

Fibromyalgia and psychiatric disorders

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Abstract. Fibromyalgia (FM) is a common and polymorphic syndrome, characterized by long-lasting, widespread musculoskeletal pain, in the presence of 11 or more tender points located at specific anatomical sites. A heterogeneous series of disturbances, mainly involving autonomic, neuroendocrine and neuropsychic systems, is usually present. Even if subjective, the chronic psychophysical suffering state of FM adversely affects the patient's quality of life, performance and mood. Cognitive behavioural therapy and antidepressant drugs are useful in FM treatment, suggesting a close link between the syndrome and psychiatric, psychological and behavioural factors. Our aim was to evaluate the personality profiles of FM patients, as well as the aggregation and relationships between FM and psychiatric disorders (PD), reviewing the available evidences in current literature on this comorbidity. Personality variables associated with psychological vulnerability are frequent in FM patients. Personality disorders are rarely reported. Compared with controls, FM patients show a significantly higher prevalence of depressive and anxiety disorders, reported in 20-80% and 13-63.8% of cases, respectively. This high variability may depend on the psychosocial characteristics of patients, since most of the studies were performed on tertiary care consulting patients, however, even referring to the lower percentages, the occurrence of PD is significantly higher in FM subjects compared to the general population (7%). Moreover, elevated frequencies of PD have been detected in relatives of FM patients. The FM/PD aggregation suggests a common physiopathology, and alterations of neurotransmitter systems may constitute the shared underlying factor. (www.actabiomedica.it)

Key words: Fibromyalgia, personality profiles, personality disorders, psychiatric disorders, anxiety disorders, mood disorders, depression

Introduction

Fibromyalgia (FM) is a common and complex musculoskeletal disorder, characterized by widespread (i.e., in the axial skeleton, in the left and right sides of the body, above and below the waist) and long-lasting (i.e., present for at least 3 months) pain, in the presence of tender points (TPs) located at specific anatomical sites (Table 1) (1, 2). A heterogeneous series of other symptoms, including marked fatigue, stiffness, sleep disorders, cognitive disturbances, psychological distress, paresthesias, headache, genitourinary manifestations, irritable bowel syndrome, bladder dyskinesia,

atypical thoracoalgias, effort intolerance, orthostatic hypotension and tachycardia, is usually present (1, 2).

The FM prevalence ranges between 0,5 and 5% in the general population, being one of the most frequent diagnosis in the rheumatologic practice (2). The syndrome predominantly affects middle aged women, and females usually present a more rich symptomatology and a greater number of TPs than men (2).

The FM etiopathogenesis is presently undefined, but is likely multifactorial. Triggering factors are often identifiable, such as physical trauma (especially of the axial skeleton), surgical interventions, infections (by *Borrelia Burgdorferi*, Parvovirus, Coxsackievirus, he-

Table 1. Anatomical sites of the tender points (1)

Occiput	bilateral, at the suboccipital muscle insertions
Low cervical	bilateral, at the anterior aspects of the intertransverse spaces at C5-C7
Trapezius	bilateral, at the midpoint of the upper border
Supraspinatus	bilateral, at the origins, above the scapula spine, near the medial border
Second rib	bilateral, at the second costochondral junctions, just lateral to the junctions on upper surfaces
Lateral epicondyle	bilateral, 2 cm distal to the epicondyles
Gluteal	bilateral, in upper outer quadrants of buttocks, in anterior fold of muscle
Greater trochanter	bilateral, posterior to the trochanteric prominence
Knee	bilateral, at the medial fat pad, proximal to the joint line

patitis C and human immunodeficiency virus), acute or chronic emotional stress (traumatic childhood events, psycho-physical violence, sexual abuse, divorce, abandonment, war, occupational stress, or an overactive and perfectionistic lifestyle) (2). The role of genetic influences is underlined not only by the FM familial aggregation (3), but also by the surprisingly high prevalence of the syndrome (7.3%) among Amish adults, given the elevated rate of inbreeding in this socio-cultural isolated community (4).

