Chapter 12
The Functional Syndromes as Fibromyalgia Comorbidities

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Introduction

Fibromyalgia (FM) is a condition characterized by chronic widespread pain (CWP) associated with sleeping and cognitive disorders, fatigue, and many other symptoms which alter the quality of life [1].

Its diagnosis can be difficult due to the unavailability of specific diagnostic markers, and the symptom of CWP can be also found in other conditions. For years, the American College of Rheumatology (ACR) classification criteria published in 1990 have been used in clinical practice. These criteria required the presence of CWP for at least three consecutive months on both sides and on the superior and inferior part of the body, in addition to the positivity of at least 11 out of 18 specific points on the body resulting tender on palpation [2]. It is clear how the ACR 1990 criteria were focused only on the concept of peripherical pain [3].

The most recent ACR 2010 classification criteria define CWP as a condition associated with other systemic and somatic symptoms such as fatigue, sleeping, and cognitive disorders, and require the use of the widespread pain index (WPI), the evaluation of the number of painful body areas, the assessment of the somatic symptoms, and a somatic symptoms scale to evaluate the severity of these symptoms, in particular with regard to fatigue, sleeping, and cognitive alterations [4, 5].

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J. N. Ablin, Y. Shoenfeld (eds.), *Fibromyalgia Syndrome*,
https://doi.org/10.1007/978-3-030-78638-0_12

Therefore, these ACR 2010 criteria switch from the concept of FM as a "peripheral pain-defined disease" to a "systemic symptom-based disease" [3].

The formulation of new classification criteria is based on the concept that the fibromyalgia syndrome (FMS) is not only a condition characterized by peripheral chronic pain but also a more complex clinical condition. If on the one hand the ACR 1990 classification criteria risked to underestimate its diagnosis, on the other hand the new criteria conversely risk to overestimate it, defining as FM also other conditions included within the functional somatic syndromes (FSS) [6]. However, FMS itself belongs to the wide category of FSS with whom frequently is associated and shares part of the etiopathogenetic hypotheses. Some authors also consider FMS as the "whole-body variant" of FSS [6].

FSS are clinical conditions where the typical symptoms of each syndrome are always accompanied by chronic pain. Amongst them, in addition to FM, there is the irritable bowel syndrome (IBS), chronic fatigue syndrome (CFS), vulvodynia, interstitial cystitis, chronic migraine, temporomandibular disorder, chronic lower back pain, chronic pelvic pain and all those conditions characterized by the presence of not clinically justifiable chronic pain. In fact, in this context pain is not supported by clinical or laboratory abnormalities, peripheral tissue alterations, or alterations of those peripheral nerves involving the body areas where the patient reports pain [7].

However, pain is not the only key symptom they have in common, and other symptoms are fatigue, sleeping disorders, cognitive problems, physical dysfunction, and affective disorders (i.e., anxiety, anger, depression) [8].

Moreover, several disorders belonging to FSS are frequently associated with each other in the same individual, and some authors define these as "chronic overlapping pain conditions" (COPCs)" [8, 9].

FMS, in addition to be frequently associated with other FSS and sharing some of their characteristics, also shares with them several etiopathogenetic hypotheses, including the concept of central sensitization. Some authors, such as Yunus, prefer the definition "central sensitivity syndromes" (CSSs), underlining the pathogenetic role undertaken by "central sensitization" [10] a condition which has been operationally defined as heightened generalized pain sensitivity due to pathological nociceptive processing within the central nervous system (CNS). The concept that CSSs are associated with FMS is based on the fact that they: (a) cluster in the same patient groups more frequently than in an appropriate control group; (b) share many clinical features; (c) are not associated with microscopic or macroscopic tissue damage; (d) respond to a similar group of centrally acting medications; and (e) share similar central and neuroendocrine alterations.

However, although central sensitization appears to have a key role as a pathogenetic mechanism, it does not seem to be the only one involved.

