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Recognize Comorbid Fibromyalgia Syndrome in Order to Better Evaluate Selected Rheumatic Diseases

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Abstract

The prevalence of comorbid fibromyalgia syndrome in autoimmune rheumatic diseases is clinically significantly higher than is fibromyalgia syndrome in the general population. By increasing pain sensitivity and fatigue, it disproportionately inflates subjective signs and symptoms, thereby obfuscating composite indices used to measure biological disease activity, the degree of disability, and the quality of life. By modifying primary disease phenotype, it also interferes with diagnostic precision. This review documents its effects on rheumatoid arthritis, the spondyloarthropathies, and systemic lupus erythematosus; and offers a general remedial strategy.

Keywords: fibromyalgia, disease activity, diagnosis, outcomes

1. Introduction

Subjective symptoms such as patient global assessment of health (PtGA), fatigue, tenderness of joints at palpation (TJC), and even patient report of functional ability encountered in the evaluation of rheumatic diseases are very important not only because they reflect the individual patient's impression of disease activity and degree of disability, but also because patients place great faith in them [1]. Patients' estimation of pain, fatigue, and distress, which drive those subjective measures, is multidimensional, due to both biological disease activity as well as factors unrelated to disease-specific biological inflammation. Some of these factors include mechanical damage from comorbid osteoarthritis or disease-specific joint destruction and neuropathy from other disease, psychosocial factors, and even idiopathic poor sleep disorder. All of these factors can result in disproportionately higher subjective symptoms [2–4].

Composite indices such as the disease activity score (DAS) models are widely used to determine disease activity in clinical trials and everyday practice. Unfortunately, they may be misleading when used to evaluate apparent inflammatory activity in patients with comorbid chronic pain syndromes often coupled with psychological distress, which are synonymous with fibromyalgia syndrome (FMS). Comorbid FMS is associated with relative overestimation of subjective symptoms, which then inappropriately inflate the DAS models.

Fibromyalgia syndrome is comorbid in all rheumatic disease with prevalence as high as 25% in rheumatoid arthritis (RA), and 30% in systemic lupus erythematosus (SLE) and the spondyloarthropathies (SpA) [5–8]. The focus of this review will be on RA, SpA, and SLE.

1.1. Rheumatoid arthritis

In the past, when I spoke to rheumatologists about FMS, they often responded, “Why should I see patients with fibro? So many symptoms. And these patients with their personality disorders on top of anxiety and depression just wear me down. They’re the worst.”

The easy moral response might be, “Because these patients come to you for care, and you took an oath.”

“I know, but why me?”

There are at least two other responses, both persuasive. The first appeals to the intellect. Fibromyalgia syndrome is a symptom complex at the severe end of a pain-distress spectrum [4, 9, 10]

It is a fascinating illness: a primary response to distress with demonstrated secondary process factors and dysfunction related to the endocrine [11] autonomic system [12], central nervous system [13], sleep quality [14], and arguably, even the immune system [15].

These process factors give rise to a plethora of symptoms including diffuse pain, fatigue, cognitive dysfunction, sleep disturbances, more severe morning stiffness, irritable bowel syndrome (IBS), headaches, Raynaud-like phenomenon, sicca symptoms, paresthesias, auditory dysfunction, bladder dysfunction, and among others [16–18].

The second is a practical response. The prevalence of FMS in the general population ranges from 2 to 8% [19–22]. As previously noted, the prevalence in rheumatic diseases is much higher. With practice, the clinician will become familiar with the FMS phenotype and be able to recognize it as a comorbidity in autoimmune rheumatic diseases. The reason that recognition is so important is, as we will see, that comorbid FMS, is often associated with psychological difficulties, that in concert with FMS can modify both the apparent phenotypic presentation and severity of clinical disease by inflating subjective symptoms.

