

Pain and systemic lupus erythematosus

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SUMMARY

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by heterogeneous clinical manifestations involving virtually the entire body. The pain in SLE can have different causes. The SLE classification criteria include mainly the musculoskeletal manifestations of pain, which are commonly reported as initial symptoms of SLE, such as arthralgia, arthritis and/or myalgia. Chronic widespread pain, which is typical of fibromyalgia (FM), is frequently associated with SLE. The aim of this review is to describe widespread pain and fatigue in SLE, and the association of SLE and FM. Although secondary FM is not correlated with the disease activity, it may interfere with the daily activities of SLE patients. Therefore it is necessary to identify its symptoms and treat them promptly to improve the quality of life of patients. In conclusion, it is essential to identify the origin of pain in SLE in order to avoid dangerous over-treatment in patients with co-existing widespread pain and FM.

Key words: Systemic lupus erythematosus, Fibromyalgia, Chronic widespread pain, Fatigue, Pain.

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■ INTRODUCTION

Chronic widespread pain and fibromyalgia (FM) are frequently associated with rheumatic autoimmune diseases. FM co-exists in 30% of patients with rheumatoid arthritis, 50% of those with Sjögren syndrome (SjS), and 30% of those with systemic lupus erythematosus (SLE) (1). SLE is an autoimmune disease characterized by heterogeneous clinical manifestations involving skin, joints, kidneys, heart, nervous system and virtually any other organ in the body.

Its association with FM, which is a syndrome characterized by chronic widespread pain and symptoms such as fatigue and sleep disturbances, can sometimes complicate the evaluation of pain, which should be differentiated from SLE-related disease activity or chronic damage. The most widely used indices to measure objectively the disease activity in SLE are the British Isles lupus assessment group (BILAG) index, the European consensus lupus activity measurement (ECLAM), and the systemic

lupus erythematosus disease activity index (SLEDAI), none of which are specifically meant to evaluate musculoskeletal pain *per se*. The health-related quality of life (HRQoL) of SLE patients can be assessed by means of questionnaires, such as the short form 36 (SF-36) (2), and the patient acceptable symptom state, which is a simple questionnaire to assess well-being in patients with various rheumatic conditions, including SLE (3).

The classification criteria started to be developed already in the early 1970s, where the criteria currently in use were introduced by the American College of Rheumatology (ACR) in 1982, and revised in 1997 (4). In 2012, the Systemic Lupus International Collaborating Clinics (SLICC) group proposed a new set of criteria that also include less specific clinical manifestations that are frequently reported by SLE patients (5), with pain being mainly confined to the musculoskeletal system. The aim of this review is to describe widespread pain and fatigue in SLE, and the association of SLE and FM.

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■ PATHOGENESIS

Pain in SLE can be attributable to various causes (*e.g.* inflammatory, neuropathic, and central pain), although it is most often associated with joint inflammation. The ACR SLE classification criteria refer to the presence of synovitis in two or more joints (characterized by swelling or effusion), whereas the proposed SLICC criteria extend the definition of musculoskeletal involvement to inflammatory arthralgia (tenderness in two or more joints with morning stiffness lasting at least 30 minutes) (4, 5). Joint manifestations can precede other SLE features, and typically consist in arthralgia and/or non-erosive, non-deforming arthritis. However, in some cases, arthritis can lead to reducible deformities, known as Jaccoud's arthropathy (6).

Like in other inflammatory joint diseases, the pathogenic mechanisms of inflammatory arthritis in SLE involve the production of cytokines such as interleukin (IL)-6, IL-17, interferon- α , IL-18, tumor necrosis factor- α and B lymphocyte stimulator. These inflammatory mediators play a crucial role in the differentiation, maturation and activation of the immunocompetent cells involved in the local inflammatory process and tissue injury (7).