Pathogenesis

From a pathogenetic point of view, many authors justify the occurrence of FSS through the biopsychosocial model [8], where multiple generic factors, if associated with environmental exposures (such as injuries, infections, physical and

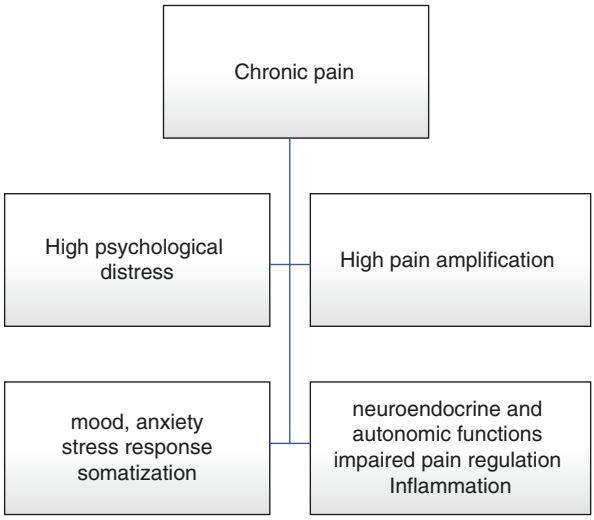

Fig. 12.1 Chronic pain and risk factors

psychological trauma), increase the susceptibility to FFS through heightened sensitization to pain and/or through impaired psychological vulnerability [7, 8, 11] (Fig. 12.1).

Genetic Predisposition

Pain and cognitive and affective responses associated with it are regulated by physiological processes. Subjects developing a pain hypersensitivity mechanism and having a psychosocial vulnerability to pain itself appear to have a genetic predisposition. This predisposition would be determined by polymorphisms affecting genes involved in the synthesis of proteins responsible for regulating pain and the affective response connected to it. When this genetic predisposition interacts with environmental factors such as physical or emotional stress, leads to the phenotype that is vulnerable to the development of FSS.

Examples of genes involved in pain sensitivity include the adrenergic receptor β2 [12], catechol-O-methyltransferase [13–15], dopamine D4 receptor [16], guanosine-5′-triphosphate cyclohydrolase 1 [17], μ-opioid receptor [18, 19], and serotonin transporter [20]. However, these genes are also involved in those mechanisms regulating the emotional sphere. In fact, certain polymorphisms affecting them are also associated with a greater risk for the development of psychological disorders such as depression [12, 21, 22], anxiety [12, 23], and stress response [24–26].

This suggests that the emotional sphere and the mechanism of pain transmission share some mechanisms and this would explain the association that is often found between psychological/psychiatric disorders and chronic pain syndromes. For example, the single nucleotide polymorphism of codon 158 (Val ^{158}Met) of the catechol-O-methyltransferase gene is associated with pain amplification [27], risk

of developing TMD [14] and FM [28], as well as to develop certain affective disorders [29]. The common polymorphisms in the serotonin transporter gene promoter are associated with depression, susceptibility to stress [30], anxiety [31], somatization, and risk of TMD [32].

However, it should be stressed that a variation of a single gene is not considered necessary or sufficient to determine a genetic predisposition for the development of one or more FSS, but necessary is the association of polymorphisms affecting multiple genes [8].

Psychosocial Factors

The increased psychosocial vulnerability represents an additional risk factor for the development of FSS. In fact, many patients tend to have anxiety disorders, depression, and increased susceptibility to stress [8]. Patients with Fibromyalgia syndrome have a higher prevalence of psychiatric disorders than the general population, such as anxiety and mood disorders. This increased prevalence has been also found in other syndromes associated with chronic pain [33]. A 2004 study observed, in fibromyalgia patients with anxiety disorder, a strong association with symptoms attributable to post-traumatic stress syndrome and sexual or physical abuse, while fibromyalgia patients with mood disorders (first of all depression), showed affective disorders [33].

Psychosocial factors also seem to be involved in other FSS, such as irritable bowel syndrome [34], chronic low back pain [35], or temporomandibular syndrome [36]. In fact, there is evidence in favor of a link between the experience of abuse in childhood and the development of conditions characterized by chronic pain [37–41].

In this context, the so-called "sensitization hypothesis" was formulated. According to this hypothesis, individuals who experienced traumatic experiences in childhood, subsequently present more intense responses to stress factors [42], partly also due to a dysregulation of the Hypothalamic–pituitary–adrenal (HPA) axis in response to stress [43]. Furthermore, childhood adversity is assumed to be related to "pro-inflammatory tendencies," a condition that continues to sustain itself throughout life, representing a risk factor for the development of chronic painful conditions [44, 45]. Childhood adversity is also associated with the manifestation in adulthood of cognitive disorders of various extent [46, 47]. For instance, abuse by parental figures is associated with a state of hypervigilance which can favor the development of states of cognitive distortions, altering in turn the pain sensitivity threshold [48, 49].