A central and peripheral hyper-excitability of the nociceptor system is thought to represent the pathophysiological basis of the affection, whose hallmarks are TPs and a widespread hyperalgesia/allodynia (increased sensitivity to painful stimuli/pain elicited by a non-noxious stimuli), therefore FM has been defined a "hypervigilance syndrome" (2). However, since objective organic abnormalities are lacking, the FM legitimation is still debated, and the syndrome has even been considered as an "iatrogenic" disorder (5).

Even if subjective, the chronic psychophysical suffering state of FM patients adversely affects their quality of life, performance and mood, since they have to confront an "invisible disability" every day (6). FM patients present an equal or greater functional disability, a lower adaptation to their illness (7), and a higher tendency to emphasize their pain compared to patients with rheumatoid arthritis (RA) (8). Moreover, FM patients have high lifetime rates of utilization of all types of medical services, and report more comorbid or associated conditions than patients with other rheumatic diseases (8). Interestingly, cognitive

behavioural therapy and antidepressant drugs are useful in the FM treatment, suggesting that the link between FM and psychiatric, psychological and behavioural factors may be very close.

Our aim was to evaluate the personality profiles of FM patients, as well as the aggregation and the possible relationship between FM and psychiatric disorders (PD), reviewing the available evidences in current literature on this comorbidity, whose hypothetical neurobiological basis we here also discuss.

Methods

A detailed research was performed in PubMed (National Library of Medicine) and Biosis indexes, using the following key words: fibromyalgia, personality variables, personality disorders, psychiatric disorders, anxiety disorders, mood disorders, and depression. Psychiatric diagnoses were reported by the Authors according to the Diagnostic and Statistical Manual of Mental Disorders III, IV and IV Revised Edition (9-11), or to the 10th International Classification of Diseases (ICD-10) revision criteria (12).

Results

Personality variables associated with psychological vulnerability, such as low-self esteem, dependence, passivity, victimization, catastrophizing, irritability, avoidance, and maladaptive response to loss, are fre-

quent in FM patients (13-15), so that negativistic thought processes and poor coping skills have been suggested to be an intrinsic part of the psycho-pathogenesis of FM (8). Women with FM are more prone to catastrophizing than women with RA (14).

FM patients, compared with psychogenic pain patients and healthy controls, showed reduced relation to reality, emotional vacancy in relationships, and aggression as personality features (16).

Alexithymia and anger towards oneself were found to be significantly higher in FM patients than in controls or in patients with RA in some studies (17, 18), but not in another (19).

Compared to children with arthritis and control subjects, children with juvenile FM demonstrated significantly more behaviour problems and greater temperamental instability, irregularity of daily habits, low task orientation, high distractibility, high levels of anhedonia, negative mood, inactiveness, and negative self-esteem, other than increased levels of anxiety and depression (20).

On the basis of the Minnesota Multiphasic Personality Inventory, a study showed that FM adult patients compared with RA patients had statistically significant elevations in scores of hypochondriasis, hysteria, paranoia and schizophrenia scales (21), while another demonstrated increased scores in psychopathic deviancy, psychasthenia and paranoia scales (22).

Significantly higher score on the hypochondriasis scale of the Basic Personality Inventory was found in FM patients than in RA patients and healthy controls (23).

However, studies based on other assessment tools did not show significant differences in personality patterns of FM patients compared with general medical outpatients or RA patients (24, 25).

Recently, on the basis of the Structured Clinical Interview for DSM-IV, personality disorders were diagnosed in 8.7% of a large FM patient group, 5.25% borderline personality disorder, and 1.75% revealing either an avoidant personality disorder or dependent personality disorder, resulting their frequency slightly lower than in general population (10%) (26).

