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Is Fibromyalgia a Variant of Sjögren's Syndrome?

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Abstract

Although fibromyalgia syndrome has previously been shown not to turn into an autoimmune disease the issue remains that such patients may be difficult to differentiate from those with mild and early connective tissue disease, especially Sjögren syndrome. All the more as general physicians rarely ask for the tests required to insure the diagnosis of this disease.

Keywords: Fibromyalgia syndrome; B-cell; Scintigraphy; Sialography; Schirmer's test; Keratoconjunctivitis

Mini Review

Usually the fibromyalgia syndrome (FMS), a moot situation, reminds of a rheumatologic illness. So much so that some of these patients cannot be distinguished from those with a newly-beginning connective tissue disease (CTD). It follows that, when in doubt, careful questioning and physical examination must be completed by a biological check-up, to make the diagnosis feasible. In this regard, note that anti-nuclear antibodies (ANA) are common in CTD, above all systemic lupus erythematosus (SLE), and to a lower extent Sjögren's syndrome (SS). Intriguingly, some FMS patients present with, not only ANA, but also a clinical pattern of SLE at the start [1]. Even worse, other cases, though testing negative for autoantibodies (Ab), look like SS. Caution should thus be exercised with regard to the search for moderate symptoms. Representative examples will be analyzed below.

An attractive candidate to fit with FMS turns out to be SS. This is a chronic auto-immune disease in which the exocrine glands become sites of intense immunologic ac-tivity, leading to tissue damage that manifests as mucosal dry eyes, i.e. keratoconjunctivitis sicca, and dry mouth, i.e. xerostomia. This syndrome occurs, either alone as primary SS, or on a background of another CTD, such as SLE or rheumatoid arthritis (RA). The prevalence of SS in RA depends on the patient population, the tools for diag-nosis, and the disease criteria. There, SS has been associated with severity, and a higher risk of developing lymphoma.

The diagnosis of SS takes up a challenge, so that the American European Consensus Group in 2002, as well as the American College of Rheumatology in 2012, request minor salivary gland (SG) biopsy, Schirmer's test, ocular staining, sialography, salivary flow and scintigraphy, to substantiate their classification criteria. Such tests are invasive, expensive, possibly painful, or simply unavailable. With regard to the auto Ab, such as rheumatoid factor or anti-SSA/SSB Ab, the trouble is that, to be of any help, they need to test positive. Conversely, the anticitrullinated peptide Ab, despite being a hallmark for RA, is encountered in 33% of the pSS patients. This is the reason why the SG ultrasonography and blood B-cell subset profile have been recently promo-ted to the rank of diagnostic tools. These new assays notwithstanding, the diagnosis of SS remains extremely difficult. After all, there is such a crucial need for relevant diagnostic criteria that pSS might be mistaken for FMS, and inversely. As an attempt to address this issue, memory B-cell aggregates have been identified in skin biopsies of pSS-suspect patients, and claimed to be diagnostic [2]. Unfortunately, we're dealing here with a quite sophisticated technique. Small-fiber polyneuropathy (SFPN) has also been found in the foot skin biopsy of patients with juvenile-onset widespread pain syndrome reminiscent of FMS. Interestingly, two of them proved to suffer from pSS. A biopsy from a 19-year white male patient showed that epidermal and dermal nerve fibers were reduced, and the diagnosis of SFPN confirmed by skin biopsy from his distal leg skin [3] In a preliminary electron microscopic study of the skin, myelinated Schwann cells were found to be ballooned in nine of 13 patients, whereas this was not the case in the unmyelinated Schwann cell sheaths, while myelinated nerve fibers looked sound. In the skin of FMS patients, one can observe unusual patterns of unmyelinated nerve fi-bers as well as associated Schwann cells [4].

Of interesting note, women with pSS complain of their sexual behavior, around the menopause, and indeed dyspareunia is significantly more frequent in them than in age-matched controls. The so-called female sexual function index could well be the relevant method to assess this possibility which has long been overlooked [5]. In the initial setting up of the FMS patient-reported symptoms [6], a one-page response form for SFPN has been designed, and evaluated in 179 individuals (there were 73% female and 92% Caucasian, aged 46.6±15.6 years, in the series). SFPN, mostly idiopathic, was demonstrated in 85 of them. Principal components analysis defined five clusters of symptoms of FMS. They were more severe in the participants with confirmed SFPN than in the remainder. Furthermore, the authors showed that, among symptoms, noteworthy were headache, sexual disturbance, fatigue, and ocular complains (dryness, light sensitivity, difficulty to focus) which is also seen in SS. Of note is that females (75%) and Caucasians (94%) predominated, again reminiscent of SS. At the end of the day, the relationships of FMS with SFPN, and with CTD, most notably SS, yields to the facts.

