Is panic disorder associated with clinical severity of fibromyalgia? A preliminary study in a tertiary-care centre

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ABSTRACT

Objective. *To investigate the influence of panic disorder (PD) with/without agoraphobia on the clinical severity of fibromyalgia (FM).*

Methods. *Eighty-one patients with FM, among those consecutively referring to a tertiary-care setting, were included in this cross-sectional study. Psychiatric diagnoses were made by the structured clinical interview in accordance with the 4th-TR version of the diagnostic and statistical manual of mental disorders. The clinical severity of FM was measured by means of the following self-administered scales: Fibromyalgia Impact Questionnaire (FIQ), Fibromyalgia Assessment Status (FAS), Health Assessment Questionnaire (HAQ).*

Results. *A final sample of 66 females with FM with or without past PD was included in the analyses. The two groups did not significantly differ in age, years of education, length of illness or medication distribution. We did not find significant differences between the two groups in the FIQ and FAS scale scores, whereas subjects with FM and past PD showed significantly higher HAQ scale scores than those without past PD (p<.001).*

Conclusion. *A history of PD in patients with FM increases the severity of functional impairment in performing a wide range of daily-life activities, as measured by the HAQ scale, with no effects on the severity of other clinical dimensions of FM. Potential underlying mechanisms and clinical implications will be discussed.*

Introduction

Fibromyalgia (FM) is a condition characterised by widespread musculoskeletal pain and diffuse tenderness at specified anatomical locations (tender points), generally accompanied by fatigue and sleep disturbance (1). FM has a lifetime prevalence of about 2% and females are more frequently affected than males (rate of approximately 13:1) (2). FM is associated with severe impairment of daily-life functioning, leading to disability, increased work absenteeism, social retirement and high use of health care services (3).

In both tertiary-care clinical samples and general population, subjects with FM display high rates of comorbid psychiatric disturbances (4), especially depressive and anxiety disorders (5). Major depression (MD) is the most studied psychiatric comorbidity in FM, because of a high lifetime prevalence (60-80%) in subjects with FM and some similarities in clinical picture, pathophysiology and pharmacological treatments (6).

Contrary to depression, the relationship between FM and panic disorder (PD) received little attention, despite they may share some pathophysiological mechanisms and preliminary findings of high comorbidity between the two disorders.

PD is a highly prevalent (lifetime prevalence is 3-4%) invalidating anxiety disorder, that more frequently affects females than males (rate of approximately 2:1) (7). Some studies found a high prevalence of PD in samples of patients with FM, showing rates of lifetime PD ranging from 17% to 27% (8-10) and rates of current PD from 9% to 18% (8, 9). On the other hand, in subjects seeking treatment for PD about 40% reported chronic musculoskeletal pain and 10% were using analgesic compounds on a daily basis (11). Similarly, 71% of a sample of patients with PD complained of headache (55%) and/or chest pain (34%) and/or joint pain (25%) (12).

PD results from the interplay of unexpected (*i.e.* occurring out of the blue) panic attacks (PAs) (*i.e.* sudden episodes of intense fear/discomfort, as-

sociated with a surge of somatic symptoms such as chest pain, palpitations, breathlessness, dizziness) and other symptoms following the occurrence of PAs, *i.e.* anticipatory anxiety and phobic behaviours associated with expected panic attacks (*i.e.* induced by feared cues, such as situations where PAs have occurred or physical sensations resembling those occurring during an unexpected PA) (13, 14). Subjects with PD have persistent concerns about additional PAs or their consequences and show maladaptive changes in behaviour related to the attacks (*e.g.* avoidance of physical exercise or unfamiliar situations). Up to 60-70% of subject with PD also have agoraphobia, that is a condition of marked distress in / avoidance of a wide range of situations from which it might be difficult to escape or help might be unavailable when panic-like symptoms occur (*e.g.* crowds, public places, traveling alone and away from home) (13).

