Fibromyalgia syndrome and depressive symptoms: comorbidity and clinical correlates

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SHORT RUNNING HEAD: Psychiatric comorbidity in fibromyalgia.

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ABSTRACT

Objective: Fibromyalgia is characterized by chronic widespread musculoskeletal pain and higher pain perception in specific anatomic sites called tender points. Fibromyalgia is frequently associated with psychiatric symptoms, like depression and anxiety; indeed some authors have argued about the possibility to classify this syndrome into affective spectrum disorder. Few studies have analyzed the impact of depressive symptoms on pain threshold. This research is aimed at evaluating the prevalence and the clinical correlates of depressive symptoms in fibromyalgic patients, and investigating their impact on pain perception and quality of life.

Methods: Outpatients between 18 and ~~-~~75 years with diagnosis of fibromyalgia according to the criteria of the American College of Rheumatology have been included. All subjects have been evaluated with the following rating scales: HAM-D; VAS (to quantify pain); a visual analogical scale to evaluate quality of life and~~;~~ Paykel's List of Recent Life Events.

Results: Thirty subjects have been recruited. Most patients (83.3%) had clinically significant depressive symptoms as indicated by a HAM-D score >7. Depressive symptoms are associated with higher pain perception, worse quality of life and more severe life events.

Conclusion: the presence of depressive symptoms is associated with~~leads to~~ a great impairment in patients with fibromyalgia syndrome: indeed the psychiatric comorbidity lowers pain threshold and worsens the quality of life of our patients. Future studies should be conducted in order to identify the individual factors, e.g. stress or inflammatory processes, which drive the association between depression and higher severity of fibromyalgia syndrome.

Key words: Fibromyalgia – depressive symptoms – tender points – psychiatric comorbidity – major depression – extrarticular rheumatism.

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No conflict declared

INTRODUCTION

Fibromyalgia is a common syndrome of unknown etiology classified among extra-articular rheumatisms of functional nature, characterized by chronic widespread musculoskeletal pain, heightened and painful response to tactile stimuli, and the presence of eleven or more "tender points" in specific anatomic sites (18 specific points at 9 bilateral sites) that are exceptionally sensitive to the touch (Chakrabarty and Zorob, 2007) (Table 1).

FM is frequent in population and clinical samples: the prevalence was estimated between 0.5% and 5% in general population studies and up to 15% in clinical samples across different countries (White and Harth, 2001; Neumann and Buskila, 2003).

In Italy the reported lifetime prevalence is 2.2% Branco et al., 2010~~in press~~). Fibromyalgia is more common in women than in men, affecting the 3.4% of women versus the 0.5% of men (Wolfe et al., 1990).

In fibromyalgia the pain is often associated with a heterogeneous profile of autonomic and neuropsychiatric symptoms. For example, a recent study has found that the majority of patients had nausea, constipation, colicky abdominal pain, orthostatic hypotension, and dizziness (Solano et al., 2009). Besides, psychiatric symptoms such as depressive, anxious and sleep disorders have frequently been associated to FM (Berger et al., 2007; Raphael et al., 2006).

The physical and mental distress experienced by FM patients strongly affects quality of life, social and work performances, to the point that FM has been called the "invisible disability" (Sturge-Jacobs, 2002). Subjects suffering from fibromyalgia show more functional disability, less ability to adapt to limitations imposed by the disease and more tendency to emphasize the pain, compared with patients with rheumatoid arthritis (Walker et al., 1997).

Furthermore, patients with FM are frequently diagnosed with depressive and anxiety disorders (Bradley, 2005; Wolfe et al., 1990). A recent review has reported that depressive disorders are the most frequent psychiatric comorbidity in patients with FM, with prevalence rates ranging from 20% to 80% (Fietta et al., 2007). Depressive symptoms are also frequent in patients with FM, with prevalence rates around 40% (Kato et al., 2006).

Although there are several studies investigating the extant comorbidity between depressive disorders and symptoms and FM, data regarding the impact of depressive syndromes on FM patients are still scarce. For example, it is well-known that stressful life events play a major role in the onset of MDD. In particular, severe acute life events that possess a high degree of threat and

unpleasantness, such as the death of a spouse or loss of an important job, have been found consistently to precede the onset of depression (Hammen, 2005; Kessler, 1997; Monroe et al., 2001; Paykel, 2003). However, no studies have examined the association between life stress and depression in patients with FM.

