Are Patients with Systemic Lupus Erythematosus at Increased Risk for Fibromyalgia?

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Widespread chronic pain, fatigue, and distress do not represent risk factors for future systemic lupus erythematosus (SLE) or other autoimmune syndromes. On the other hand, SLE seems to be a significant risk factor for fibromyalgia (FM). Up to 47% of SLE patients fulfill FM criteria. SLE patients with concomitant FM are often highly symptomatic and dysfunctional. The presence of FM symptoms in SLE patients, however, does not predict more extensive organ involvement or lupus activity. The high concordance of SLE with FM suggests common mechanisms related to pain and distress in both patient groups. Recent research suggests involvement of *N*-methyl-D-aspartate (NMDA) and neurokinin receptor systems. Thus, autoimmune activity against these receptor systems in SLE patients could result in pain, cognitive defects, and chronic pain states including FM. Conversely, treatment of SLE-FM patients with inhibitors of NMDA or neurokinin receptors may prevent or alleviate cognitive abnormalities and chronic pain, as well as FM.

Introduction

For more than a century, chronic pain syndromes have been recognized as a cause of significant musculoskeletal morbidity [1]. One of these pain syndromes was first characterized as "fibrositis" in 1975 [2,3] and subsequently became known as fibromyalgia (FM) [4]. In most countries, FM afflicts 3% to 5% of the general population, and this prevalence steadily increases with age [5]. FM is characterized by abnormal pain processing including pain amplification [6•] and is part of the affective spectrum disorder family of diseases [7].

FM is one of the most frequent diagnoses made by rheumatologists in the United States and represents a major cause for disability [8,9]. The diagnosis of FM is symptom-based and requires the presence of musculoskeletal pain for more than 3 months, as well as widespread tenderness (allodynia) to mechanical stimuli (tender points), particularly in the neck, chest, back, and extremities. In addition, most FM patients complain of excessive fatigue, poor sleep, and affective distress. Chronic widespread pain and allodynia, however, are not specific for FM and can be detected in many other chronic conditions, including osteoarthritis [10], rheumatoid arthritis (RA) [11], and systemic lupus erythematosus (SLE) [12]. The co-occurrence of FM with other illnesses was previously labeled "secondary FM" [13], a term that subsequently has been abandoned.

No specific tests for FM exist, so many physicians feel uncomfortable with this diagnosis [14]. Thus, weakly positive antinuclear antibodies (ANA), as are found in many FM patients [15], may prompt physicians to attribute chronic pain symptoms to autoimmune syndromes, particularly SLE. Consequently, inappropriate therapy including steroids and/or hydroxychloroquine may be initiated by healthcare providers. Furthermore, chronic pain patients are often reluctant to abandon the SLE label despite obvious lack of evidence, because this misdiagnosis may validate pain symptoms and disability. On the other hand, FM is often missed or not even considered by many healthcare providers. The purpose of this review is to examine the close relationship between SLE and FM, both of which are frequently considered as mutually exclusive by patients and healthcare providers alike.

Clinical Presentation of FM in SLE Patients

SLE patients with FM (SLE-FM) often present with characteristic symptoms of heightened sensitivity and somatic focus. Typical symptoms include widespread pain, muscle soreness, nonrestorative sleep, depression, abdominal pain/bloating, menstrual pains, and high sensitivity to light and noise [16,17•]. However, the diagnosis of SLE-FM is not associated with increased SLE disease activity, as measured by the Systemic Lupus Activity Measure (SLAM), SLE Disease Activity Index (SLEDAI), British Isles Lupus

Assessment Group (BILAG), or measures of lupus-related organ damage, measured by Systemic Lupus International Collaborating Clinics (SLICC). Patients with SLE-FM, however, exhibit poorer function than SLE patients, including social support and disability [18•,19•].

Similar to FM, SLE patients are not a homogenous group but can be separated into several subgroups according to symptoms. In a large SLE cohort, principal component analysis identified six distinctive subgroups that differed by skin disease, renal involvement, thrombotic disease, lymphopenia, serology, and FM [20]. Individual components of SLE-FM subgroups included myalgias, arthralgias, muscle tenderness, headaches, and nervousness. However, other symptoms including depression, cognitive dysfunction, and fatigue were common to all SLE subgroups. Ethnic differences do not seem to play an important role in SLE-FM. In a large study of Hispanic, African-American, and Caucasian SLE patients, ethnic background did not predict membership in the SLE-FM group [18•].

Prevalence of FM in SLE Patients

Several large epidemiologic studies from the United States, Israel, and Australia showed that FM can be detected frequently in SLE patients [13,21–23,24•,25,26,27••]. In these studies, the prevalence of FM ranged from 22% to 47%. However, several studies from Great Britain [28], Spain [29], Mexico [30], and India [31] reported a lower prevalence of SLE-FM in their respective SLE populations (8.2%–10%). Whether these different rates of SLE-FM in SLE cohorts from the United States and other countries are determined by geographic, socioeconomic, ethnic, or cultural factors cannot yet be definitively answered.