For years, working at the Cleveland Clinic Foundation, a tertiary care practice, I evaluated RA patients who were referred because they were refractory to treatment, so-called “resistant arthritis” [23]. At final diagnosis, I could usually classify these patients into three categories:

The majority either had only FMS, or did have RA, but the resistant symptoms were unrelated to RA and consistent with bursitis, tendinitis, OA, and especially FMS. In the third category, a very few had truly resistant RA disease activity.

At first blush, we might ask, “How is this possible?” When we learn that most rheumatologists no longer perform joint counts at office evaluation, we might better understand [24]. By failing to perform joint counts, they rely heavily on subjective symptoms such as the patient global assessment (PtGA) and patient evaluation of joint pain. Even when joint counts are included in the evaluation, mistakes can be made. Diffuse pain is by definition nonarticular, but can also include the joints [25–27], manifesting as a higher TJC. Comorbid FMS is also associated with increased duration and severity of morning stiffness, lower values for function measured as the Health Assessment Questionnaire-Disability Index (HAQ-DI), and the physical components of the SF-36 as well as diminished quality of life measured by the mental components of the same instrument [28, 29]. It is important to note a key diagnostic finding; in these reports, comorbid FMS did not usually associate with or obfuscate the swollen joint count (SJC) or acute phase reactants such as erythrocyte sedimentation rate (ESR), or c-reactive protein (CRP).

Comorbid FMS gives rise to enhanced pain sensitivity. The mechanism responsible for enhanced pain sensitivity is mediated in the central nervous system, facilitated by depression/anxiety [30–33]. In a cross-sectional analysis of a cohort of 305 FMS patients, depression showed the highest association with core FMS signs and symptoms [34]. The degree of depression showed a dose relationship with life-long numbers of TPs [35] and was responsible for the process of comorbid FMS in RA [36]. In a unique analysis using advanced Bayesian filtering of 247 diseases among 117,392 participants, depression was shown to be a primary comorbidity associated with FMS [37].

In summary, the effects of comorbid FMS on RA disease activity measures are many. It is associated with disproportionate elevation of PtGA and TJC [26, 28, 29, 38, 39]. The elevation of the subjective components of the DAS model indices inflates the total score. It is not surprising that in a recent analysis of change in disease status in patients with multiple comorbidities, PtGA best correlated with the other subjective variables, pain, and fatigue, which are also disproportionately elevated by comorbid FMS [40].

1.2. The spondyloarthropathies (SpA)

Diagnostic confusion is a larger problem in patients with SpA. An editorial reviewed the similarities between SpA and FMS, which included overlap of disease activity measures, found in patients with presumed enthesitis [41]. They asserted that FMS tender points (TPs) were anatomically located near or at enthesitis sites, which was confirmed in a separate study [8].

Because, as will be described, comorbid FMS disproportionately increases the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Ankylosing Spondylitis Disease Activity Score (ASDAS), Bath Ankylosing Spondylitis Functional Index (BASFI), and Ankylosing Spondylitis

Quality of Life (ASQoL), it not only increases diagnostic confusion, but also interferes with accurate assessment of disease activity, disability, and quality of life. A strong case can be made for including FMS in the differential diagnosis of SpA.

Similarity between the two conditions was confirmed by Ablin and colleagues who approached the problem from the other perspective [42]. They carefully evaluated 99 patients who met 1990 ACR criteria for FMS, to determine whether some might also be classified as SpA. Ten patients fulfilled ASAS criteria for the diagnosis of axial SpA: eight of whom fulfilled the criteria based on MRI findings diagnostic of sacroiliitis, while two patients with negative MRI results fulfilled ASDAS criteria based on a positive HLA-B27 and the presence of SpA features.

One of the first studies to analyze phenotypic modification of ankylosing spondylitis by comorbid FMS was a cross-sectional study of 36 patients, 18 of each gender [43]. About 50% of women satisfied the criteria for comorbid FMS, whereas no males did. In this study, FMS correlated with the mean number of enthesitis sites. Higher BASDAI in women showed strong association with both the FMS incidence and a higher number of tender points. The perceived disability measured by BASFI was also significantly increased in patients with comorbid FMS. No association was found for the presence of FMS and the severity of physical findings or the ESR.