Aim of the study is to investigate the prevalence and clinical correlates of depressive symptoms in patients with FM, and to evaluate the impact of these comorbid depressive symptoms on pain perception and quality of life of FM patients.

METHODS

The study was conducted on patients consecutively referred to the Rheumatology Outpatient Unit of the S.C. 1° Medica at the university hospital "Ospedali Riuniti di Trieste" over a period of six months (June 2007-December 2007).

Patients diagnosed with fibromyalgia according to the criteria of the American College of Rheumatology (Wolfe et al., 1990), were recruited for the present study.

All subjects were administered a semi-structured interview that assessed socio-demographic and clinical characteristics such as age, years of education, marital status, history of psychiatric disorders, ongoing treatment with antidepressants or analgesic medications.

Depressive symptoms were assessed by means of the Hamilton Rating Scale for Depression (HAM-D) 17-items (Hamilton, 1960). In order to quantify pain, patients were administered the Visual Analogue Scale (VAS), based on 11 degrees of pain intensity: from the absence of pain (score 0) to the strongest pain one can imagine (score 10) (Aitken, 1969). Quality of life (QoL) was assessed by administering the patients a Visual Analog Scale with scores from 1 to 10, indicating a continuum from the worst (score 1) to the ideal (score 10) quality of life. Stressful life events occurred in the previous year, were assessed upon administration of the Paykel's List of Recent Life Events (Paykel et al., 1971).

All patients were divided into two subgroups according to the presence of depressive symptoms, defined by a HAM-D score higher than 7. Patients with or without depressive symptoms were then compared with regard to VAS scores, Quality of Life scores, Life Events Paykel scale scores, and the use of analgesic medications.

All statistical analyses were performed by SPSS software version 16.0. Between-group comparisons of categorical variables were made with the Pearson's $\chi 2$ test, except when the expected cell count fell below 5, in which case Fisher's exact test (two-tailed) was used. Continuous variables were compared using the independent samples t-test.

A two-tailed p-value less than .05 was considered statistically significant.

RESULTS

Thirty patients were consecutively recruited, of which 29 (96.7%) were women. The mean age of the sample was 58.33 ± 13.43. All other socio-demographic and clinical characteristics are displayed in Table 2.

The HAM-D mean score was 15.37 ± 6.27. The VAS mean score was 6.63 ± 2.27; 16 patients (53.3%) had a VAS score ≥ 6, which is considered as the cut-off for a pain of disabling intensity. As for the quality of life, the mean score was 5.07 ± 2.55. All patients showed at least one stressful life event, with different degrees of severity; the Paykel's Life Events Scale mean score was 14.85 ± 8.01.

The 83.3% of patients had clinically significant depressive symptoms, corresponding to a HAM-D total score > 7. These patients displayed significantly higher VAS scores ~~(7.12 ± 2.15 vs 4.20 ± 0.84; t = 2.96, df = 28, p = 0.006)~~, lower QoL scores ~~(4.60 ± 2.12 vs 7.40 ± 3.44; t = - 2.428, df = 28, p = 0.022)~~, and a higher Paykel Scale score, ~~(16.47 ± 7.68 vs 6.76 ± 3.52; t = 2.74, df = 28, p = 0.011)~~ than those without depressive symptoms. Patients with depressive symptoms also reported a greater use of analgesic medications (~~76% vs 0%; χ^2 = 10.36; df = 1, p = 0.001~~Table 3). Other socio-demographic and clinical variables were not significantly associated with the presence of depressive symptoms.

DISCUSSION

The high frequency of depressive disorders in patients with fibromyalgia syndrome has~~ve~~ led some authors to consider this syndrome among the "affective spectrum disorder" (Hudson et al., 2004).