These epidemiologic studies provide evidence that not only is SLE-FM common but it is also associated with considerable morbidity. In addition, FM does not appear to only coaggregate with SLE but also with several other autoimmune diseases including RA (25%) [32,33••] and Sjögren's syndrome (50%) [34]. Therefore, FM-related disease mechanisms seem to play an important role in many autoimmune syndromes.

FM Patients Misdiagnosed with SLE

Besides patients with concomitant SLE-FM, a large group of patients exist who have been misdiagnosed with SLE and lack objective evidence for this autoimmune syndrome. Many of these patients, however, qualify for the diagnosis of FM. The initial diagnosis of SLE is frequently based on clinical presentation and not supported by serologic or histologic tests of autoimmunity. Many patients with presumed SLE often do not fulfill American College of Rheumatology SLE criteria at referral or during follow-up [23]. Because many of these patients (26%) satisfy FM criteria, a critical reassessment of their SLE diagnosis appears prudent. Interestingly, many FM patients report rheumatologic symptoms reminiscent of SLE, like arthralgias/myalgias, skin problems, fatigue, and positive ANA, but they lack clinical evidence for arthritis, serositis, renal disease, and abnormal skin findings.

FM Symptoms Mimicking Autoimmune Disorders

FM patients frequently display symptoms that are usually associated with SLE [35]. Low titer (1:40) ANA are found in 9% to 30% of FM patients regardless of age [36,37]. Up to 25% of FM patients complain of joint pain in the hands, knees, and feet [38] but lack objective evidence for synovitis [39]. Similarly, Raynaud's-like symptoms are often reported by up to 40% of FM patients [15,40]. Some FM patients even have incidental findings of immunoglobulin deposits on skin biopsy [41], usually without any complement fixation [42]. Sjögren's disease symptoms, including dry mucous membranes are a frequent occurrence in FM patients [15]. Many of the FM patients' sicca symptoms, however, are related to the anticholinergic effects of tricyclic antidepressants and other medications. Cognitive dysfunction, fatigue, and depression are common complaints in both SLE [43,44•] and FM [7,45,46].

Is FM a Risk Factor for SLE?

It is not unreasonable to speculate that FM may represent a risk factor for future SLE. Many SLE symptoms such as pain, depression, fatigue, and cognitive abnormalities may result from similar mechanisms in both groups of patients. Because low-level autoantibodies are frequently detected in young women [47], ANA-positive FM patients might be at increased risk to develop lupus in the future. Long-term follow-up studies of FM patients, however, have not provided evidence for an increased risk of any rheumatologic disorder in this population [48,49].

Common Symptoms in FM and SLE

The coexistence of FM and SLE in a patient represents a clinical challenge and makes diagnosis and effective therapy difficult. Patients with SLE-FM are often highly symptomatic and display poor physical function. Similar to SLE, FM does not comprise only one predominant symptom but is associated with a multitude of somatic complaints [35] and decreased quality of life [50]. Besides chronic muscle pain, FM patients often complain of severe fatigue, interrupted sleep, and depressed mood [51]. Other symptoms may include migraine-type headaches, cold intolerance, sicca symptoms, joint pains, peripheral edema, noncardiac chest pains, temporomandibular pain, dyspnea, paresthesias, dizziness, and abdominal pain [52,53].

FM and SLE patients also present with frequent co-occurrence of other somatic syndromes, including irritable bowel syndrome, chronic fatigue, temporomandibular disorder, migraine, premenstrual syndrome, Raynaud's phenomenon, interstitial cystitis, and restless leg syndrome [54,55]. Activities of daily living are more difficult for FM patients and often require extra rest periods during the day [56]. Many patients have difficulty with repetitive motor tasks and may tolerate physical activities only for short periods of time [57]. In addition, prolonged sitting or standing and environmental factors such as heat, cold, excessive noise, and work-related stress often aggravate FM symptoms [58].

FM Pain Mechanisms

FM is a frequent pain syndrome that is part of a spectrum of chronic pain disorders [7,59]. Epidemiologic studies from the United Kingdom and the United States indicate that FM is at the extreme end of the spectrum of chronic pain, which is very prevalent in the general population (43%) [5,60]. When population samples with chronic widespread pain were examined, 82% fulfilled FM criteria (≥ 11/18 tender points). Although widespread pain seems to predict mechanical tenderness, the presence of 11 or more of 18 tender points does not predict FM [61]. In FM patients, however, mechanical allodynia of muscles is not limited to tender points but rather is widespread. In addition, FM patients show hypersensitivity to multiple noxious and non-noxious stimuli, including heat, cold, and electrical stimuli [51,62].

Systemic Lupus Erythematosus

SLE is a chronic autoimmune disease that can affect many organ systems, including the central nervous system, blood, joints, kidneys, lungs, serous membranes, and skin. The hallmark of autoimmunity in SLE is the production of autoantibodies to nuclear constituents [63]. Multiple abnormalities in the regulation of the innate and adaptive immune system result in altered function and loss of self-tolerance in SLE. Elevated serum levels of ANA are present in more than 98% of SLE patients, and high levels of antibodies to double-stranded DNA (dsDNA) are rarely seen in any other disease. SLE patients can make different types of autoantibodies, both to intracellular and extracellular antigens, which cause the clinical manifestations of the disease. Some autoantibodies can cause diseases such as glomerulonephritis, whereas other types of autoantibodies seem to target neurons and may result in brain injury in patients with SLE [64–66].

