Chapter 5
Fibromyalgia

Marina de Tommaso and Luiz Paulo Queiroz

Abstract Fibromyalgia (FM) is a common and disabling syndrome, characterized by widespread pain, fatigue, sleep disorders, and other associated symptoms such as cognitive dysfunction, irritable bowel, and headache.

FM is highly prevalent both in migraineurs and in patients with tension-type headache. The mean prevalence of FM in migraine patients is 19.4 %.

This comorbidity characterizes prevalently patients with chronic tension-type headache and chronic migraine. Frequency of headache, anxiety, pericranial tenderness, sleep disorders, and low physical quality of life were indicated as the main symptoms predisposing to FM comorbidity.

The common mechanism concurring in migraine, tension-type headache, and fibromyalgia is a dysfunction of pain modulation with enhanced expression of central sensitization symptoms.

Little evidence is available about the therapeutic approach to this comorbidity, amitriptyline being the sole drug indicated in FM, migraine, and tension-type headache. Duloxetine and pregabalin, used for FM, have limited evidence of efficacy in migraine and tension-type headache, as well as topiramate, flunarizine, sodium valproate, and beta-blockers in FM.

Non-pharmacological treatment, provided by transcranial magnetic and electrical stimulation, as well as other approaches, such as physical exercise and cognitive-behavioral therapy, should be the best choices to be tested in such critical patients.

Keywords Fibromyalgia • Migraine • Tension-type headache • Central sensitization • Pharmacological and not pharmacological treatment

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5.1 Introduction

Fibromyalgia (FM) is a common and disabling syndrome, characterized by widespread pain, fatigue, sleep disorders, and other associated symptoms such as cognitive dysfunction, irritable bowel, and headache [1, 2]. The estimated prevalence in the general population is 4.2 % in females and 1.4 % in males (2.7 % in total population [2]). Diagnostic criteria for FM have changed in the last few years, from the ACR criteria published in 1990, defining FM as a chronic widespread pain including sleep disorders, fatigue, and positivity of at least 11 out of 18 tender points, to the most recent guidelines, which removed the tender point count criterion and emphasized the presence of associated symptoms and syndromes, including headache [3, 4]. In recent years, comorbidity between headache and FM has been reported in cohorts of primary headache or FM patients, all studies indicating this association as invalidating and worth full consideration in clinical management [5].

Recent evidence confirmed the involvement of both central and peripheral nervous system in the pathophysiology of this complex and still unexplained disorder, suggesting the presence of different FM phenotypes, some of these presenting with associated migraine [6].

In the present review, we will focalize on the diagnostic criteria for FM, prevalence of FM in primary headache, clinical features of primary headache patients presenting with diffuse pain, the pathophysiological hypothesis about this association, and main evidence and possible practical guidelines for clinical management and therapeutic approach.

5.2 Diagnosis of Fibromyalgia

The diagnosis of FM is eminently clinical, as there are no biomarkers (specific diagnostic tests or image findings) that confirm this disorder. The cardinal symptom of FM is chronic widespread pain (CWP), which is a manifestation of central nervous system sensitization. This hyperalgesic state is also evident by the presence of generalized tender point positivity. FM is, however, more than just a pain disorder; a constellation of associated symptoms may be present, including fatigue, sleep disturbances, difficulties with memory and concentration, irritable bowel syndrome, headache, and depression. The diagnosis of FM requires that organic diseases are not causing these symptoms.

In 1990, the American College of Rheumatology (ACR) published a set of criteria for the diagnosis of CWP and FM (ACR1990) [1]. The proposed criteria for FM were CWP in combination with tenderness in 11 or more of 18 specific tender point sites. CWP was defined as pain on the left and the right side of the body and pain above and below the waist. In 2010, the ACR introduced new preliminary diagnostic criteria that did not require tender point examination [3]. This would be more suitable for use by primary care physicians and nonspecialists, who may find it too

difficult to apply and to interpret tender point examination. This was also an impediment for doing large epidemiological studies on FM, as they required the examination of all CWP subjects by specialists. That is why an FM survey questionnaire was developed for epidemiological and clinical studies, published in 2011, modifying the ACR2010 criteria (ModACR2010) [4].

The ACR2010 consists of two scales: the widespread pain index (WPI) and the symptom severity scale (SSS). The ModACR2010 substituted the physicians' estimate of the extent of somatic symptoms by the sum of 6 specific self-reported symptoms and created a 0–31 FM symptom scale, by adding the WPI to the modified SSS (Table 5.1). The ACR2010 and the ModACR2010 reflect a conceptual change in the diagnosis of FM, from a predominantly pain syndrome to a multisymptom syndrome [7]. The ACR1990 criteria, however, are still valid and considered the "gold standard" for the diagnosis of FM in clinical practice.