Interference with outcome measures was probably best demonstrated in an earlier study by Heikkila and colleagues [44]. They administered the BASDAI and BASFI, among other composite measures, to 24 women with SpA and 70 patients with FMS. The BASFI function demonstrated greater disability in the FMS group compared to SpA women.

If one is to rely on any one test in SpA with comorbid FMS, the ASDAS has been shown to be less obfuscated by comorbid FMS [45, 46]. These relationships to disease activity measures and a prevalence of FMS as high as 30% were largely confirmed by other studies [47–49]

The relatively high prevalence of FMS is not surprising, given the high prevalence of psychiatric problems in the SpA's estimated to be 40–50% [50]. When present, they similarly obfuscate measures of severity [50, 51]. "Patients with high risk for depression and anxiety had higher scores in BASDAI, BASFI, ASDAS-CRP, and also poorer scores for the pain visual analog scale (PVAS) and ankylosing spondylitis quality of life score" [51].

In summary, comorbid FMS complicates both diagnosis and estimation of disease activity in SpA. It follows that treatment decisions may also be obfuscated when FMS falsely inflates the BASDAI, PtGA, and BASFI [47]. This may lead to more frequent but inappropriate use of biologic agents, as it did in RA [52].

1.3. SLE

As discussed in the introduction, the prevalence of FMS in SLE has been reported to be at least as high as in RA ranging from five to 65% with a mean of ~30% [31, 53–65]. The core symptoms of FMS, diffuse pain, fatigue (low energy), cognitive difficulties, sleep disturbance, and depression will, of course, always be encountered in FMS comorbid disease.

Fatigue is present in at least 80% of patients with FMS. In a cross-sectional analysis of 100 SLE patients, fatigue correlated best with the presence of FMS, followed by depression and elevated PtGA [63]. In a very careful prospective blisibimod trial in SLE, improvement of fatigue was not clinically significant and correlated weakly only with SLE disease activity [66]. They hypothesized that, "...fatigue in SLE is multifactorial, with the 'non- SLE' component (including depression and fibromyalgia) less amenable to change during the trial."

Depression is a common comorbidity in unselected SLE cohorts ranging from 17 to 71% [31, 67]. The high prevalence of depression in SLE may help to explain the high prevalence of FMS. In a cohort study of 84 SLE patients, comorbid FMS was associated with anxiety and depression [60]. In a larger cohort of 276 SLE patients, the strongest association with both FMS and SLE/FM-like manifestations was a self-reported history of anxiety or affective disorder [65].

Quality of life (QoL) is closely associated with anxiety and depression in SLE [67]. In a study specifically designed to analyze health-related quality of life (HRQOL) in 138 SLE patients, all disease-specific HRQOL domains were significantly inversely correlated with disease activity, damage, depression, and the presence of FMS [59]. Comorbid FMS and depression was also shown to diminish QoL in two additional large SLE cohorts [68, 69].

Most analyses of health status in SLE have demonstrated that comorbid FMS is associated with increased disability [57, 60, 61, 65]. In a particularly important analysis, the number of tender points correlated with increasing disability demonstrating a dose effect [62].

Just as in RA and SpA, comorbid FMS modifies SLE disease activity measures. Sometimes, older papers are the best. In a study, published in 1994, the authors reported and analyzed differences in a cross-sectional analysis of 102 SLE patients [61]. "Twenty-two SLE patients (22%) met the American College of Rheumatology criteria for FMS, and another 24 (23%) had clinical FMS but did not meet the classification criteria," SLE patients with FMS and probable FMS (6–10 TPs) presented significantly higher Systemic Lupus Activity Measure (SLAM) scores. When the SLAM was modified by removing all subjective symptoms, neither category scored higher than SLE without FMS. This was also true for laboratory tests. Finally, patients who met criteria for FMS were much more likely to be unable to perform daily activities. By modifying components of disease severity composite indices, this early paper prefigured recent work in RA that employed the objective M-DAS or subjective DAS28-P [70, 71].