In these patients, depressive disorders are the most frequent comorbid psychiatric conditions, with prevalence figures of 20-80% (Fietta et al., 2007). Major depression is also very common in patients with FM: three controlled studies reported high rates of lifetime major depressive disorder comorbidity, ranging from 62% to 86% (Arnold et al., 2006; Hudson et al., 1985; Walker et al., 1997). Recent data also showed that depressive symptoms without a formal diagnosis of depressive disorder frequently affect patients with FM: Kato and colleagues have investigated the amount of comorbidity between depressive symptoms and FM on a community sample of 44.897 individuals, showing that 40% of patients with FM had current depressive symptoms (Kato et al., 2006).

Our data showed that as much as 83.3% of subjects had clinically significant depressive symptoms, while the 46% reported a HAM-D score above 14, which is compatible with a major depressive episode of at least moderate intensity. Like in other clinical studies, we found higher rates of depression than those reported by the community studies. This difference is most probably due to

the fact that our patients spontaneously sought treatment due to the pain: the more severe clinical picture is most probably associated with an increased prevalence of depressive symptoms.

The high comorbidity between FM and depression may have several explanations:

1. Depression can be simply regarded as a reaction to a chronic and disabling disorder. This hypothesis should be rejected, since the percentage of FM patients with depressive symptoms is significantly higher than that found in other comparably severe chronic diseases: for instance, Arnold and colleagues compared 78 patients with fibromyalgia and 40 with rheumatoid arthritis: 62% of the former patients had a lifetime major depression versus the 27% of patients with the other chronic conditions (Arnold et al., 2006). More recently, other researchers found that FM patients had higher rates of major depression than patients with comparably severe neuropathic pain (Gormsen et al., 2010).

2. FM may represent a manifestation of a subthreshold depression. However, since some patients with fibromyalgia will neither develop any depressive episodes nor significant depressive symptoms throughout their lives, this hypothesis seems unlikely.

3. FM and depression can be conceptualized as a unique disorder of the NCS with multiple manifestations, both central and peripheral, which, as already mentioned, might belong to the same affective spectrum (Epstein et al., 1999; Hudson et al., 2003). To support this hypothesis, several common pathogenetic pathways have been proposed, such as the alteration of the HPA axis with elevated levels of corticotropin-releasing hormone (Murck et al., 2003), the dysregulation of central and peripheral noradrenergic/serotonergic pathways (Legangneux et al., 2001), substance P and neurosteroides (Herpfer and Lieb, 2003). Finally, the impaired function of cytokines has also been called upon as the common underlying factor (Maier, 2003): in particular IL-6 induces both hyperalgesia and depression (Maes et al., 1999; Wallace et al., 2001) and IL-8 has been correlated with the intensity of pain in FM patients with comorbid depression (Gur et al., 2002).

Our patients with depressive symptoms displayed significantly higher VAS scores and take more analgesic drugs. This observation might be merely explained with the direct induction of depressive symptoms by stronger pain. However, several studies have pinpointed that depression is greater in FM patients than in other chronic pain conditions displaying comparable pain intensity (Gormsen et al., 2010; Birtane et al., 2007), thus the association between greater pain and depression may have other causes. As already discussed, pain and depression may indeed coexist because they share overlapping pathophysiological processes (Maletic and Raison, 2009): indeed, depression is independently associated with a reduction of pain threshold due to the altered functioning of structures modulating pain such as prefrontal and insular cortex (Giesecke et al., 2005; Fitzgerald et al., 2008), hippocampus (Vythilingam et al., 2004), amygdala, and periacqueductal grey (Norman et

al., 2010). Another explanation for the higher perception of pain in FM patients with depressive symptoms is the tendency of depressed patients to adopt a cognitive style defined "catastrophizing", which means the tendency to perceive pain as awful, horrible and unbearable (Gracely et al., 2004). Depression-driven catastrophizing increases the perception of pain through the modification of attention and the anticipation of the pain itself, emphasizing emotional responses. This cognitive style has frequently been observed in fibromyalgia patients with depression (Hassett et al., 2000; Roth et al., 2005).

Another interesting finding is that all patients in our study reported at least one recent particularly stressful life event (bereavement, financial difficulties, etc.). A recent study found that FM patients tend to report more stressful life events than controls; the authors interestingly found that this was due to the tendency of FM patients to rate more severely mild stressful events (Stisi et al., 2008). Therefore, the particularly high number of events in our patients might be due to increased perception of stress in patients with FM. Also, we found that patients with depressive symptoms displayed higher scores at the Paykel Life Events scale. Thus, stressful life events might be a further risk factor for the development of depressive symptoms in FM patients.