Environmental Factors

Patients who develop FSS generally report an acute event during their lives preceding the onset of a chronic pain syndrome. Physical stress such as surgeries, physical injuries, or road accidents have been described as precipitating factors in patients

with FM [50]. In patients with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME), the most frequent acute events preceding the onset of CFS/ME are: infectious episodes (64%) mainly affecting the respiratory tract and more frequently caused by herpes virus and parvovirus B19, accidents (39%) and exposure to environmental toxins (20%) [51].

As previously mentioned, an association between emotional trauma caused by psychological, physical, or sexual abuse and the risk of developing FSS has been also observed. A meta-analysis reported a risk 2.7 higher of developing an FSS in subjects who underwent emotional trauma compared to subjects who did not suffer from it [52].

Increased Sensitisation to Pain

The increased sensitization to pain seems to be a distinguishing feature of FSS [10]. However, it is not clear yet whether it represents a determining factor in the onset of one of the FSS or if it is a maintenance mechanism consolidating the chronic and persistent perception of the painful experience [8]. The results of a study aimed at assessing chronic pain in patients who develop a temporomandibular disorder suggest that the amplification of pain plays a more relevant role in maintenance and chronicization than in the onset of FSS [53]. Central sensitization (CS) manifests with the presence of hypersensitization of the subject to various types of stimuli, both harmful (such as pressure and heat) and non-harmful, such as touch [54]. In other words, the subject presents hyperalgesia (excessive sensitivity to normally painful stimuli, such as pressure), allodynia (pain to usually painless stimuli, such as touch), spatial extension of pain (pain is felt in larger areas than the terminations nerves involved in the stimulus), temporal extension (the painful impulse is transmitted longer), and finally the persistence of unpleasant sensations such as numbness or tingling after the painful stimulus has been removed [10].

This situation is determined by an abnormal and intense “enhancement” of pain caused by the central nervous system (CNS) [54].

Physiologically, the presence of harmful stimuli determines the activation of peripheral nociceptors, expressed both viscerally and somatically [55]. The generated nociceptive signal reaches the dorsal horns of the spinal cord via the A-delta and C fibers, where the second-order neurons are present. The A-delta fibers transmit acute, pungent, and well-localized pain (primary pain), while the slower C fibers transmit a less localizable and deeper pain sensation (secondary pain), and are involved in chronic pain. Second-order neurons are of two types: nociceptive specific (NS), which respond specifically to painful stimuli, and those with wide dynamic range (WDR: Wide Dynamic Range), which respond to stimuli of varying intensity. In fact, the latter integrates impulses from A-delta and C fibers, but also from A-beta fibers which transmit non-nociceptive impulses [54]. In the presence of intense activation of nociceptive fibers, the surrounding non-nociceptive fibers can also be activated, which are usually stimulated by the A-delta fibers. In this way, a painless stimulus, such as touch, is perceived as a painful sensation [10].

Second-order neurons transmit the stimulus to the thalamus, hypothalamus, limbic system, and finally to the somatosensory cortex. These supra-spinal structures are involved in the elaboration of the different dimensions of pain such as sensory, evaluative, and affective dimensions [55–57].

Once activated, the nociceptive C fibers, in correspondence with their terminal afferent portion in the dorsal horns of the medulla, release a series of neurotransmitters/neuromodulators such as substance P (SP), glutamate, and the nerve growth factor (NGF). These substances interact with receptors on post-synaptic second-order neurons, leading to their activation. For example, SP activates the Neurokinin-1 (NK-1) receptor, glutamate activates the *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionate (AMPA), and metabotropic glutamine (mGlu) receptors, while NFG activates the tyrosine kinase B receptor.

Some of these substances and receptors seem to be involved in the CS mechanism. Amongst these, SP is believed to play an important role. In the presence of CS, SP, which is involved in the mechanisms of transmission and amplification of pain, recruits also silent receptor structures present on second-order neurons, leading to their hyperexcitability. In addition, SP can spread causing the activation of other adjacent neurons, leading to an anatomical expansion of the painful area [55–57]. Therefore, the excessive release of SP and other neurotransmitters such as NFG and glutamate in the synaptic space determines the hyperexcitability of second-order neurons [57]. This neuronal hyperexcitability is at first functional, with time causing neuroplasticity, and as a final result leading to an excessive amplification of peripheral stimuli. Consequently, a harmless stimulus such as touch is perceived as pain. Amongst the post-synaptic receptors, those mainly involved in these mechanisms seem to be NMDA [57].