In the Wolfe et al. 2011 publication [4], with an FM symptom scale score of ≥13, the sensitivity was 96.6 % and the specificity 91.8 %, allowing to differentiate FM from other rheumatologic diseases, such as systemic lupus erythematosus, rheumatoid arthritis, and osteoarthritis, in 93.0 %. In a validation study of the ModACR2010 criteria, in 2014, Bennett at al. [8] reported a sensitivity of 83 %, a specificity of 67 %, and a correct classification of 74 %.

The evaluation of patients with probable FM comprises a complete physical examination, including palpation of tender points and a neurological examination, and ordering some tests, to exclude underling diseases that could be the cause of the FM symptoms. With respect to "routine" laboratory tests, they should be limited to a complete blood count, routine serum chemistries, thyroid-stimulating hormone,

Table 5.1 Modified 2010 American College of Rheumatology diagnostic criteria [3]

1. *Widespread pain index (WPI):* Note the number of areas in which the patient has had pain over the last week. In how many areas has the patient had pain? Score will be between 0 and 19
Left shoulder girdle, right shoulder girdle, left upper arm, right upper arm, left lower arm, right lower arm, left hip (buttock, trochanter), right hip, left upper leg, right upper leg, left lower leg, right lower leg, left jaw, right jaw, chest, abdomen, upper back, lower back, neck
2. *Symptom severity score:* fatigue, waking unrefreshed, cognitive symptoms
For each of these 3 symptoms, indicate the level of severity over the past week using the following scale:
0 = no problem; 1 = slight or mild problems, generally mild or intermittent; 2 = moderate, considerable problems, often present and/or at a moderate level; 3 = severe, pervasive, continuous, life-disturbing problems
The symptom severity score is the sum of the severity of the 3 symptoms (fatigue, waking unrefreshed, and cognitive symptoms) plus the sum of the number of the following symptoms occurring during the previous 6 months: headaches, pain or cramps in lower abdomen, and depression (0–3). The final score is between 0 and 12

The diagnostic criteria for FM are satisfied if the following three conditions are met

1. The WPI is ≥7 and the SSS ≥5; or the WPI is 3–6 and the SSS ≥9
2. Symptoms have been present at a similar level for at least 3 months
3. The patient does not have a disorder that would otherwise explain the pain

and erythrocyte sedimentation rate and/or C-reactive protein [9]. Other tests may be ordered, depending on diagnostic hypothesis.

The main differential diagnoses of FM are rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, Sjögren syndrome, polymyalgia rheumatica, myofascial pain, myosites, myopathies, peripheral neuropathies, multiple sclerosis, entrapment syndromes, multiple myeloma, occult malignancy, hypothyroidism, adrenal dysfunction, systemic inflammation or infection, non-icteric hepatitis, Lyme disease, and anemia [9, 10].

5.3 Prevalence of Fibromyalgia in Primary Headache

The prevalence of FM has been evaluated in many studies around the world. The mean prevalence in the general population is 2.7 % (4.1 % in female and 1.4 % in male), with a female-to-male ratio of 3:1 [2]. In 2015, however, in a prevalence study comparing the three ACR criteria [1, 3, 4], Jones et al. [7] showed that FM prevalence rates vary with the different sets of classification criteria applied, being higher with the ModACR2010. In population studies, the mean 1-year prevalence of headache in general is 46 %, migraine 11 %, and tension-type headache (TTH) 42 % [11].

Some studies have estimated the prevalence of FM in patients with primary headache, especially migraine. The prevalence rates of FM in some primary headaches are shown in Table 5.2. FM is highly prevalent, both in migraineurs and in patients with TTH. The mean prevalence of FM in migraine patients in these nine studies is 19.4 % (Table 5.2).

The prevalence of headache in patients with FM has also been estimated. Marcus, Bernstein, and Rudy [21] reported that 76 % of FM patients complained of headache; 63 % of them had migraines. Vij et al. [22] found 55.8 % of migraine in FM sufferers.

5.4 Clinical Features of Headache Patients with FM Comorbidity

Recent studies in primary headache patients sharing FM comorbidity indicated that this comorbidity involves prevalently chronic tension-type headache and chronic migraine. Many studies focused on selected groups of migraine patients [12, 13], whereas in studies conducted on larger cohorts of primary headache patients, only migraine and tension-type headache seemed prone to this association, while other forms of primary headache, as cluster headache, did not show a relevant presence of patients with diffuse pain [15]. Among primary headache patients, frequency of headache, anxiety, pericranial tenderness, sleep disorders, and low physical quality of life were indicated as the main symptoms predisposing to FM comorbidity [15].