In the same year, Morand and colleagues reported the same phenomena in 87 SLE patients, 22, with FMS [57]. Manifestations of biological SLE disease activity, measured by the severity of specific organ system involvement, showed no difference between groups. The Systemic Lupus Activity Measurement scores were not significantly different. However, frequency of glucocorticoid use, antibodies to double-stranded DNA, the presence of at least four ACR criteria for SLE, and physician's global assessment (PhGA) were higher in the patients without FMS indicating more severe objective, biological disease in this subset. This analysis suggested that comorbid FMS in SLE can inappropriately increase the SLAM score.

Other indices appear to be relatively unaffected. In a cross-sectional analysis of 119 SLE patients, patients with FMS showed no effect on Systemic Lupus Erythematosus Activity

Index (SLEDAI) or Damage index, but did show poorer scores in all eight domains of the Short Form-36 [58]. The SLEDAI SLE disease activity score was also not influenced by FMS in another cohort of 100 SLE patients [63]. In another analysis of a much larger population of 458 SLE patients, comorbid FMS did not affect the 16-item SLE Symptom Scale [72]. These authors did not evaluate other composite indices.

Comorbid FMS signs and symptoms may also complicate the diagnostic process. For instance, when 149 presumed SLE patients with up to 5 years of disease duration were rigorously analyzed, 22 (14.3%) had only FMS with positive antinuclear antibodies (ANA) [73]. Depression, anxiety, fatigue, and sleep disturbance were the prominent symptoms in this group. Symptoms that indicated SLE included swollen joints, skin lesions, alopecia, renal disease, and serositis [72, 73].

The anti-nuclear antibody (ANA) test can be very confusing from the perspective of diagnosis. The high sensitivity of most and relatively low specificity of some ANA tests is problematic. Nonspecific (+) ANA in any titer can be found in roughly 30% of the general population, more likely in women and individuals 65 years and older [74–77]. Even titers as high as 1:320 are likely to be false positive in some settings, such as hospitalized patients [77]. The ANA is positive in low titer in at least 38% of individuals with FMS alone [78]. Furthermore, FMS patients with positive ANA tests are no more likely to have symptoms of autoimmune rheumatic disease than ANA-negative patients [53, 79], nor are they likely to later develop symptoms of an autoimmune disease in the future [80].

In summary, comorbid FMS inappropriately inflates some measures of SLE biological disease and, when patient with FMS have positive ANA testing, can interfere with diagnostic precision.

1.3.1. Parsing comorbid FMS: the RA models

Comorbid FMS in other diseases is not necessarily occult. It can be discovered both by clinical maneuvers and the use of validated questionnaires.

A very important study provided a basis for these maneuvers. The DAS28 was administered to 62 patients with RA and 26 patients with FMS alone [81]. Both groups had total scores consistent with moderate RA disease activity. But the component values were very different; the RA patients scored uniformly high for all components while the FMS cohort scored very high for the subjective TJC and PtGA and low on the objective SJC and ESR.

One clinical maneuver, which can be applied in RA, makes use of that observation; comorbid FMS disproportionally raises the TJC relative to the SJC. Comorbid FMS is likely to be present if the numerical difference is ≥ 7 when the SJC is subtracted from the TJC (39 Pollard). Alternatively, ratios of the TJC compared to the SJC may be used [30, 82]. In the third of these studies, depression, and by inference, pain, was shown to be a mediator of higher tender-to-swollen joint ratios [30].

To summarize, these last few studies have demonstrated that when the TJC is disproportionately higher than the SJC in RA: (1) comorbid pain amplification/FMS is a likely comorbidity, (2) biological RA disease activity, measured as the SJC and CRP/ESR, may be lower than

indicated by the DAS28 composite score, and (3) joint count discordance should initiate a search for depression or other comorbidities that contribute to pain.