Dopamine also appears to play a role in amplifying nociception in CS. It has two opposite functions in the context of neuronal excitability: On the one hand, it has an excitatory effect if binding to D1-like receptor structures, whereas, on the other hand, it has an inhibitory effect if binding to D2-like receptors. To reinforce the hypothesis of a role of dopamine in CS, the results of a double-blind study reports that piraxone (D2-like receptor agonist drug) has shown positive effects in fibromyalgia patients [58].

In addition to the hyperexcitability of the ascending pathways responsible for the transmission and processing of pain, an inhibitory mechanism of the pain inhibitory descending pathways also appears to have a role, which is the physiological task of modulating and attenuating the physiological stimulus [59].

In summary, in the presence of CS, there is a general hyperexcitation of the CNS neurons responsible for the transport of peripheral stimuli. This general hyperexcitation can also explain hypersensitivity to many environmental (i.e., noise, weather, stress) and chemical (i.e., pesticides and drugs) stimuli. With time, due to neuroplasticity phenomena, CS becomes self-sufficient without further stimuli, and it is probably accentuated by the presence of chronic diseases [54]. Hence, initially harmful stimuli may increase neuronal sensitivity to a level where further stimuli, even non-harmful, may be sufficient to support and perpetuate hyperalgesia and

allodynia [60, 61]. The affective dimension of pain, such as unpleasantness and emotional reactions, is mediated by spinal pathways toward the limbic structures, the medial thalamic nuclei, and by the anterior insular cortex, the anterior cingulate cortex, and the somatosensory cortical areas [62].

Fibromyalgia and Functional Syndromes

The association between fibromyalgia syndrome and other FSS, or in general the mutual association between them, was observed as early as 1981 [63]. Below we analyze the association of fibromyalgia with the main FSS most often associated with this syndrome (Table 12.1).

Fibromyalgia and Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is a fairly frequent and widely spread condition characterized by abdominal pain associated with alterations of the bowel function which cannot be justified by anatomical, structural, or metabolic alterations. Nonspecific symptoms such as nausea, bloating, flatulence, and fecal urgency are often present [64, 65]. The diagnosis is made when the Rome IV criteria for the diagnosis and treatment of functional gastrointestinal disorders are met. These define IBS as a condition characterized by recurrent abdominal pain (at least one day a week), present for at least 3 months, and related to at least 2 of the 3 following conditions: defecation, alterations in the frequency of the bowel function, alterations in the consistency of feces [66, 67].

The pathogenetic mechanism leading to IBS is not entirely clear, although the hypothesis of a dysregulation of the intestine–brain axis seems to be the most favored [68]. The dysregulation is probably multifactorial, with multiple elements contributing to the development of IBS: impaired intestinal motility, visceral hypersensitivity, alterations of the intestinal mucosa and of immunological functions, changes in the intestinal microbiota, and altered processing of the intestinal sensory input by the CNS [69, 70].

Numerous studies have shown an increased prevalence of IBD in patients with fibromyalgia [71, 72]. According to these results, other studies have observed a higher frequency of fibromyalgia in patients with IBD [73, 74].

Whitehead et al. reported a prevalence of fibromyalgia in patients with IBD of 32.5% (range: 28–65%) and a prevalence of IBS in patients with fibromyalgia syndrome of 48% (range: 32–77%) [75].

In a study conducted in Oslo aimed at studying a group of patients who reported food hypersensitivity, most of them presented with IBD, and extra-gastrointestinal symptoms indicative of fibromyalgia syndrome were found in 71% of these patients [72].