Features of "pain proneness" or "hyperarousal" can be commonly found in FM, explaining the eleva-

ted levels of stress observed in patients (27, 28). The high level of psychological distress was suggested to be intrinsically related to the syndrome (29), other than constituting an important prognostic factor (30). Moreover, psychological distress is more frequent and severe in FM patients than in controls with chronic widespread musculoskeletal pain of other origin (31), or in RA patients (32).

A high frequency of psycho-affective disturbances was demonstrated in FM (33), so that the syndrome was included in the "affective spectrum disorders" (34). FM patients are characterized by significantly lower levels of positive affect and extraversion than controls suffering from chronic pain due to osteoarthritis, and this dysfunction in affective regulation is considered to be a key feature of FM (35).

Increased rates of life-time and current PD are apparent in FM patients (7, 15, 21, 30, 36-38). PD, mostly identified by psychiatric assessment (27), were found to usually start after the onset of FM, but may also be associated with it, or precede it (30, 39-41).

Among adult FM patients, anxiety and depressive disorders are the most frequent psychiatric comorbidities, whereas eating disorders are uncommon (26, 38, 39).

The frequency of the anxiety disorder ranges from 13% to 63.8% (7, 26, 33, 34, 36, 37, 40, 42-47), and that of the depression ranges from 20% to 80% (7, 25, 26, 33, 34, 36, 37, 43, 48-52). The high variability may depend on the psychosocial characteristics of patients (26), since most of the evaluations were performed on tertiary care consulting patients; however, similar results were reported in clinical, community or population studies (29, 31, 43, 47, 53-55).

Even referring to the lower percentages, the PD occurrence is significantly higher in FM subjects than in the general population (7%) (56).

A link between posttraumatic stress disorder (PTSD) and FM was observed in both community samples (57, 58), and in care-seeking cohorts (59, 60), in which more than 50% of FM patients showed PTSD (59, 60). Compared to the prevalence of PTSD in the general population (6%), FM patients exhibited a greatly increased rate, similar to Vietnam veterans and victims of natural disasters or motor vehicle accidents (61).

The risk of lifetime anxiety disorders, particularly obsessive-compulsive disorder and PTSD, has been estimated to be 5-fold higher among women with FM than without (47).

Other than for the elevated frequency, the evidence for an association between FM and major depressive disorder (MDD) is particularly strong also on the basis of overlapping symptomatology and similar pattern of comorbidity, as well as for the high rates of MDD among relatives of patients with FM (39, 62). Although the prevalence of depression in FM patients is high, "depressotypic" personality style was not found to be a necessary part of the syndrome (52).

FM and depressive symptoms are also aggregated in preadolescents, and FM children show significantly higher total emotional and behavioural scores than controls (63).

Psychiatric comorbidity was reported to be higher in FM patients than in RA patients in some studies (22, 33, 38), but not in other ones (50, 64).

Relatives of FM patients (3, 33, 39, 44, 65) presented PD more frequently than those of adult (3) and paediatric (20) RA patients, and showed a significantly higher pain sensitivity (3, 20). These findings may suggest not only that genetic factors may be involved in pain perception control and in FM pathogenesis, but also that FM and PD may share these factors (3, 66). A recent study confirmed this hypothesis, due to a similar frequency of depression that was found in relatives of depressed patients and in FM patient kindred without history of PD (67).

Of note, the pain intensity and the pain persistence in FM are independent of a coexistent depression (54) or a concomitant psychological distress (68), while the pain intensity is positively related to the severity of anxiety (69, 70), and the TP number is strongly influenced by the level of distress (68). Moreover, patients with comorbid anxiety report the greater number of FM physical symptoms (26).

Discussion

Personality profiles of FM patients are quite heterogeneous. Differences in the assessment tools and in the patient populations studied may probably con-

tribute to this variability. Personality variables associated with psychological vulnerability are common, and patients demonstrate considerable elevation on scales that emphasize mood and personal emotional adjustments. However, personality disorders are rarely diagnosed in FM. Thus, premorbid personality patterns do not seem to be directly associated with FM *per se*.