Another source of pain is lupus headache, which is reported by 32-66% of SLE patients and can have various causes, including neuropsychiatric SLE (NPSLE) (8-10). In NPSLE patients, a close association was identified between cognitive impairment and depression, pain and fatigue, but the underlying causes are still unclear. Auto-antibodies cross-reacting with DNA and N-methyl-D-aspartate receptors, anti-endothelial antibodies and anti-phospholipid antibodies are the most common factors associated with the pathogenesis of NPSLE (11, 12). Depression, pain, and fatigue may also sometimes reflect an underlying central nervous system (CNS) disorder (13). Abdominal pain is reported by 8-40% of SLE patients (14), and may be due to various causes, including mesenteric vasculitis and pancreatitis (15). The association of pain and cutaneous lupus has been recently

evaluated and it was found that the pain was more intense in patients with vasculitic and bullous lesions, followed by patients with oral ulcers (16).

One of the first symptoms reported by SLE patients is pain resulting from musculoskeletal involvement (17), which affects approximately 50-90% of patients during the course of the disease (18).

Chronic widespread pain, which affects 5-10% of the general population (19), is reported by 65-80% of SLE patients (20, 21). Central sensitization, characterized by an enhanced peripheral nociceptive input and abnormal central pain processing of the CNS, seems to be the pathogenic mechanism causing hyperalgesia and allodynia (22). Fatigue is the most common constitutional symptom associated with pain in SLE patients (23) and has a prevalence ranging from 50% to over 80% (24). It can also be the most debilitating symptom (25,26), although it is not associated with the disease activity or the chronic organ damage, but only with anemia.

■ PUBLISHED FINDINGS

Chronic widespread pain is the cornerstone of FM, which is characterized by tenderness on palpation of at least 11/18 tender points (TPs) (27). FM is also characterized by fatigue and multiple associated symptoms, such as sleep, mood and neurocognitive disorders, as indicated by the 2010 ACR classification criteria (28).

A number of studies investigated the prevalence of FM in SLE patients, and evaluated how concomitant FM can influence the symptoms and the activity of SLE. The prevalence of FM varies depending on the ethnic group suggesting a possible influence of geographical, psychological and socio-cultural factors. Its prevalence was found to be 8.2% in a cohort of Indian SLE patients, 9.5% in Mexican SLE patients, 10% in a Spanish cohort, and 25% among Turkish SLE patients (29-32).

Various authors studied the prevalence of FM in LES patients. Morand et al. reported a 25.3% prevalence in a cohort of

87 SLE patients (33), while Middleton et al. reported a 22% prevalence in a group of 102 SLE patients (34). However, although 23% of the patients in the latter study presented widespread pain, they did not meet the 1990 ACR classification criteria. The authors reported that SLE patients with concomitant FM have significantly more frequent and severe symptoms, but no significant difference in SLE activity measures was identified between patients with or without FM (34).

Similarly, the presence of FM in 21% of a Canadian cohort of 119 SLE patients did not correlate with the disease activity and the damage indices, but it was closely correlated with the quality of life which was measured on the basis of the SF-36 questionnaire (35). Friedman et al. confirmed that there was no correlation between the clinical scores of disease activity, disease damage, specific organ dysfunction and concomitant FM, which was diagnosed only in 5% of SLE patients (36).

Taylor et al. investigated whether FM was more frequent in patients who complained fatigue, and found that only 10% of these patients fulfilled the criteria for FM (37).

An Israeli group found that SLE patients with FM had significantly lower HRQoL scores than those without FM (38). In 2005, Akkasilpa et al. evaluated the association between tender point positivity and health status in a group of 173 SLE patients using the health assessment questionnaire (HAQ): 17.3% of the patients had ≥ 11 TPs and the number of TPs was significantly associated with their HAQ scores (39).

We have recently analyzed the prevalence of widespread pain and fatigue in a group of Italian patients with SLE or SjS. FM was diagnosed in a significantly higher percentage of SLE patients (33% vs 18%). Moreover, the SLE patients showed a correlation between HAQ scores and fatigue and pain, whereas no correlation was found between the associated FM and the disease activity indices (21).