Table 5.2 Prevalence of fibromyalgia in primary headache patients

Author	*N*	Type of headache	Prevalence of fibromyalgia, %	Setting	Country
Peres et al. [12]	101	Transformed migraine	35.6	Headache clinic	Brazil
Ifergane et al. [13]	92	Episodic migraine	17.4	Headache clinic	Israel
de Tommaso et al. [14]	217	Primary headaches	36.4	Headache center	Italy
		Migraine	28.5		
		TTH	59.0		
de Tommaso et al. [15]	849	Primary headaches	19.6	Pain clinic	Italy
		Migraine	17.8		
		TTH	35.1		
Tietjen et al. [16]	1,413	Episodic and chronic migraine	6.9	Headache clinic	USA
Tietjen et al. [17]	223	Migraine	11.7	Headache clinic	USA
Le et al. [18]	8,044	Migraine	1.2	Twins cohort	Denmark
Küçüksen et al. [19]	118	Migraine	31.4	Headache clinic	Turkey
Marcus et al. [20]	1,439	Migraine	24.3	Online	Internet

In other studies on episodic migraine, high headache frequency was not indicated as a common feature of FM comorbidity [19], but evaluations were conducted in smaller case series not including chronic migraine. Moreover, also in those episodic migraine groups, severe headache intensity typified FM patients [19]. Another still unclear point is the low representation of FM symptoms among patients with migraine with aura [15]. In most of the studies, groups of migraine with aura included few patients [13, 14, 16, 19] in agreement with the lower frequency of this type of migraine in the general population. The reason why we did not find FM comorbidity in pure migraine with aura patients may be the low frequency of attacks in those patients, while patients with associated migraine without aura or evolving into chronic form showed FM-associated symptoms [15]. This observation, though worth further assessment in lager series, may confirm that frequency of headache is an important factor predisposing to FM comorbidity in migraine and tension-type headache groups. In other headache syndromes, such as chronic forms of TACs, FM was rarely represented, suggesting that these headache types probably do not have pathophysiological factors predisposing to widespread pain. Features of sleep were also described in a recent study of our group [23], showing that the reduced quantity of sleep as assessed by the MOS scale was associated with frequent and invalidating migraine, though patients with FM comorbidity presented with a more complex sleep disturbance, including deterioration of sleep quality and severe sleep disorders.

The general impression emerging from these studies is that the identification of features of FM comorbidity in primary headache patients includes the assessment of headache frequency, pericranial tenderness, quality of life, anxiety scores, and sleep features, which may be easily obtained in a routine clinical examination, as detailed below.

5.5 Pathophysiology of Fibromyalgia Comorbidity

The common mechanism concurring in migraine, tension-type headache, and fibromyalgia is a dysfunction of pain modulation with enhanced expression of central sensitization symptoms [24, 25].

Sensitization is a physiological phenomenon of the sensory system, which supports a progressive amplification of sensory neuron activation under repetitive stimulation, favoring the development of memory against potentially dangerous events by neuroplastic changes enabling a prompt defensive response. This phenomenon develops at both peripheral and central levels, given that increased excitability occurs in single neurons and at synaptic level. In neuropathic pain, where a lesion occurs at peripheral or central level [26], increased excitability of sensory neurons has a compensatory function and is determined as soon as the neuronal tissue is damaged. The natural evolution of any kind of persisting noxious stimulation leads to the progressive increase in sensory sensitization, contrasted by the modulation of the descending control, which is very complex and finalized to the adaptation of the subjective sufferance to the general context, cognitive and emotional status, and cultural trends [27]. In addition, brain structural or functional changes may influence the outcome of the descending modulation [27]. Allodynia, which determines an innocuous tactile and mechanoreceptive stimulus to be perceived as painful, is a clinical sign of central sensitization, indicating a change in the function of second-order wide-range sensory neurons in spinal cord and trigeminal nucleus. This symptom is present in both migraine and FM. Since many years, studies by Burstein group [28] ascertained an early development of allodynia during migraine attack, causing the skin and muscles to become painful in the pericranial and even somatic level. The spreading of pain outside the pericranial sites indicates sensitization at third-order thalamic-sensory neuron level [29]. In tension-type headache, pericranial tenderness is initially subtended by different causes, as postural problems, but symptoms persist for a central dysmodulation, which does not inhibit but rather enhances primary and secondary nociceptive neurons firing and the consequent muscular activation [30]. So far, allodynia and pericranial tenderness are symptoms of central sensitization which can predispose primary headache patients to diffuse somatic pain. In fact, in FM, pain at tender points is evoked by an innocuous mechanic stimulation and is provoked by sensitization of second-order nociceptive neurons in the spinal cord [25]. Migraine and FM are characterized by a predisposition to central sensitization as suggested by neurophysiological evidence. In fact, habituation of the sensory system, which is a physiological phenomenon occurring during repetitive stimulation to contrast the progressive increase of neuronal activation, is lacking in both migraine and FM syndrome, with special regard to nociceptive input processing [6, 31, 32]. New evidence about an involvement of the peripheral nervous system in the pathogenesis of pain in FM is opening a new scenario on this very complex syndrome and associated conditions. Skin biopsy findings suggested a dysfunction of small myelinated and unmyelinated afferents, which may be a phenotypical feature peculiar for FM [33, 34].