Two other RA studies created clinical maneuvers by modification of the DAS-model indices. In the first, the models were changed by removing the TJC and PTGA and adding the PhGA [70]. This “objective” DAS, termed the M-DAS, correlated better than the original DAS model with longitudinal magnetic resonance imaging (MRI) and radiographic outcome, providing better construct validity.

An alternative modification, DAS28-P, was created to reflect the proportion of the DAS28 derived from the PtGA and TJC [71]. This “subjective” index model correlated with higher articular and nonarticular pain pressure thresholds, fatigue, poorer mental health, and most importantly, the presence of FMS.

Another instrument that has been specifically designed to recognize FMS alone or as a comorbid condition is the Polysymptomatic Distress Score (PSD) [83]. This instrument incorporates questions about pain and core symptoms of FMS, and has been demonstrated to measure comorbid FMS prevalence and severity in RA [84].

In summary, both comorbid FMS and depression disproportionately inflate symptoms of pain and fatigue which, in turn, amplify PtGA and other subjective patient-report-only indices. These disproportionately higher subjective components then raise the total score of the composite index, falsely indicating higher biological disease. Biological disease activity is not worsened by comorbid FMS; it is only the measures, the ratings, that are obfuscated by FMS.

1.3.2. Remedies

One appropriate approach to the comorbid FMS problem in all of these diseases might be to construct two separate indices: one comprised of symptoms that arise from patient perceptions of pain, distress, and fatigue (PtGA, TJC, number of enthesitis sites, disability) and the other measures of objective inflammatory burden (acute phase reactants, SJC) and target organ damage. If these two separate indices are discordant, those symptoms and signs of FMS or autoimmune biological disease activity are treated separately and differently. Treatments for FMS and psychological disorders versus biological disease activity are distinctly different. This strategy should limit potential inappropriate over-treatment of the primary disease and provide better control of pain, distress, and fatigue, factors that are not necessarily intrinsically related to biological disease activity.

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None

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classification criteria for SLE. Associations: 19.6% with FMS with SLE disease activity, damage, fibromyalgia and depression and with poor HRQOL in this sample of Mexican SLE patients

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with both FM and SLE/FM-like manifestations was a self-reported history of anxiety or affective disorder ($P = 0.0237$, $OR = 4.6$ and $P = 0.0068$, $OR = 3.4$, respectively). Poorer self-reported physical functioning was associated with the SLE/FM-like phenotype ($P = 0.0443$, $OR = 0.96$). Clinical measures of disease activity, disease damage, specific organ dysfunction, sociodemographic factors and serologic features were not correlated with FMS in this early SLE cohort

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Disease Activity Index (CDAI) essentially replicated the M-DAS28 findings. The TJC and PtGA demonstrate poor construct validity, which diminished the validity of DAS28. According to the authors, “These findings speak to the subjectivity of the TJC28 and the patient global assessment, each of which can be high in subjects with relatively low levels of inflammation.”

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- [84] Wolfe F, Michaud K, Busch RE, et al. Polysymptomatic distress in patients with rheumatoid arthritis: Understanding disproportionate response and its spectrum. *Arthritis Care Research*. 2014;**66**:1465-1471. In a very important paper, Wolfe and coworkers analyzed 300 RA patients prior to therapy using the PSD scale. Among those RA patients, 123 (41%) had widespread pain and 61 (20.3%) met 2010 Preliminary Criteria for FMS. As the PSD score increased, all variables; CDAI, and individual composite measures, as well as pain, Health Assessment Questionnaire-II (HAQ-II), and the Patient Activity Scale-II (PAS-II) also increased. This increase was most pronounced in the more “subjective” measures including pain, TJC, PtGA, HAQ-II and PAS-II. Even “objective” variables, including PhGA and the SJC were increased, but less dramatically. Alternatively, low PSD scores were associated with discordantly lower values. The authors concluded that, “These findings indicate that DAS model composite index disease activity measures have low precision.” The authors further opined that, “These data suggest a certain futility in using a single composite measure to evaluate RA illness. Inflammation and joint damage are just that; they are not pain or suffering or tender joints

