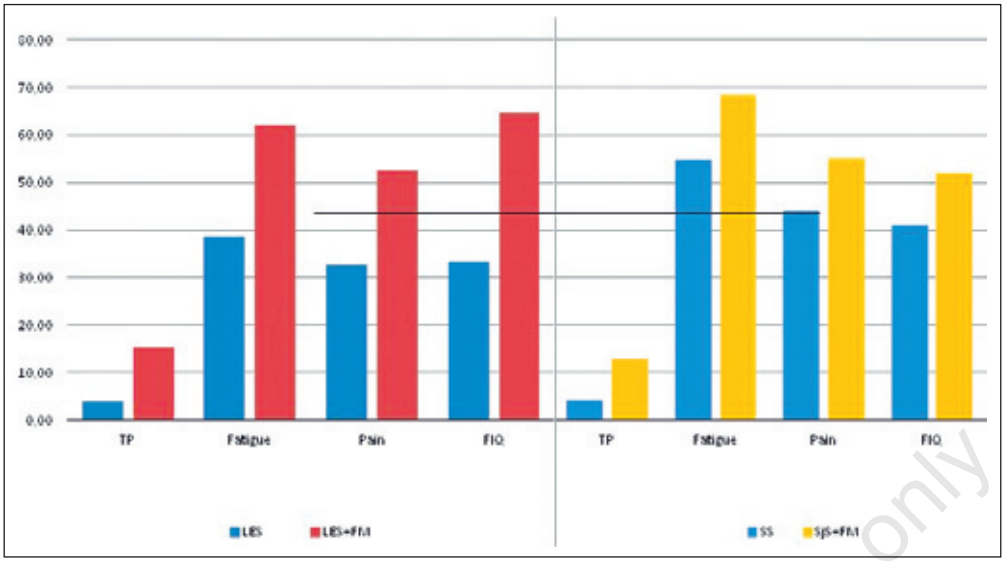

Figure 1 - Fibromyalgia was diagnosed in a higher percentage of systemic lupus erythematosus patients *versus* Sjögren's syndrome patients (32% *vs* 18%, P=0.022).

myalgia was significantly lower in the SjS group compared with the SLE group (9/50 *vs* 16/50). Figure 1 shows the data about tender points, fatigue, pain and FIQ in the group of patients with co-morbid fibromyalgia versus those with the connective tissue disease only. Remarkably, the percentage of patients that reported fatigue and pain was higher in patients with SjS, even in the group of patients without FM. The authors concluded that fibromyalgia contributes more significantly to the presence of pain in SLE patients than in SjS patients, suggesting that the causes for fatigue and widespread pain are different in these two connective tissue diseases.

In a recent paper the psychological aspects of catastrophizing were investigated in patients with SjS (29). The authors evaluated various aspects of the disease through questionnaires, which included questions on pain, fatigue and catastrophizing, and explored the influence of each variable on pain, using a linear regression curve. The results show that catastrophizing is highly predictive of pain, fatigue, anxiety and depression, independently from the immunological status, therefore an approach aimed at reducing this psychological symptom may be useful to improve the QoL of patients with SjS.

CONCLUSIONS

Although SjS patients frequently complain of pain, this symptom is not included in the diagnostic criteria of the disease. However, both clinical experience and the limited scientific literature available show a correlation between pain and SjS. Neuropathic pain, especially when small fibers are involved, seems to be the most frequent, although its pathogenic mechanisms have not yet been clarified. Furthermore, the difficulty in classifying the type of neuropathic pain may lead to an underestimation of this symptom.

The inflammatory pain related to the autoimmune origin of the disease mostly involves the joints and manifests itself as arthralgia/arthritis pain, and is therefore a more common symptom.

SS patients also often complain of widespread pain, which seems to be caused by comorbid fibromyalgia and must be clearly diagnosed to administer a proper treatment and avoid overtreatment. Finally, affective and mood disorders are often present in SjS and catastrophizing adversely affects the perception of pain and quality of life of the patient.

In conclusion, although the classification criteria do not include an assessment of

pain, a correct approach to SjS patients should take it into account, especially when it is not due to an inflammatory or neuropathic mechanism, to implement an adequate therapeutic strategy to improve their quality of life.

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