Table 12.1 Fibromyalgia and functional syndromes

Functional syndrome	Clinical picture	Prevalence	Symptoms/conditions shared with FM	Risk factors
Irritable bowel syndrome (IBS)	Recurrent abdominal pain (at least 1 day/week), for at least 3 months and related to at least 2 of the following conditions: defecation, change in the frequency of stool, alterations in the consistency of stool	From 32 to 77%	Sleep disorders, chronic fatigue, anxiety and/or depression as comorbidities	Stressful or traumatic events
Chronic pelvic pain (CPP)	Non-cyclical pain, for at least 6 months, involving the pelvic region, the anterior abdominal wall below the navel, and posteriorly the lumbosacral region, with an extent of the pain such to alter the quality of life	From 12 to 65% of FM patients complain of CPP, 44% of FM patients report vulvodynia, 48% pelvic floor hypertonicity	Comorbidity with anxiety and/or depression	History of abuse
Painful bladder syndrome/interstitial cystitis (PBS/IC)	Chronic condition of pelvic pain, pressure, or discomfort perceived in the bladder and with at least one urinary symptom such as urinary urgency or increased urinary frequency	From 11 to 17% of patients with PBS/IC have FM	Urinary urgency (UP) and urinary frequency (UF) scores significantly higher in FM patients than in controls	Urinary infections; inflammatory or autoimmune processes; abnormalities of the bladder mucosa; urinary toxins; local neurological dysfunctions
Temporomandibular disorders	Pain or dysfunction of the masticatory muscles, temporomandibular joint (TMJ), and/or related structures	From 10 to 18.4%	Sleep disturbances, cognitive problems, gastrointestinal disorders, and diffuse myalgias	Genetic polymorphism; physical or emotional trauma
Chronic tension-type headache (CTTH)	CTTH: Headache on ≥15 days/month for >3 months with episodes lasting from 30 minutes to 7 days and at least 2 of the following 4 characteristics: bilateral location; pressing quality; mild/moderate intensity; not aggravated by routine physical activity		Low back pain	High intake of alcoholic beverages low level of education

Chronic migraine (CM)	CM: Headache on ≥15 days/month for >3 months with attacks lasting 4–72 hours and at least 2 of 4 characteristics: unilateral location; pulsating quality; moderate/severe pain intensity; aggravation by physical activity	Ranges from 11.7% prevalence of FM (ACR 1990 criteria) in patients with CM from 11% to 22% prevalence of FM (ACR 2010 criteria) much higher (69.9%) in patients with CM than in those with CTTH (25.7%)	Low back pain cutaneous allodynia in patients with CM there was an association with anxiety disorder, depression, and somatic symptoms more frequently than in patients with CTTH,	Smoking, obesity
Multiple chemical sensitivity (MCS)	Symptoms involving multiple organ systems caused by low levels of exposure to multiple chemically unrelated substances Symptoms improve when the chemical agents are removed	16.7% of patients with chronic fatigue syndrome (CSF) met the criteria for all the three conditions. CFS/MCS/FMS	Fatigue, muscle and joint pain, headache, cognitive impairment, gastrointestinal problems high levels of anxiety, and depressive symptoms	Substances causing skin irritation, fatigue, fevers, neurocognitive dysfunction
Myalgic encephalomyelitis/ chronic fatigue syndrome (ME/CFS)	Medically unexplained, new onset, disabling fatigue for at least 6 months, not relieved by rest and not resulting from overexertion and at least 4 symptoms as listed: sore throats; painful lymph nodes; muscle/joint pain; headaches; altered sleep; cognitive problems; post-exertional malaise of more than 24 h.	From 20 to70% of patients with FMS meet the criteria for CFS, 35–70% of those with CFS also have FMS	Pain fatigue sleep disorders irritable bowel syndrome chronic headaches cognitive impairment dizziness	Infections and physical and/or psychological stressors specific gene mutations

Slim et al. [76] in their work focused the attention on the gastrointestinal symptoms reported by fibromyalgia patients, observing a high incidence rate of IBD among patients with FMS. In a national prospective cohort study, Yang et al. [71] compared 33,729 patients with FMS and 134,915 controls. During the follow-up period from 2000 to 2011, they found an overall incidence of IBS higher in FM patients than in patients without FM (7.47 vs. 4.42 per 1000 person/year), with an index of crude risk of 1.69 (95% CI 1.59–1.79). After adjustment for age, sex, and comorbidities, FM was associated with a 1.54-fold increased risk of IBS.

FM and IBS share numerous aspects: a predominance in women, the association with sleep disorders, chronic fatigue, anxiety, and/or depression as comorbidities [77]. Both disorders alter the quality of life of the affected patients and represent a major health care cost. Their onset is often associated with stressful or traumatic events, and they have similar therapeutic schemes such as psychotherapy, cognitive-behavioral therapy, and the use of antidepressant drugs [77, 78]. Both FM and IBS are categorized within the "central sensitivity disorders" (preferred terminology by some to identify FSS), since in both cases the presence of CS is assumed. In the case of IBS, there is chronic visceral hyperalgesia, while in FM the chronic pain is somatic [76].

