Cytokine patterns in fibromyalgia and their correlation with clinical manifestations

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Abstract

Objective

To examine the possible role of the soluble factor in fibromyalgia (FM) by studying the correlation of cytokine levels with the patients' clinical and psychiatric profile.

Methods

Eighty FM patients underwent clinical and psychiatric evaluations, and plasma levels of cytokines (IL-1, IL-6, IL-8, IL-10, TNF-α), aspecific markers of inflammation, rheumatoid factor (RF), anti-extractable nuclear antigen (ENA) antibodies, and anti-nuclear factor (FAN) were measured.

Results

Higher levels of IL-10, IL-8 and TNF-α were found in FM patients than in controls. Significant correlations between the biochemical parameters and clinical data were found.

Conclusion

The higher levels of cytokines found in FM patients suggest the presence of an inflammatory response system (IRS) and highlight a parallel between the clinical symptoms and biochemical data. They support the hypothesis that cytokines may play a role in the clinical features of fibromyalgia. In addition, the similar cytokine patterns found in FM patients with different psychiatric profiles suggests that IRS impairment may play a specific role in the disease.

Key words

Fibromyalgia, cytokines, psychiatric comorbidity, inflammation.

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Introduction

Fibromyalgia (FM) is a syndrome that is believed to arise from the abnormal central sensory processing of pain signals, involving the interaction between neurotransmitters, external stressors, behavioural constructs, hormones and the sympathetic nervous system. FM is characterized by stiffness and pain (1), associated with sleep disturbances (non-refreshing sleep, hypersomnolence) (2, 3) the presence of specific painful sites (tender points) (4), and is often accompanied by fatigue and depression (5). Although cytokines have been suggested to play a role in FM, the exact dynamics of their contribution are not clear (6). Recent evidence linking sleep disorders, hyperalgesia, cognitive dysfunctions, fatigue, stress and anxiety to cytokines prompted us to re-examine their expression in FM.

The etiopathogenesis of FM has not yet been clarified and there are no specific hematochemical or instrumental tests on which to base a diagnosis. Some authors have hypothesized that the modulation of the pain system is compromised in these patients. Recent studies have posited a connection between cytokines and certain symptoms of FM, and it also appears that these molecules may play a role in the communication between the immune and nervous systems. However, several studies have reported conflicting results with respect to the levels of certain cytokines in the blood and in culture supernatants, finding increased (6-8), normal (5, 9, 10) or decreased (11) production of inflammatory cytokines in stimulated and unstimulated culture supernatants of peripheral blood mononuclear cells (PBMC) from fibromyalgic and chronic fatigue syndrome patients. Wallace (6) did not find marked differences in serum cytokine levels between FM patients and controls, but reported significantly higher levels of certain cytokines in stimulated and unstimulated fibromyalgic PBMC.

A new syndrome referred to as "sickness behaviour" has been described in the literature (12) – a coordinated set of subjective, behavioural and physiological changes that develop in sick individuals during the course of an infection, and whose symptoms (anorexia, lethargy, slow-wave sleep, decreased social behaviour, and decreased reproductive behaviour) are attributed by the author to the effects of pro-inflammatory cytokines on brain cellular targets. Because some of the symptoms of "sickness behaviour" are similar to those found in FM patients, and considering the contrasting results present in the literature, we decided to conduct a detailed investigation of the cytokine network in FM patients. In this study, we characterized a cohort of 80 FM patients by means of several clinical investigations (rheumatological and psychiatric evaluations), biochemical analyses comprising plasma levels of pro-inflammatory and anti-inflammatory cytokines, aspecific markers of inflammation and immunological antibodies. Statistical analyses were used to search for correlations between biochemical data and clinical symtoms and to create a model (function) to diagnose FM and its severity.

Patients and methods

Patients

Eighty consecutive patients diagnosed with primary fibromyalgia based on the ACR criteria (13) were recruited at the Division of Rheumatology, University of Pisa (S. Chiara Hospital). All patients were female, with a mean age of 50.6 ± 12.2 (mean age ± SD). Exclusion criteria were: associated rheumatic or other medical disorders whose symptoms could overlap with those of fibromyalgia. Patients on medical treatment underwent a two-week drug-free period before blood samples were taken. Forty-five healthy female controls matched for age were also evaluated. This study was approved by the local Rheumatology and Psychiatry Ethics Committee, and all subjects gave their informed written consent before participating.