Unexpected PAs may be related to the activation of phylogenetically primitive brain structures which process basic physiological functions (*e.g.* brainstem, hypothalamus, insula), whereas anticipatory anxiety, phobic behaviours and agoraphobia may be influenced by the amygdala, the limbic system and the prefrontal cortex, that modulate fear conditioning, emotional-learning processes and the development of defensive behaviours to threats (15-18).

The conditioning processes involved in phobic behaviours of subjects with PD may partly overlap with some mechanisms implicated in FM. FM is considered a centralised pain state with central nervous system (CNS) origin and/or amplification of pain (19). In addition to these "core" processes, an involvement of "fear-avoidance" mechanisms in the development of the disorder have been hypothesised (20). Negative appraisals about pain and catastrophic thinking about its consequences may lead to widespread pain-related fear associated with avoidance of several daily activities that are expected to produce pain (21). Longstanding avoidance of physical activity may have a detrimental impact on the musculoskeletal system leading to a 'disuse syndrome' (22) with physical deconditioning, impairment in muscle activities and coordination with guarded movements and increased nociception (23).

Finally, a dysregulation of the serotonergic system may play a role in both FM and PD, since serotonin is involved in pain transmission, fear conditioning processes and PAs (24, 25).

The aim of this study was to investigate the influence of PD with /without agoraphobia on the clinical severity of FM in a tertiary-care setting. We hypothesised that the comorbidity with PD may be associated with higher severity of clinical symptoms and/or functional impairment in subjects with FM. To the best of our knowledge, no published studies investigated this issue.

Methods

Participants

Eighty-one patients with FM, among those consecutively referring to the Rheumatology Unit in Milan, from May 2010 to May 2011, were included in this study.

Inclusion criteria were: a) Age: 18-70 years; b) to meet the American College of Rheumatology (ACR) criteria for FM requiring widespread pain, for at least 3 months, above and below the waist and on both sides of the body, as well as pain present in 11 or more of 18 "tender points" detected by a pressure of 4 kg/cm^2 applied for a few seconds (1).

Exclusion criteria were: a) inflammatory causes of pain, b) severe and uncontrolled medical illnesses c) lifetime neurological disorders, d) alcohol/drugs abuse or dependence, e) any clinical condition that may interfere with assessment, f) pregnancy, g) any other concurrent psychiatric disorder except PD with / without agoraphobia (13).

All of the patients provided written informed consent after receiving a complete description of the study. The research was approved by the Ethics Committee at the L. Sacco University Hospital.

Procedure

During the clinical examination, the rheumatologist invited all of the patients to undergo a psychiatric assessment in the framework of a research study. Clinical and socio-demographic data were collected using interviewer-administered questionnaires and recorded through a structured interview format. When available, data were validated by means of medical records and interviews of family members.

Psychiatric diagnoses

The *Structured Clinical Interview for DSM-IV- TR* (SCID) (26) was used to assess past and current psychiatric diagnoses in accordance with the 4th-TR version (13) of the Diagnostic and Statistical Manual of Mental Disorders.

Clinical severity of fibromyalgia

The clinical severity of FM was measured by the following self-administered scales:

• *Fibromyalgia Impact Questionnaire (FIQ)*

The Italian version of FIQ (27) is a 10 item scale measuring FM-related symptoms. The first item contains 10 sub-items regarding physical functioning, each of which is rated on a 4-point Likert-type scale. Items 2 and 3 ask the patients to mark the number of days they felt well and the number of days they were unable to work because of FM symptoms. In items 4-10 the patients have to rate work difficulty, pain, fatigue, morning tiredness, stiffness, anxiety and depression on horizontal linear scales marked in 10 increments. Maximum possible total score is 100. Severely affected patients usually score 70 or more.

• *The Fibromyalgia Assessment Status (FAS)*

FAS is an index (28) that combines in a single measure (range: 0-10) the patient's assessment of fatigue, sleep disturbances and pain evaluated on the basis of the 16 non-articular sites listed on the Self-Assessment Pain Scale (SAPS).