A neuronal dysfunction at both central and peripheral level in FM may thus be idiopathic and probably genetically determined. Complex and largely unexplored genetic disorders involving ionic channels may support both central dysfunction with associated clinical conditions as migraine and peripheral nerve involvement with a peculiar clinical phenotype of small fiber neuropathy [33, 34].

5.6 Possible Therapeutic Approach to Migraine and Tension-Type Headache Patients with FM Comorbidity

In migraine and tension-type headache patients, a correct symptomatic treatment may contribute to a reduction of the intensity and duration of the single episode, slowing the development of central sensitization. However, no study is available about the best symptomatic approach to prevent central sensitization. In migraine attacks, triptans may exert a modulation of 5HT receptors at the level of the peripheral trigeminal afferents, with a modulation of nociceptive inputs at central level [35]. Also the calcitonin gene-related peptide (CGRP), which is a neurotransmitter involved in sterile inflammation and trigeminal activation during migraine attack, is specifically inhibited by triptans [36]. However, no evidence is available regarding a possible protective effect of triptans on the development of central sensitization and its possible persistence outside the migraine attack. The timely interruption of a migraine attack may stop the evolution of central sensitization, so triptans may be the best choice, provided their early assumption. Few studies are available on the association between FM comorbidity and analgesic overuse, which contributes to the development of chronic migraine. Medication overuse was observed in only 8 % of 76 FM patients with migraine [20], but there is no sufficient evidence about the risk connected to an early symptomatic treatment in favoring drug abuse and headache worsening in patients with diffuse somatic pain. In regard to preventive treatment for migraine and tension-type headache, in patients with associated symptoms of FM, amitriptyline is the sole drug indicated in all of these conditions [24]. Duloxetine and pregabalin, used for FM, have limited evidence of efficacy in migraine and tension-type headache [5, 37], as well as topiramate, flunarizine, sodium valproate, and beta-blockers in FM [5]. Botulin toxin is a treatment of proven efficacy for chronic migraine [38] and symptoms of central sensitization [39]. Despite the lack of studies assessing the effects on associated FM, evidence of efficacy in FM is scarce. Cannabinoids may be a new opportunity for chronic migraine and FM, although recent meta-analyses indicated insufficient evidence of efficacy for management of chronic diffuse musculoskeletal pain [40] and migraine [41], even though the treatment is promising and worth confirmation and further evaluation. Transcranial magnetic and direct electric modulation of motor cortex have shown efficacy in FM, with a possibility to obtain long-lasting plastic changes of the nociceptive cortex [42–44]. Modulation of DLPF also seemed efficacious in controlling pain in FM patients [45, 46]. rTMS and TDCS efficacy was less studied in migraine [46–48], but interest in these non-pharmacological approaches is increasing [49]. An integrated and

individualized non-pharmacological approach is recommended in chronic headaches sharing FM. In FM, physical exercise and cognitive-behavioral therapy are first-line treatments, showing a high level of evidence [50]. Evidence is also growing in regard to a beneficial effect in chronic migraine [51].

In the treatment of migraine patients with associated FM, tai chi, yoga, meditation and mindfulness-based interventions, hypnosis or guided imagery, electromyogram biofeedback, and balneotherapy/hydrotherapy may be a choice also for diffuse pain, while qigong, acupuncture, chiropractic interventions, and electroencephalogram (EEG) biofeedback have shown low efficacy in FM [52].

5.7 Final Remarks

Fibromyalgia seems to be a relevant aspect in many patients suffering from primary headaches, potentially associated with increased invalidity. The standard clinical assessment of FM, according to the most recent criteria [3], together with the evaluation of pain at tender points [1], seems easy to perform and not significantly time consuming and useful in detecting complex patients, to be managed through an integrated therapeutic approach. Features of anxiety and depression as well as sleep disorders, allodynia, and pericranial tenderness are important factors predisposing to symptoms of diffuse pain, which can be evaluated in headache centers by standardized clinical scales [14]. Clinical assessment of the association between primary headaches, with special regard to migraine, and fibromyalgia, could also open up a new scenario on the genetic and environmental factors predisposing to these invalidating but still largely unexplained diseases.

Conflict of Interest The authors declare no conflict of interest.

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