Several studies found that quality of life is worsened in FM patients (Birtane et al., 2007; Gormsen et al., 2010; Hoffman and Dukes, 2008; Pagano et al., 2004; Tander et al., 2008; Walker et al., 1997). However, only two studies have reported that this effect might be not only mediated by chronic pain, but also by the presence of depressive symptoms (Gormsen et al., 2010; Tander et al., 2008). In the first study, the authors compared quality of life scores in 30 patients with fibromyalgia, 30 with rheumatoid arthritis, and 30 controls. All domains of quality of life were worse in FM patients than controls, and even worse than rheumatoid arthritis in the domains of physical role, social functioning, and bodily pain; depressive symptoms strongly correlated with the worse quality of life in FM patients (Tander et al., 2008). In a similar study, Gormsen and colleagues compared 28 patients with fibromyalgia, 30 with neuropathic pain, and 26 controls. Both FM patients and neuropathic pain patients had similar pain intensities; however, FM patients displayed a worse role function, general health, vitality, social function, and mental health, which was related with the presence of significant depressive symptoms (Gormsen et al., 2010). In our study, FM patients with depressive symptoms also displayed a worse quality of life, thus confirming previous results. However, due to the small number of non-depressed patients in this study, the association with a worse quality of life in our depressed patients with fibromyalgia should be seen as preliminary.

In conclusion, our study found that depressive symptoms are the rule more than the exception in patients with fibromyalgia. Since these depressive symptoms are ~~independently~~ associated with

increased pain perception and worsened quality of life, they must be screened and properly treated in order to improve the pain symptomatology as well as the quality of life of these patients.

REFERENCES

Aitken, R.C.B., 1969. Measurement of feelings using visual analogue scales. Proc. Royal. Soc. Med. 62, 989.

Arnold, L.M., Hudson, J.I., Keck, P.E., Auchenbach, M.B., Javaras, K.N., Hess, E.V., 2006. Comorbidity of the fibromyalgia and psychiatric disorders. J. Clin. Psychiatry. 67(8), 1219-1225.

Berger, A., Dukes, E., Martin, S., Edelsberg, J., Oster, G., 2007. Characteristics and healthcare costs of patients with fibromyalgia syndrome. Int. J. Clin. Pract. 61(9), 1498-1508.

Birtane, M., Uzunca, K., Tastekin, N., Tuna, H., 2007. The evaluation of quality of life in fibromyalgia syndrome: a comparison with rheumatoid arthritis by using SF-36 health survey. Clin. Rheumatol. 26, 679-684.

Bradley, L.A., 2005. Psychiatric comorbidity in fibromyalgia. Curr. Pain. Headache. Rep. 9(2), 79-86.

Branco, J.C., Bannwarth, B., Failde, I., Abello Carbonell, J., Blotman, F., Spaeth, M., Saraiva, F., Nacci, F., Thomas, E., Caubère, J.P., Le Lay, K., Taieb, C., Matucci-Cerinic, M., 2010. Prevalence of Fibromyalgia: A Survey in Five European Countries. Semin. Arthritis. Rheum. 39 (6), 448-453.

Chakrabarty, S., Zoorob, R., 2007. Fibromyalgia. Am. Fam. Physician. 76(2), 247-254.

Epstein, S.A., Kay, G., Clauw, D., Heaton, R., Klein, D., Krupp, L., Kuck, J., Leslie, V., Masur, D., Wagner, M., Waid, R., Zisook, S., 1999. Psychiatric disorders in patients with fibromyalgia. A multicenter investigation. Psychosomatics. 40, 57-63.

Fietta, P., Fietta, P., Manganelli, P., 2007. Fibromyalgia and psychiatric disorders. Acta. Biomed. 78(2), 88-95.

Fitzgerald, P.B., Laird, A.R., Maller, J., Daskalakis, Z.J., 2008. A meta-analytic study of changes in brain activation in depression. Hum. Brain. Mapp. 29(6), 683-695.