Their coexistence in the same individual can be explained by the fact that some visceral and somatic pain fibers affect the same areas at the level of the spinal cord and brain. For instance, the anterior cingulate cortex, which modulates the affective response and induces pain, receives both visceral and somatic inputs, and is believed to be an area involved in the pain processing of both disorders [77–79]. The insula and the somatosensory cortex also play an important role in the processing of pain in both FM and IBS [80]. Furthermore, in both syndromes, the attenuation of the pain inhibition mechanisms by the descending pathways is hypothesized [77]. Finally, both in patients with FM and in patients with IBS, a pronounced hyperalgesia at the lumbosacral level has been observed, which could also explain the increased thermal sensitivity and visceral hypersensitivity that has been observed in patients with IBS or FM plus IBS, compared to healthy controls [81]. Probably, the coexistence of visceral and somatic hyperalgesia at this level is due to an anatomical convergence of both somatic and visceral nociceptive fibers within a common pool of neurons at the level of the spinal cord [81].

Fibromyalgia and Chronic Pelvic Pain

Chronic pelvic pain (CPP) is a non-cyclical pain, lasting at least six months, involving the pelvic region, the anterior abdominal wall below the navel, and posteriorly the lumbosacral region, with an extent of the pain such to alter the quality of life of those affected [82]. In some cases, it can be associated with the coexistence of organic conditions with endometriosis and the presence of adhesions as the most frequent [83, 84]. However, after laparoscopic surgical treatment of these associated organic conditions (i.e., endometriosis), in 30–40% of cases, a resolution of the pain was not observed [85, 86], assuming independence from the presence or absence of

organic conditions, and considering them at most as triggering elements in the context of a multifactorial genesis. Conversely, in other cases, there is no association with organic pathologies [83]. Specifically, after laparoscopic evaluation of patients with CPP, no underlying causes could be identified in 30% of cases [84]. For this reason, CPP is considered to belong to the functional somatic syndromes, being not associated with damages or pathologies of the affected tissues, and often presenting hypersensitivity to pain [83]. It affects women more than man and is related to histories of sexual or physical abuse and to states of anxiety or depression [84]. Furthermore, as with other FSS, it can coexist in the same individual with other conditions of chronic pain, such as IBS, FM, temporomandibular syndrome, and migraine [82–84].

Fibromyalgia is frequently associated with chronic pelvic pain (CPP). Depending on the studies considered, from 12 to 65% of fibromyalgia patients complain of CPP [87, 88].

Furthermore, 44% of patients with FM report vulvodynia, and 48% of these present pelvic floor hypertonicity [89]. Women with both these conditions have a greater intensity of widespread chronic pain, and they are more prone to anxiety and depression disorders. Furthermore, FM in the presence of CPP has a more severe presentation than in patients with FM alone. Conversely, patients with CPP have a higher prevalence of fibromyalgia and other FSS [83]. CPP also shares some etiopathogenetic hypotheses with fibromyalgia and other FSS, including psychosocial factors, such as histories of abuse, anxiety disorders or depression, and the central sensitization hypothesis, triggered following an insult of various nature, but which persists even after the removal of this. In consideration of these etiopathogenetic similarities, according to some authors, CPP reflects a "visceral sensitization," and could be defined as "pelvic fibromyalgia" [90].

Fibromyalgia and Interstitial Cystitis/Painful Bladder Syndrome

Painful bladder syndrome/interstitial cystitis (PBS/IC) is defined by the European Society for the Study of Interstitial Cystitis as a "chronic condition of pelvic pain, pressure or discomfort perceived in the bladder and with at least one urinary symptom such as urinary urgency or increased urinary frequency" [91]. The presence of glomerulations or "Hunner's ulcers" are present in less than a third of the cases [92]. There is no precise estimate of its prevalence, but according to some studies, it affects 2% of the general population with a female–male ratio of 9:1 [91, 93]. PBS/IC is a condition frequently associated with other syndromes characterized by chronic regional or widespread pain including fibromyalgia, irritable bowel syndrome, migraine, and temporomandibular disorder [94]. Literature data have shown that 11–17% of patients with PBS/IC have FM. Nickel et al. reported the presence of FM in 17.7% of patients with PBS/CI compared with 2.6% of controls [95–97]. Hamed et al. evaluated the presence of symptoms related to the presence of PBS using the "Fibromyalgia Bladder Index (FBI)" in women with fibromyalgia [98]. The FBI presents 2 types of assessments: one aimed at assessing bladder pain and