• *Health Assessment Questionnaire (HAQ)*

HAQ is a 20-item questionnaire investigating difficulties in performing eight daily-life activities categories (dressing and grooming, rising, eating, walk-

ing, hygiene, reach, grip, and outside activities) (29). Each category has at least two sub-category questions. For each item, the patient is asked to rate the level of difficulty experienced over the preceding week in performing each activity using a 4-point scale ranging from 0 (no difficulty) to 3 (unable to perform). The final HAQ score is the average score of the eight categories. It ranges from 0 (no problem) to 3 (the worst score).

Statistical analyses

To investigate the mean differences between the two groups (*i.e.* patients with and without comorbid PD) in the FM severity scales, we performed three independent samples t-test analyses with group as between-group factor and the three severity scales of Fibromyalgia (FIQ, FAS, HAQ) as dependent variables. Because of the very small sample size, we excluded from the analyses both males (6 subjects, 7.4% of the whole sample) and the subjects with FM with current PD (9 subjects, 12% of the subjects with lifetime PD). Thus, we compared patients with FM with past PD and those without past PD. Preliminary analyses for confounding variables did not find any mean difference between the two groups in age, years of education, length of illness (FM) or medication distribution. The Levene's test indicated that variances between groups for the HAQ test (p=.003) were not homogenous. Considering the unequal sample sizes of the two groups, to avoid biases related to violation of the *t*-test assumption of homogeneity of variances, we used the Welch's independent samples t-test analyses, a modified version of the t-test that does not assume equal variances among groups. Statistical significance was set at α=0.01 and all analyses have been conducted in *R* (30)

Results

Fifty-four (72%) out of 75 female subjects with FM had comorbid lifetime PD (including current and past PD). Nine patients (12%) had current PD (8 patients with agoraphobia, 1 patient without) and 45 patients (60%) had past PD (33 patients with agoraphobia, 12 patients without). As described above, we included in the analyses only patients with past PD. A final sample of 66 patients with FM with or without past PD was considered. Descriptive statistics and temporal relationships between FM and PD are reported in Table I. The two groups did not significantly differ in age, years of education, length of illness (FM) or medication distribution (data not shown). The majority of patients (75%) have been taking antidepressant for treating pain, in particular duloxetine (53%), venlafaxine or amitriptyline. About 1/4 of the patients who received antidepressants was in maintenance treatment for PD. No patients in both groups took part in the CBT's session. Welch's independent samples *t*-test analyses did not show significant differences between the two groups in both the FIQ and FAS scale scores, whereas subjects with FM and past PD showed significantly higher scores in the HAQ scale than those without past PD (p<.001) (Table II).

Table I. Socio-demographic and clinical characteristics.

Whole sample n=66			
		mean	SD
Age		45.23	11.78
Age at onset of FM		33.65	13.26
Length of illness (FM) (years)		11.43	10.11
		n	%
Gender	Female	66	100.00
Comorbidity with past PD	no PD	21	31.82
	PD without Agoraphobia	12	18.18
	PD with Agoraphobia	33	50.00
Medication	Serotonin Norepinephrine Reuptake Inhibitors	42	63.04
	Selective Serotonin Reuptake Inhibitors	16	24.24
	Gabapentinoids	39	59.10
	Opioids	1	1.52
	Non-steroidal anti-inflammatory drugs (at least twice a week)	66	100.00
	Miorelaxants	4	6.10
	Tricyclic compounds	8	12.12
Sample of subjects with FM and past PD n=45			
		Mean	SD
Age at onset of PD		27.73	14.51
		n	%
Temporal relationship between PD/FM	PD onset precedes FM onset	16	33.55
	PD and FM with close temporal onset	23	51.11
	FM onset precedes PD onset	6	13.33

FM: fibromyalgia; PD: panic disorder.

Table II. Welch's indipendent samples *t*-test analyses.