Giesecke, T., Gracely, R.H., Williams, D.A., Geisser, M., Petzke, F., Clauw, D.J., 2005. The relationship between depression, clinical pain, and experimental pain in a chronic pain cohort. Arthritis. Rheum. 52, 1577-1584.

Gormsen, L., Rosenberg, R., Bach, F.W., Jensen, T.S., 2010. Depression, anxiety, health-related quality of life and pain in patients with chronic fibromyalgia and neuropathic pain. Eur. J. Pain. 14(2), 127.

Gracely, R.H., Geisser, M.E., Giesecke, T., Grant, M.A., Petzke, F., Williams, D.A., Clauw, D.J., 2004. Pain catastrophizing and neural responses to pain among persons with fibromyalgia. Brain. 127, 835-843.

Gur, A., Karakoc, M., Erdogan, S., Nas, K., Cevik, R., Sarac, A.J., 2002. Regional cerebral blood flow and cytokines in young females with fibromyalgia. Clin. Exp. Rheumatol. 20, 753-760.

Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatr. 23, 56.

Hammen, C., 2005. Stress and depression. Annu. Rev. Clin. Psychol. 1, 293-319

Hassett, A.L., Cone, J.D., Patella, S.J., Sigal, L.H., 2000. The role of catastrophizing in the pain and depression of women with fibromyalgia syndrome. Arthritis. Rheum. 43(11), 2493-2500.

Herpfer, I., Lieb, K., 2003. Substance P and Substance P receptor antagonists in the pathogenesis and treatment of affective disorders. World. J. Biol. Psychiatry. 4(2), 56-63.

Hoffman, D.L., Dukes, E.M., 2008. The health status burden of people with fibromyalgia: a review of studies that assessed health status with the SF-36 or the SF-12. Int. J. Clin. Pract. 62(1), 115-126.

Hudson, J.I., Hudson, M.S., Pliner, L.F., Goldenberg, D.L., Pope, H.G. Jr., 1985. Fibromyalgia and major affective disorder: a controlled phenomenology and family history study. Am. J. Psychiatry. 142(4), 441-446.

Hudson, J.I., Mangweth, B., Pope, H.G. Jr., De Col, C., Hausmann, A., Gutweniger, S., Laird, N.M., Biebl, W., Tsuang, M.T., 2003. Family study of affective spectrum disorder. Arch. Gen. Psychiatry. 60(2), 170-177.

Hudson, J.I., Arnold, L.M., Keck, P.E. Jr., Auchenbach, M.B., Pope, H.G. Jr., 2004. Family study of fibromyalgia and affective spectrum disorder. Biol. Psychiatry. 56, 884-891.

Kato, K., Sullivan, P.F., Evengard, B., Pedersen, N.L., 2006. Importance of genetic influences on chronic widespread pain. Arthritis. Rheum. 54, 1682-1686.

Kessler, R.C., 1997. The effects of stressful life events on depression. Annu. Rev. Psychol. 48,191-214

Legangneux, E., Mora, J.J., Spreux-Varoquaux, O., Thorin, I., Herrou, M., Alvado, G., Gomeni, C., 2001. Cerebrospinal fluid biogenic amine metabolites, plasma-rich platelet serotonin and [3H]imipramine reuptake in the primary fibromyalgia syndrome. Rheumatology. 40(3), 290-296.

Maes, M., Libbrecht, I., Van Hunsel, F., Lin, A.H., De Clerck, L., Stevens, W., Kenis, G., de Jongh, R., Bosmans, E., Neels, H., 1999. The immune-inflammatory pathophysiology of fibromyalgia: increased serum soluble gp130, the common signal transducer protein of various neurotrophic cytokines. Psychoneuroendocrinology. 24, 371-383.

Maier, S.F., 2003. Bi-directional immune-brain communication: implications for understanding stress, pain, and cognition. Brain. Behav. Immun. 17(2), 69-85.

Maletic, V., Raison, C.L., 2009. Neurobiology of depression, fibromyalgia and neuropathic pain. Front. Biosci. 14, 5291-5338.