urinary urgency (UP), and the other one at assessing urinary frequency and nocturia (FN). The mean UP score was significantly higher in the FM patient group (10.29 ± 5.61) than in controls (1.65 ± 2.65; $p = 0.001$). The FN score was also significantly higher in patients with FM (9.93 ± 5.37) compared to controls (2.95 ± 3.27, $p = 0.001$). Numerous etiological factors have been hypothesized as involved in the onset of PBS/IC, such as urinary infections, inflammatory or autoimmune processes, abnormalities of the bladder mucosa, the role of urinary toxins, or the presence of local neurological dysfunctions. However, to date, the actual etiopathogenetic mechanisms leading to the development of PBS/IC are largely unknown [99]. According to some authors, it could be considered a functional somatic syndrome or a manifestation of an FSS, also considering the frequency of association with other FSS, first of all, fibromyalgia and IBS [94, 100]. Even in this case, amongst the various pathogenetic mechanisms proposed, there is the development of central sensitization [97–100]. PBS/IC may be the result of a central sensitization in the lower spinal cord. This CS may also be triggered by other chronic pain syndromes unrelated to the bladder, which would initiate spinal sensitization with subsequent spatial expansion to the point that the bladder would also be perceived as a site of pain. Once the CS is triggered, also when the noxious stimulus is removed, the pain perceived in the organ persists, since even non-painful stimuli are perceived as such [99]. This may also explain why patients with PBS/IC have significant discomfort with very small bladder volumes compared to normal subjects, and why these patients still have pain after cystectomy [101, 102].

Fibromyalgia and Temporomandibular Disorders

The term "temporomandibular disorders" refers to a set of different clinical conditions affecting the masticatory muscles or the temporomandibular joint. These are mainly characterized by the presence of joint and muscle pain, and dysfunctions such as reduced motility or joint noises are also often associated, as well as earache, headache, dizziness, or tinnitus. TMDs can be of a congenital nature, resulting from neoplasms, inflammatory processes, or trauma. However, in a percentage of cases, an underlying organic cause is not recognized, thus defining this disorder as functional TMD. In this case, the etiology is still unknown, but a multifactorial genesis is hypothesized [103]. TMD is diagnosed when the "Research Diagnostic Criteria for Temporomandibular Disorders" (RDC/TMD) are met [104]. Functional TMD is considered an FSS [52], and as with other FSS, it is often associated with symptoms such as sleep disturbances, cognitive problems, gastrointestinal disorders, and diffuse myalgias, which alter the patient's quality of life, as well as tending to coexist with other functional chronic pain conditions [105]. Some epidemiological studies have shown a strong association between FM and TMD. It is estimated that 71–94% of fibromyalgia subjects have a TMD with a component of myofascial pain [106–108]. Conversely, when temporomandibular pain has an arthrogenic origin, the prevalence of TMD in fibromyalgia sufferers drops to 19% [109–111]. Amongst those patients diagnosed with TMD, the prevalence of FM ranges from 10 to 18.4%

[112–114]. As for the other FSSs, the functional temporomandibular disorder, especially if with a myofascial component, shares some etiopathogenetic hypotheses and risk factors recognized in FM, such as the association with some polymorphisms in genes encoding for molecules involved in the transmission of painful impulse and the emotional processing of this, as well as the association with physical or emotional trauma, or with the concept of central sensitization [105].

Fibromyalgia, Chronic Migraine, and Chronic Tension-Type Headache

Chronic migraine (CM) and chronic tension-type headache (CTTH) are both very common types of headache [115]. An increased prevalence of FM in patients with these types of headaches is a well-established fact in the literature [116, 117].

The prevalence of FM (diagnosed with the aid of the ACR 1990 criteria) amongst patients with migraine varies from 11% to 22% [117–119]. Furthermore, one study observed that the frequency of FM increases to 35.6% when the association with transformed migraine is evaluated (a term previously used to describe a form of CM) [119]. The frequency of FM is even higher in patients with chronic tension-type headache (CTTH) with values ranging from 35% to 59% [117, 120]. One study evaluated the prevalence of FM diagnosed by following the ACR 2010 criteria in patients with CM and CTTH. In this study, the prevalence of fibromyalgia was much higher (69.9%) in patients with CM than in those with CTTH (25.7%) [115]. It was also observed that in patients with CM more frequently than in patients with CTTH, there was an association with anxiety disorder, depression, and somatic symptoms. Conditions that, as previously stated, often coexist also in patients with FM [115]. FM also shares with CM and CTTH the pathogenetic hypothesis of central sensitization. In fact, it is believed that the cephalic allodynia reported by migraine patients may be caused by a central sensitization mechanism in the second-order neurons of the spinal trigeminal nucleus [121]. The trigeminal neurons are subjected to sensitization following the constant painful impulse transmitted by the perivascular meningeal painful fibers [122]. In addition to the cephalic level, the presence of chronic pain in extra-cephalic areas has also been reported by patients with CM, underlining that central sensitization in these patients can be widespread [115]. Furthermore, skin allodynia appears to be more severe in patients with CM than in those with recurrent CTTH [123].