The tender points were evaluated in each subject using the Fischer dolorimeter (14); a rheumatologist applied the instrument at a rate of 1 Kg/s and the patient was instructed to say when the procedure became painful. The pain threshold (TP) was calculated for 18 points, and each TP was assigned a score between 0 and 3 based on the patient's degree of pain. The total fibro-

Table I. Age, Fibromyalgia Impact Questionnaire (FIQ) score, tender point (TP) score, and plasma cytokine levels (IL-1, IL-6, IL-8, IL-10 and TNF-α) in: (a) FM patients with depression; (b) FM patients with anxiety disorders (panic disorder, generalized anxiety disorder); (c) FM patients without any psychiatric illness; in the total group of FM patients; and (d) in 45 healthy controls. Values are expressed as the mean ± SD.

Variables	FM (a) n = 43)	FM (b) (n = 19)	FM (c) (n = 18)	Total FM (n = 80)	Controls (d) (n = 45)	Significant comparisons Kruskal-Wallis with Dunn's post-hoc Q test
Age	50.30 ± 12.60	51.30 ± 12.10	50.70 ± 15.00	50.60 ± 12.20	48.30 ± 14.90	-
FIQ	62.53 ± 23.01	52.85 ± 16.20	52.65 ± 15.28	59.24 ± 19.62	10.59 ± 10.05	-
TP	14.00 ± 4.00	13.00 ± 4.00	15.00 ± 3.00	14.00 ± 3.00	0.60 ± 0.90	-
IL-10 (pg/ml)	36.65 ± 44.22	17.50 ± 17.49	15.34 ± 15.55	24.54 ± 33.06	1.60 ± 3.54	d *vs* a, b, c, total FM
TNF-α (pg/ml)	24.73 ± 25.80	26.91 ± 36.31	17.89 ± 27.64	22.59 ± 29.25	11.07 ± 6.77	-
IL-8 (pg/ml)	64.79 ± 173.7	21.20 ± 31.98	66.30 ± 113.80	61.89 ± 149.00	7.90 ± 17.50	d *vs* c, total FM
IL-6 (pg/ml)	2.93 ± 4.66	3.44 ± 4.32	2.11 ± 3.24	2.76 ± 3.99	4.34 ± 4.51	-
IL-1 (pg/ml)	5.82 ± 12.18	4.94 ± 10.06	0.97 ± 1.55	4.54 ± 9.70	7.44 ± 6.62	d *vs* a, b, c total FM

IL-10: d *vs* a, $p < 0.001$; d *vs* b, $p < 0.001$; d *vs* c, $p < 0.01$; d *vs* total FM $p < 0.001$.
IL-8: d *vs* c, $p < 0.01$; d *vs* total FM, $p < 0.05$,
IL-1: d *vs* a, $p < 0.01$; d *vs* b, $p < 0.01$; d *vs* c, $p < 0.001$; d *vs* total FM, $p < 0.001$.

myalgic tender point score (right + left) was used for the statistical analysis. The tender point count was determined based on the number of tender points with a threshold ≤ 4 kg/cm^2. We also calculated the Tender Point Index (TPi) as the sum of the positive TP scores divided by the total number of TP.

To estimate the impact of fibromyalgia on the quality of life, all patients and controls completed the 10-item Fibromyalgia Impact Questionnaire (FIQ) (15, 16, 17). The total FIQ score reflected the impact of fibromyalgia and ranged from 0 (no impact) to 100 (maximum impact). The severity of pain was evaluated based on the pain items in the FIQ, each (except the first) of which consisted of a visual analogue scale from 0 to 10.

The onset of the FM symptoms was recorded as < 2 years or > 2 years before the present examination, according to Wallace (6).

The psychiatric evaluation was based on the administration of the Structured Clinical Interview for DSM-IV axis-I disorders (SCID-I/P) (18). This assessment was conducted by psychiatrists trained and certified in the use of this instrument by the Department of Psychiatry of the University of Pisa.

Laboratory tests

Blood samples were drawn from the patients and controls between 8.00 and 9.00 am and analyses were performed for aspecific markers of inflammation (ESR, CRP), fibrinogen, and the cytokines IL-1, IL-6, IL-8, IL-10, and TNF-α.