	No PD (n=21)		past PD (n=45)			
	Mean	Sd	Mean	Sd	t	*p*
FIQ	73.69	12.05377	80.11	9.95	-2.127	0.041
FAS	7.5014	1.09569	7.74	1.07	-0.846	0.403
HAQ	0.795	0.19938	1.15	0.42	-4.693	<0.001

FIS: fibromyalgia clinical status; FAS: fibromyalgia assessment status; HAQ: health assessment questionnaire; PD: panic disorder; Sd: standard deviation; t statistic of Welch's indipendent samples *t*-test analyses; *p*: *p*-value of t.

Discussion

We investigated the influence of the comorbidity with PD with/without

agoraphobia on the clinical severity of FM in a sample of women referring to a tertiary-care centre. We found that a history of PD in patients with FM increases the severity of functional impairment in performing a wide range of daily-life activities, as measured by the HAQ scale, with no effects on the severity of other clinical dimensions of FM. These results should be considered preliminary since the sample size was small and no previous studies investigated this issue.

In line with previous findings, in our sample the prevalence of PD was higher than in the general population. Our rate of current PD was similar to rates previously found in samples of patients with FM (8, 9), while our rate of lifetime PD was even higher (8-10). The discrepancy may be explained by several methodological differences among studies, including diversities in recruitment methods and instruments of psychiatric assessment, that make the samples not fully comparable. Despite this, the high co-occurrence rates of FM and PD suggest that these conditions are related in some way (*i.e.* if they were fully independent the rate of co-occurrence would be expected to equal the product of their separate probabilities). However, cross-sectional findings of co-occurrence do not provide information either about the nature of the association between FM and PD or about the mechanisms by which they are related. Several complex scenarios are possible, for example one condition may increase the vulnerability to or cause the other, or they may influence each other in some mutually maintaining way and/or some shared factors (genetic and/or environmental) may increase vulnerability to both.

We observed that the rates of PD occurring before FM or in close temporal onset with FM are similar and higher than the rate of FM occurring before PD. This is in line with previous findings showing high rates of preexisting anxiety disorders in samples of subjects with chronic musculoskeletal pain (31, 32) or chronic neuropathic/idiopathic pain (33). However, our finding should be interpreted with caution. Due to the cross-sectional design of our study, the age at onset of the disorders was investigated retrospectively and it is often difficult to accurately determine when symptoms of FM started. Future prospective studies are needed to clarify the temporal patterns of association between FM and PD and the mechanisms underlying this association.

The main finding of our study is that patients with FM and past PD had more severe functional disability than those without past PD. The former group showed significantly higher impairment in performing a wide range of daily-life activities (HAQ scale) than the latter. Conversely, they did not differ in severity of FM clinical symptoms. The groups did not significantly differ in socio-demographic features, FM duration or medication distribution, thus it is unlikely that these variables explain our results. The findings differ from a previous study by Epstein and coworkers (8) that did not found differences in the 36-item Short-Form Health Survey (SF-36) physical functioning domain between patients with FM with lifetime anxiety disorders and those without. However these results are not fully comparable to ours, because the inclusion of different anxiety disorders as a group did not allow to disentangle the influence of PD on physical functioning (8).

Although findings are mixed (34), some previous studies suggested a role of anxiety in FM clinical severity. The severity of current anxiety symptoms was the only predictor of marked functional impairment in a sample of patients with FM, half of which had current anxiety/depressive disorders (8). Patients with FM and current anxiety disorders (considered as a group) showed more FM clinical symptoms and lower general activity than patients with FM and current depression (5).