Fibromyalgia and Multiple Chemical Sensitivity

Multiple chemical sensitivity (MCS) is a chronic condition that has been found in 6% of adults in California [124]. Its reproducible symptoms involving multiple organ systems are caused by low levels of exposure to multiple chemically unrelated substances and improve or resolve when the chemical agents are removed [125]. Chemical avoidance has been found to be effective in 93% of patients [126].

MCS is common in patients with CFS and/or FMS. In a sample of 33 Gulf War veterans with CFS, 42% had concurrent MCS and 6% concurrent FMS [127]. Brown and Jason [128] studied 114 men and women with CFS, finding that 43.9% of them met the criteria for CFS alone, 23.7% the criteria for CFS and MCS, 15.8% the criteria for CFS and FMS, and 16.7% the criteria for all the three conditions. The CFS/MCS/FMS patients were more disabled than those with CFS alone in terms of physical functioning, general health, and bodily pain, indicating that having more than one illness exacerbates disability beyond CFS alone.

Fibromyalgia and Chronic Fatigue Syndrome

Fatigue is a frequent symptom in the general population, being reported by up to 50% of the respondents to large-scale surveys [129, 130]. It is attributable to underlying systemic diseases such as diabetes, cardiopulmonary disease, or rheumatoid arthritis, but may also accompany psychiatric conditions such as depression, panic disorder, or somatization. When fatigue cannot be explained by a medical condition such as depression, cancer, infections, or inflammatory disorders, it may be due to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). In fact, a clinical diagnosis of ME/CFS can only be made when all the other possible etiologies of fatigue have been excluded [131–133]. Although considerable progress has been made, there is still no unifying construct concerning some of the major pathogenetic mechanisms of ME/CFS. Current research is investigating the involvement of the immune and adrenal systems, genetics, stress-related syndromes, and impaired neuropsychological functions. As many of the symptoms are the same as those of viral infections, some physicians have hypothesized a post-infectious etiology [134].

Genetic susceptibility is supported by the findings of one study showing that patients with exercise-induced CFS differently express certain genes that play a role in metabolism and immune responses [135], and another study has shown a correlation between specific gene mutations, ME/CFS, and some viral infections associated with CFS [136]. The fact that ME/CFS is often associated with depression has led many physicians to believe that it is a purely somatic illness [137], but there is no evidence supporting this conclusion. The risk of developing ME/CFS may be increased as much as six times by a childhood trauma, which may reduce resilience and also increase the risk of adrenal system dysfunction [138]. ME/CFS may be considered one of the central sensitivity syndromes (CSS) [54]. It is therefore possible that specific peripheral fatigue and pain pathways in ME/CFS patients are sensitized by still unknown mechanisms (infections and physical and/or psychological stressors) [139–141], continuous inputs from which maintaining the state of chronic fatigue and chronic widespread pain. Chronic fatigue syndrome (CFS) frequently overlaps with FMS [142], and therefore it is possible that the same patient may simultaneously meet the diagnostic criteria for more than one CSS. It has been estimated that between 20% and 70% of patients with FMS meet the criteria for

CFS and that 35–70% of those with CFS also have FMS [143]. Many people suffering from FMS have those symptoms generally observed in CFS. Patients who meet the criteria for both FMS and CFS have a worse overall health status [142].

Conclusions

It is known that FMS and dysfunctional syndromes may coexist:

- FMS is not a distinctive disease entity, but a complex spectrum of problems with frequently overlapping symptoms. It also substantially overlaps functional somatic syndromes.
- The symptoms of FMS vary from patient to patient, as does their severity.
- All patients with chronic widespread pain should be assessed for FMS on the basis of their medical history (including psychosocial factors) and TPs.

In conclusion, in patients suffering from widespread pain and fatigue, it is necessary to rule out the presence of any medical condition or disease that is known to cause these symptoms.

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