Monroe, S.M., Harkness, K.L., Simons, A.D., Thase, M.E., 2001. Life stress and the symptoms of major depression. J. Nerv. Ment. Dis. 189, 168-175.

Murck, H., Held, K., Ziegenbein, M., Künzel, H., Koch, K., Steiger, A., 2003. The renin-angiotensin-aldosterone system in patients with depression compared to controls--a sleep endocrine study. B.M.C. Psychiatry. 3, 15.

Neumann, L., Buskila, D., 2003. Epidemiology of fibromyalgia. Curr. Pain. Headache. Rep. 7, 362-368.

Norman, G.J., Karelina, K., Zhang, N., Walton, J.C., Morris, J.S., Devries, A.C., 2010. Stress and IL-1β contribute to the development of depressive-like behavior following peripheral nerve injurj. Mol. Psychiatry. 15(4), 404-414.

Pagano, T., Matsutani, L.A., Ferreira, E.A., Marques, A.P., Pereira, C.A., 2004. Assessment of anxiety and quality of life in fibromyalgia patients. Sao. Paulo. Med. J. 122(6), 252-258.

Paykel, E.S., 2003. Life events and affective disorders. Acta. Psychiatr. Scand. 108, 61-66

Paykel, E.S., Prusoff, B.A., Uhlenhuth, E.H., 1971. Scaling of life events. Arch. Gen. Psych. 25, 340-347.

Raphael, K.G., Janal, M.N., Nayak, S., Schwartz, J.E., Gallagher, R.M., 2006. Psychiatric comorbidities in a community sample of women with fibromyalgia. Pain. 124, 117-125.

Roth, R.S., Geisser, M.E., Theisen-Goodvich, M., Dixon, P.J., 2005. Cognitive complaints are associated with depression, fatigue, female sex, and pain catastrophizing in patients with chronic pain. Arch. Phys. Med. Rehabil. 86(6), 1147-1154.

Solano, C., Martinez, A., Becerril, L., Vargas, A., Figueroa, J., Navarro, C., Ramos-Remus, C., Martinez-Lavin, M., 2009. Autonomic dysfunction in fibromyalgia assessed by the Composite Autonomic Symptoms Scale (COMPASS). J. Clin. Rheumatol. 15(4), 172-176.

Stisi, S., Venditti, C., Saracco, I., 2008. Distress influence in fibromyalgia. Reumatismo. 60(4), 274-281.

Sturge-Jacobs, M., 2002. The experience of living with fibromyalgia: confronting an invisible disability. Res. Theory. Nurs. Pract. 16(1), 19-31.

Tander, B., Cengiz, K., Alayli, G., Ilhanli, I., Canbaz, S., Canturk, F., 2008. A comparative evaluation of health related quality of life and depression in patients with fibromyalgia syndrome and rheumatoid arthritis. Rheumatol. Int. 28(9), 859-865.

Vythilingam, M., Vermetten, E., Anderson, G.M., Luckenbaugh, D., Anderson, E.R., Snow, J., Staib, L.H., Charney, D.S., Bremner, J.D., 2004. Hippocampal volume, memory, and cortisol status in major depressive disorder: effects of treatment. Biol. Psychiatry. 56(2), 101-112.

Walker, E.A., Keegan, D., Gardner, G., Sullivan, M., Bernstein, D., Katon, W.J., 1997. Psychosocial factors in fibromyalgia compared with rheumatoid arthritis: II. Sexual, physical, and emotional abuse and neglect. Psychosom. Med. 59(6), 572-577.

Wallace, D.J., Linker-Israeli, M., Hallegua, D., Silverman, S., Silver, D., Weisman, M.H., 2001. Cytokines play an aetiopathogenetic role in fibromyalgia: a hypothesis and pilot study. Rheumatology. 40(7), 743-749.

White, K.P., Harth, M., 2001. Classification, epidemiology, and natural history of fibromyalgia. Curr. Pain. Headache. Rep. 5(4), 320-329.

Wolfe, F., Smythe, H.A., Yunus, M.B., Bennett, R.M., Bombardier, C., Goldenberg, D.L., Tugwell, P., Campbell, S.M., Abeles, M., Clark, P. 1990. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis. Rheum. 33, 160-172.