These findings extend these previous results, suggesting that vulnerability to panic, even in the absence of current full-blown PD, may be relevant for at least one clinical aspect, *i.e.* functional disability, in patients with FM. Several potential mechanisms may be involved. First, past PD may confer to patients with FM a higher propensity toward fear-conditioning processes in response to pain. This may lead to more severe avoidance behaviours resulting in more severe deterioration of everyday functioning in this subgroup of patients. Conditioning processes in response to interoceptive/exteroceptive cues are thought to be involved in conditioned anxiety and phobic behaviours of patients with PD (35). In experimental conditioning paradigms, these patients showed impaired discriminative fear-conditioning, with elevated fear responding to learned safety-cues (36), and a proclivity toward fear overgeneralisation (37). In PD these processes contribute to the development/maintenance of phobic avoidance toward several daily-life situations up to full-blown agoraphobia (35). Similarly, avoidance of physical activity was found in about 40% of patients with FM (38) and active avoidance of common daily-life situations was associated with higher levels of functional disability in FM after controlling for demographic variables and pain intensity (39). Conditioning processes toward events that are expected to produce pain, including daily-life activities, may contribute to avoidance behaviours and functional impairment of patients with FM (21). Accordingly, in a recent study with an experimental fear-conditioning paradigm with thermal stimuli, subjects with FM showed inability to identify and learn safety cues (contingency learning deficits) with higher expectancy of aversive events than healthy controls and subjects with rheumatoid arthritis (20). Thus an underlying vulnerability to conditioning processes may be more marked in the subgroup of patients with FM and a history of PD and negatively influence their daily-life functioning in response to pain. This idea is speculative and should be tested by comparing the responses of patients with FM with or without comorbid PD to experimental fear-conditioning paradigms. In addition, any conclusion about causality cannot be drawn. A shared vulnerability to conditioning processes may influence the development of both PD and a condition of FM with a peculiar functional impairment, or repeated conditioned responses in PD may sen-

sitise subsequent conditioning processes to pain in patients with FM, or other common factors may specifically increase vulnerability to conditioning in the subgroup of patients with FM and comorbid PD. Longitudinal studies are needed to clarify these issues.

Second, the serotonergic system may be implicated in the association between FM with past PD and higher functional disability. In patients with FM decreased levels of serotonin, serotonin precursor (L-tryptophan) and metabolites in serum and central nervous system were found, as well as reduced rates of serotonin transport into the cerebrospinal fluid (3, 24). Recently, an association was found between serotonin 2A (5-HT2A) receptor 102T/C polymorphisms and susceptibility for FM (24). Substantial evidence showed the involvement of the serotonin system in PD, notably the therapeutic effectiveness of selective-serotonin reuptake inhibitors (40), the influence of experimental manipulations of serotonin (5-HT) system on PAs (41, 42), the associations between polymorphisms of serotonin transporter gene (SLC6A4) (43) and serotonin 2A/1A (5-HT2A/5-HT1A) receptors and susceptibility for PD (44, 45), and the association between serotonin 2A (5-HT2A) receptor polymorphisms and PD symptoms severity (45). Serotonin transporter promoter polymorphisms (5-HTTLPR) were associated with symptoms severity of PD (46) and the efficacy of both exposure-based behaviour therapy (42) and paroxetine (47). Since serotonin system and variation in the 5-HT genes are implicated in fear conditioning and extinction (25, 46), we could hypothesise that patients with both FM and a history of PD have peculiar imbalances in the serotonergic system than those with FM only, that may affect vulnerability to conditioning processes with higher functional impairment in this subgroup of patients.

Third, higher functional disability in patient with FM and past PD may be related to current sub-threshold panic-phobic symptoms. Up to 40-50% of subjects who suffered from PD still have residual panic-phobic symptoms after 3-6 years from pharmacotherapy discontinuation, despite not meeting diagnostic criteria for full-blown disorder (40). Residual panic-phobic symptoms may affect the daily-life functioning of patients with FM by further reducing their ability to cope with FM symptoms (indirect mechanism) and/or by interfering with some specific categories of daily-life activities, such as walking outdoors, physical activities, stay away from home, that are often feared even by patients without full-blown PD (direct mechanism). Further studies should investigate sub-threshold panic-phobic symptoms in subjects with FM and the potential influence of these symptoms on different categories of daily-life activities.