Interestingly, features of CTD are noticeable in patients FMS, possibly develop-ping latter on. For example, monitoring of 192 FMS patients and 80 pain-free healthy controls [7], supervised attributes of FMS, e.g. endless pain, and CTD, e.g. Raynaud's phenomenon (RP). ANA-positive patients were followed-up, on average, for 3.3 years. RP appeared in 9 % of the female patients, compared with 3% of the controls, whereas idiopathic subjective dryness of the mouth occurred in 12 % of the FMS patients and never in the controls. The frequency of features of other CTD than SS was similar in ANA-positive and ANA-negative patients. No CTD could be diagnosed in the patients seen once referred, or followed-up. ANA and evidence of CTD were equally frequent in FMS patients and healthy controls, with the exception of subjective dry mouth more frequent in the patients. Unfortunately, the SG biopsy was not done in these patients, so that the cause of dryness in a proportion of patients is unknown. That's the reason why we don't take the conclusion of Yunus that none of them suffered from SS. The rationale of another study, on a three-year period of time, was to ask the question as to whether low-titer ANA-positive FMS patients (12/137) develop CTD, more often than 12 age- and sex-matched ANA-negative FMS patients and 225 patients with osteoarthritis (OA), of whom 20 displayed ANA [8]. Patients who developed at least three criteria of CTD were further investigated. Fourteen of 20 FMS and 17 of 30 OA patients presented with at least three symptoms of CTD afterwards. On full assessment, one of the ANA-positive FMS patient met the criteria for SLE, one of the ANA-negative FMS patients met those for pSS, and one of the ANA-positive OA patients was next diagnosed as suffering from RA. This study suggests that, even at low titer, ANA may be a good predictor for the development of various CTD, including pSS.

Psychiatric disorders are frequently recorded in patients giving a history of juvenile FMS, and, conversely, physical complications are more severe in FMS patients who complain of mood problems than in those who do not. In other words, these disorders warrant to be identified and treated as soon as possible in patients with juvenile FMS [9]. A blind control study has also established that neurologic signs and symptoms are more frequent than normally in FMS, although the correlation between symptoms and signs was marginal [10]. Notable differences concerned photophobia (70 versus 6%), poor balance (63 versus 4%), weakness (58 versus 2%) and tingling in the arms and legs (54 versus 4%).Poor balance or coordination, tingling or weakness in the arms or legs and numbness in any part of the body correlated with appropriate neurologic examination findings in the FM group. Noteworthy is the work about evidence of Small-Fiber Polyneuropathy (SFPN) in unexplained juvenile-onset, widespread pain syndromes (5): 73% of these polyethnic patients were female and 68% of them chronically disabled. Some cases seemed to be immune-mediated to such an extent that immunotherapy proved to be efficient [3].

A nationwide retrospective cohort of pSS patients enabled [11] to watch for psychiatric disorders developing. There appeared that depression, anxiety and insomnia, all disorders affecting the quality of life, were more common in the patients than in the controls. In fact, such a variety of sleep disturbances have been described in pSS patients that there is a crucial need for polysomnography studies to confirm their night awakening and obstructive sleep apnea. These pSS patients with excessive daytime somnolence should, therefore, be examined in search for comorbid sleep disorders and treated accordingly [12]. In addition, pSS patients have been shown to complain of headache and display signal hyperintensities on brain magnetic resonance imaging [13].

A few cases of PSS following vaccine delivery and silicone exposure have been described [14]. Thus PSS may be another facet of the ASIA syndrome or Shoenfeld syndrome induced by adjuvants.This syndrome incorporates five immune mediated conditions all associated with previous exposure to various agents such as vaccines, silicone implants and several others. The emergence of this syndrome is associated with individual genetic predisposition and results from exposure to external or endogenous factors triggering auto-immunity in both animal models and humans via a variety of proposed mechanisms [15]. The five immune mediated conditions are as follows: the post vaccination phenomena, the macrophagic myofasciitis syndrome, the gulf war syndrome, siliconosis and the sick building syndrome. All these conditions share similar clinical manifestations including myalgia, myositis, arthralgia, neurological manifestations, dry mouth and cognitive alterations, fever and chronic fatigue syndrome.Another aspect related to ASIA as well as to PSS is the common presence of sleep disturbances that possibly contributes to the onset of fatigue in such patients.However the most important clinical symptoms (xerostomia, xerophthalmia) and biological signs (antinuclear antibodies, specially anti -SSA and anti SS-B, rheumatoid factor) and linkage with HLA are more frequent in PSS than in ASIA [14]. Similarly fibromyalgia might be a variant of PSS if we consider the clinical symptoms but the lack of antinuclear antibodies, rheumatoid factors, linkage with HLA, and the fact that, physicians rarely use tests included in the classification criteria to diagnose the disease [16] explain that if fibromyalgia might be a variant of PSS it remains an hypothesis.

In conclusion, FMS still is a nascent field with promising possibilities. Although FMS has previously been shown not to turn into an autoimmune disease [17], the issue remains that such patients may be difficult to differentiate from those with mild and early CTD, especially SS. All the more because general physicians rarely ask for the tests required to insure the diagnosis of this disease [16].

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