Grafe et al. observed that FM was more frequent in SLE patients (prevalence of 16.7%) than in patients with cutaneous lupus. The patients with SLE and concomi-

tant FM also reported significantly more often symptoms such as headache, morning stiffness, diffuse alopecia, and arthralgia (40).

Pain is associated with perceptions of reduced physical functioning and coping resources, and higher levels of anxiety and depression. Consequently SLE patients need psychosocial interventions in order to relieve pain and distress and improve coping skills (41). Pain coping cognitions, such as self-efficacy for pain control and pain catastrophizing, may influence symptoms such as pain, stiffness, fatigue, and psychological distress in SLE patients. Recent data demonstrates that patients with low levels of self-efficacy for pain control and/or high levels of pain catastrophizing reported more physical symptoms and psychological distress, and highlights the importance of assessing coping constructs in SLE patients (42).

Apart from FM, pain can interfere with the quality of life, and the SLE patients who experience the highest levels of pain also report stiffness and fatigue. Pain can also cause functional limitations that lead to a significant economic burden on the society as a whole (43). The working productivity of SLE patients with the highest levels of pain is lower than that of SLE patients with less pain (44), and pain also predicted negative energy levels (45). Pettersson *et al.* found that the most frequently reported symptoms by SLE patients are fatigue, pain and musculoskeletal distress, all of which are related to low HRQoL scores, although only fatigue has an impact on both mental and physical components (46).

Table I - Common symptoms of systemic lupus erythematosus and fibromyalgia.

Musculoskeletal pain
Fatigue
Stiffness
Sicca symptoms
Cold-induced vasospasm
Cognitive dysfunction
Depression
Headache
Abdominal pain

The differential diagnosis of SLE and FM may be difficult because the two diseases have some symptoms in common (Tab. I). In a recent study, 15 patients with FM had been previously misdiagnosed as having connective tissue diseases, including SLE (47). Low antinuclear antibody (ANA) titers are commonly reported in both the general population and FM patients, and so it is necessary to evaluate the clinical data in order to avoid misdiagnoses. Wallace *et al.* described a group of 44 patients referred for a rheumatologic visit because of pain and ANA positivity in order to rule out lupus. After six months of follow-up, 19 (43%) fulfilled the ACR criteria for SLE, and 14 (32%) fulfilled the ACR criteria for FM (48). Although secondary FM is not associated with the disease activity, it may worsen the quality of life of patients with SLE, who may experience increased fatigue because of FM. Moreover, chronic fatigue without FM can influence their HRQoL even if it is not related to SLE disease activity or organ damage (49). A recent study has confirmed that SLE patients have lower SF-36 scores than the general population; FM is independently associated with a poorer HRQoL, underlining the need to treat pain promptly and accurately (50).

■ THERAPY

The treatment of pain in SLE patients requires a differential diagnosis. In particular, it is necessary to establish whether pain is localized or widespread, visceral or musculoskeletal. The first step is to evaluate the SLE activity, and optimize a specific SLE treatment with immunosuppressive drugs and steroids (51, 52).

FM symptoms in an SLE patient may be misinterpreted as lupus disease activity, thus leading to over-treatment. Once it is excluded that the cause of pain is not attributable to the disease activity, the same treatment used for FM can be administered. Analgesic drugs, such as acetaminophen or tramadol, can be safely used in patients with widespread pain and SLE (53). Anti-epileptic drugs, such as gabapentin

and pregabalin, have been approved for the treatment of neuropathic pain. Pregabalin is also approved by the American Food and Drug Administration (FDA) for FM. Both drugs have a favorable safety and tolerability profile (54). Low doses of tricyclic antidepressants are useful in the case of musculoskeletal pain and headache. Selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors, such as duloxetine (approved by the FDA for FM), can be used in SLE patients with pain and depression (55). In many cases non-pharmacological treatments, such as aerobic exercise and cognitive behavioral therapy, may also be useful (56).

In conclusion, an accurate diagnosis of musculoskeletal, inflammatory and SLE-related or FM-associated pain is essential in order to start the right therapy and avoid dangerous over-treatment in SLE patients with co-existing widespread pain and FM.

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