Depressive and anxiety disorders strongly aggregate with FM. The prevalence of these disorders has been reported in 20-80% and in 13-63.8% of patients, respectively. Increased frequencies have been observed not only in clinical studies, but also in community and population studies. The association between FM and psychiatric symptoms was also found in children with FM.

Various hypothesis may explain such a comorbidity between FM and PD: 1) PD may be a consequence of FM; 2) FM may be an effect of an underlying PD; 3) both FM and PD may be caused by a common, presently unknown abnormality.

The first hypothesis is that PD may be reactive to the FM chronic pain and disability, but the observations that PD may precede FM, and the high rates of PD reported among relatives of FM patients are inconsistent with this hypothesis.

The second hypothesis argues that FM is due to an underlying psychiatric disorder, but many FM patients never develop PD at all.

The third hypothesis deserves serious consideration. The common physiopathogenetic factor may be represented by altered neurotransmitter signalling, observed in FM patients (2,71) and in individuals suffering from depression (72). Polymorphisms in genes related to the dopaminergic (73, 74) and serotonergic (75, 76) systems may play a role in the pathogenesis of both disorders. Notably, a higher frequency of the short/short (S/S) genotype of the promoter region of the serotonin (5-HT) transporter (5-HTT) gene was found in FM patients compared to healthy controls (75). The S/S FM subgroup exhibited higher mean levels of depression, psychological distress (75) and anxiety (76).

In an epidemiological study, adult individuals carrying one or two copies of the S-allele of the 5-HTT promoter polymorphism showed more depressive symptoms, diagnosable depression, and tendency

of suicide than homozygous for the long allele (77). Moreover, S/S genotype carriers were found to have two or more first-degree relatives with a history of depression (78). Furthermore, an excess of the S/S-genotype and of the S-allele was also found among MDD children (79).

However, several findings are in contrast with a FM/PD common physiopathology. Firstly, the peculiar nociception pattern (lower pain threshold) and sleep disturbances of FM are not shared by PD patients (2). In addition, PTSD and MDD patients showed elevated serum and urine levels of cortisol (80), as well as a hypercortisolemic response to the dexamethasone suppression, unlike FM patients (2, 80, 81). Moreover, FM is not characterized by the activation of cell-mediated immunity, in contrast with MDD (82, 83). As a matter of fact, MDD patients showed significantly higher urinary neopterin excretion than both normal volunteers and FM patients (83). Finally, a recent study on a cohort of FM patients evidenced, by functional magnetic resonance imaging, that the depressive comorbidity did not interfere either in the sensory-discriminative pain perception or in the activation of brain regions implicated in pain processing (i.e., somatosensory cortex), but increased the magnitude of the neural activity in brain areas related to the motivational-affective dimension of pain (i.e., the amygdalae and anterior insula) (84). On the contrary, no altered neural activity in the insula was observed in patients with depression. These findings, other than support the existence of parallel, somewhat independent neural processing networks for sensory and affective pain dimensions, provide an explanation for the variability of the analgesic effects displayed by antidepressants, often produced at lower doses than required to treat depression (84).

In conclusion, personality profiles of FM patients are quite heterogeneous. Premorbid personality patterns do not seem to be directly associated with FM *per se*. FM patients compared with controls show a significantly higher prevalence of depressive and anxiety disorders, reported in 20-80% and 13-63.8% of cases, respectively. Moreover, elevated rates of PD are detectable in relatives of FM patients.

Given the close association between FM and PD, a common physiopathology may be suggested, and al-

terations of the neurotransmission might constitute the shared underlining factor.

Further studies may elucidate the neurobiological basis of this comorbidity. Due to the high frequency of the FM/PD aggregation, a careful clinical assessment is needed to identify FM patients who may benefit from adding specific pharmacologic and psychotherapeutic interventions.

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