The clinical manifestations of SLE may present in three different and often overlapping ways: cutaneous lupus, drug-induced lupus, and the most clinically relevant, SLE. Cutaneous lupus primarily affects the skin and subcutaneous tissues. Drug-induced lupus erythematosus is usually temporary and most often resolves after discontinuation of the offending drug. Musculoskeletal problems frequently associated with SLE consist of arthritis, arthralgia, myalgia (tenderness/weakness), subcutaneous nodules, synovial effusion, and tenosynovitis.

Neuropsychiatric SLE

SLE is characterized by activation of the immune system leading to autoantibody production, activation of complement cascades, and cytokine production. Recent evidence suggests that such autoantibodies cannot only damage kidney, skin, and the fetal heart, but they may also mediate brain damage in SLE [67••]. One group of autoantibodies associated with brain dysfunction are antiphospholipid antibodies [68,69]. These pathologic autoantibodies have been linked to ischemic and hemorrhagic brain injury. Other autoantibodies, including antiribosomal P protein antibodies have been associated with psychosis in several studies [70,71].

Recently, an important subset of autoantibodies has been identified in the serum and cerebrospinal fluid of SLE patients, which is directed against *N*-methyl-D-aspartate (NMDA) receptors, specifically the NR2A and NR2B subunits. Excessive activation of these receptors can result in neuronal activation and possibly excitotoxic cell death [64]. Because NMDA receptors are widely distributed in the central and peripheral nervous system, including the hippocampus, amygdala, and hypothalamus, these antibodies may have adverse effects on other important functions such as pain processing, cognition, and emotional behavior [72].

Shared Mechanisms in SLE and FM

By definition, all FM patients have widespread body pain [4]. In addition, most FM patients have extensive mechanical hyperalgesia, some of which is detectable at so-called tender points. Almost all FM patients display not only evidence for mechanical hyperalgesia but also a reduction in pain thresholds to multiple stimulus modalities, including heat, cold, and electrical pulses [6•,51]. These and other observations suggest that most FM patients have a generalized pain amplification disorder.

The widespread hyperalgesia of FM is most likely related to long-lasting changes in the central nervous system (neural plasticity) [73,74]. Neural plasticity was first described in 1965 when investigators noted that repeated stimulation of C-pain fibers led to a progressive increase of the electrical response recorded from dorsal horn neurons of the spinal cord [75]. This temporal summation of C-fiber–mediated pain stimulation was termed "wind-up" and plays a crucial role in the initiation and maintenance of chronic pain. Wind-up is a relevant mechanism of increased pain susceptibility termed "central sensitization." This central pain mechanism plays an important role in the pain experience of all chronic pain patients, including FM and SLE patients (Table 1).

Table 1. Central sensitization

Definition
Increased and prolonged excitability of neurons in the central nervous system.
Neurologic manifestations
1. Reduction in the activation threshold of central neurons.
2. Recruitment of neurons that are not dedicated to pain transmission.
3. Expansion of receptive fields of central neurons.
Behavioral manifestations
1. Heightened pain sensitivity (ie, primary or secondary hyperalgesia).
2. Spatial spreading of pain (ie, secondary hyperalgesia).
3. Pain elicited by activation of nonpain fibers (A beta fibers) (ie, allodynia).

Temporal summation of C-fiber activity or wind-up is the result of NMDA receptor activation [76]. Besides glutamate, which is the main ligand for NMDA receptors, substance P also plays a major role for wind-up and central sensitization [77]. Substance P is a neuropeptide that activates the neurokin-1 receptor and results in lowering of neuronal thresholds. Thus, the threefold increase of substance P levels detected in the cerebrospinal fluid of FM patients may reflect activation of neurokin-1 receptor systems [78,79]. Pain-related brain activity can be demonstrated by several imaging techniques, including positron emission tomography, single photon CT, and functional MRI. The hyperalgesia of FM patients to mechanical stimuli has been elegantly shown by functional MRI of pain-related brain activity [80].

Conclusions

SLE patients with concomitant FM are often highly symptomatic and dysfunctional. The presence of FM symptoms in SLE patients, however, does not predict more extensive organ involvement or lupus activity. The high frequency of FM in SLE patients (up to 47%) suggests common mechanisms related to pain and distress in both groups of patients. One of these mechanisms could be associated with autoimmune activation of CNS receptor systems that are associated with pain signaling and processing, cognition, and affect. Likely candidates for such interactions are NMDA and neurokinin receptor systems. Thus, characterization of autoimmune activity directed against one or both of these receptor systems in SLE patients could predict current pain and cognitive defects as well as future risks for the development of chronic pain states such as FM. Conversely, treatment of SLE-FM patients with pharmacologic modulators of NMDA or neurokinin receptors may prevent or alleviate cognitive abnormalities and chronic pain as well as FM.

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