We did not find any differences in severity of FM clinical symptoms (FIQ/FAS scales) between patients with FM with and without past PD. Our results are in line with some previous findings that showed lack of difference in clinical symptoms severity between patients with FM with past anxiety disorders (considered as a group) (8, 34). On the contrary, an influence of current anxiety disorders on clinical symptoms of FM or different chronic pain conditions was previously found (5, 32). Overall these findings suggest that active symptoms of physiological and psychological arousal may maintain/exacerbate pain and/or clinical symptoms of FM more than an underlying vulnerability to anxiety not expressed in a current full-blown disorder. A possible additional explanation is that in subject with comorbid FM and PD an initial higher pain intensity was present, possibly due to a shared involvement of the midbrain periaqueductal gray in both disorders, that is a key region for the descending nociceptive inhibitory pathway and the unconditioned defensive reactions to interoceptive cues (48, 49).

We could hypothesise that an initial higher level of pain was controlled by enhanced avoidance of physical activity, and thus it has become undetectable, over time, by the FM clinical severity questionnaires. Finally, a high prevalence of the Joint Hypermobility Syndrome (JHS) was found in patients with both FM and PD (50). Since JHS is characterised by increased flexibility of the connective tissue and arthralgia, it may have partly contributed to enhance the initial pain intensity and the subsequent activity avoidance in patients with FM and PD. In addition, JHS has been linked to increased fear responses (51), behavioural inhibition and heightened interoceptive sensibility (52).

However, both FIQ and FAS scales used in our study provide global scores that encompass patient's assessment of several clinical dimensions, including pain, fatigue, sleep disturbances. Thus, we cannot exclude that these global scores may have masked potential influences of past PD on current specific clinical dimensions of FM. Further studies with instruments that separately measure different clinical dimensions of FM may clarify this issue. Finally, future studies should investigate whether possible residual panic-phobic symptoms, even in absence of full-blown PD, may influence severity of pain or other clinical symptoms of FM.

Our study has several shortcomings, in addition to those discussed above. First, the small sample size may have masked potential differences between the two groups (type II error). Second, due to the very small sample size of subjects with PD without agoraphobia we considered all patients with PD as a group. This did not allow to disentangle the role of PD with agoraphobia from that of the PD *per se*. For the same reason we cannot investigate whether current or past PD has different influence on clinical condition of patients with FM. Third, the lack of comparison groups with other anxiety disorders does not allow to draw conclusions about the specificity of our results. Future studies with larger samples, also including subjects with different anxiety disorders, are needed. Fourth, although we excluded subjects with concurrent Major Depression at the time of evaluation, we cannot exclude that subthreshold depressive symptoms may have influenced our results. We also cannot exclude that other past comorbid disorders in addition to PD may have affected our findings. Finally, a sample recruited among patients refer-

ring to a tertiary-care centre may limit the generalisability of our findings to all patients with FM. Much more work is clearly required to confirm and extend our preliminary results.

In conclusion, this is the first study that examined functional and clinical dimensions in a population of patients with FM with and without PD. We found that patients with FM and past PD had more severe functional disability than those without. Our findings suggest that vulnerability to panic, even in the absence of current full-blown PD, may be relevant for daily-life functioning in patients with FM. If confirmed, our results may have clinical implications. The assessment of past PD should be considered in the clinical approach to patients with FM, especially in those with higher levels of disability. In patients with FM and past PD, therapeutic interventions based on cognitive behavioural therapy (CBT) may be particularly recommended to improve functional daily-life impairment. According to the idea of a peculiar propensity toward fear-conditioning processes in patients with FM and PD, CBT interventions with exteroceptive/interoceptive exposure techniques may contribute to ameliorate daily-life functioning in this subgroup of patients, by improving discriminative learning, decreasing fear generalisation and aversive responses to common daily-life activities (53-56).

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