Cytokines were measured by ELISA in plasma diluted 1:2 (Bender MedSystem, Austria, Europe): IL-1 (BMS224/2, standard range 3.9-250 pg/ml, normal range 0-21 pg/ml), IL-6 (BMS213/2CE, standard range 1.6-100 pg/ml, normal range 0-8.5 pg/ml), IL-8 (BMS204/3, standard range 16-1000 pg/ml, normal range 0-47 pg/ml, dilutions of the standard were made to estimate the concentrations of controls), IL-10 (BMS215HS, standard range 0.39-25 pg/ml, normal range 0-8.9 pg/ml, FM plasma were diluted 1:4), and TNF-α (BMS223/3, standard range 8-500 pg/ml, normal range 0-14 pg/ml). All assays for the controls and patients were carried out blindly by a single operator at the same time and in the same runs. The intra-assay coefficients of variation were less than 8% for all cytokines.

Rheumatoid factor (RF) was measured in serum samples by means of the RapiTex®RF kit (Dade Behring), which is an enhanced immunoturbidimetric assay. Anti-nuclear factors (FAN) were detected by indirect immunofluorescence on Hep-2 cells. Anti-extractable nuclear antigen (ENA) antibodies were evaluated by means of the immunodiffusion technique.

Statistical methods

Data analysis was performed using non-parametric Kruskal-Wallis ANOVA with Dunn's *post hoc* test and Spearman's correlation.

Results

Table I reports the age, FIQ, tender points and cytokine levels of the FM patients and the controls. Symptom duration was less than 2 years in 26 patients and more than 2 years in 54 patients, with a mean disease onset of 8.1 ± 7.7 years (mean ± SD). The TP index (TPi) was 2.0 ± 0.6 (mean ± SD). Higher than normal levels of IL-10, TNF-α, and IL-8 were found in 42%, 24%, and 16.4% of the patients, respectively.

Psychiatric evaluation yielded the following results: 43 of the patients had a depressive disorder, 12 a panic disorder, 0 an obsessive compulsive disorder, 7 a generalized anxiety disorder, and 18 had no psychiatric illness. For our analysis, we also subdivided the FM patients into three groups based on their psychiatric profile (Table I): (a) FM patients with depression, (b) FM patients with anxiety disorders (panic disorder, generalized anxiety disorder), and, (c) FM patients with no psychiatric illness.

Statistical analysis showed that IL-10 levels were higher in all three subgroups of FM patients with respect to controls (IL-10: d *vs* a, $p < 0.001$; d *vs* b, $p < 0.001$; d *vs* c, $p < 0.01$; d *vs* total FM, $p < 0.001$), IL-8 levels were higher in patients without any psychi-

Table II. Measurements of CRP, ESR and fibrinogen in: (a) FM patients with depression; (b) FM patients with anxiety disorders (panic disorder, generalized anxiety disorder); (c) FM patients without any psychiatric illness; and in the total FM group. For the controls the normal range is reported. Values are expressed as the mean ± SD.

Variables	FM (a) (n = 43)	FM (b) (n = 19)	FM (c) (n = 18)	Total FM (n = 80)	Controls Normal range
CRP	0.44 ± 0.25	0.61 ± 0.79	0.40 ± 0.25	0.47 ± 0.44	0.05 mg/dl
ESR	12.42 ± 8.73	14.06 ± 9.39	12.33 ± 8.31	13.50 ± 9.10	0-30 mm
Fibrinogen	314.50 ± 71.15	345.10 ± 131.10	279.90 ± 56.52	314.10 ± 85.86	200-400 mg/dl

atric illness and in the total FM group with respect to controls (IL-8: d *vs* c, $p < 0.01$; d *vs* total FM, $p < 0.05$), while IL-1 was significantly lower in all three subgroups of patients with respect to controls (IL-1: d *vs* a, $p < 0.01$; d *vs* b, $p < 0.01$; d *vs* c, $p < 0.001$; d *vs* total FM, $p < 0.001$).

CRP levels (mean ± SD: 0.47 ± 0.44; normal range: 0-0.50 mg/dl) were higher in 25% of the FM patients, fibrinogen levels (314.10 ± 85.86; normal range: 200-400 mg/dl) were higher in 12%, and ESR (13.50 ± 9.10; normal range: 0-30 mm) was higher in 5% of the patients. No differences in CRP, fibrinogen or ESR values were found between the patients subdivided according to their psychiatric evaluation (Table II).

Immunological tests in the FM patients yielded the following results: 1.8% anti-ENA antibodies, 22.2% FAN (speckled), and 10.2% rheumatoid factor.

The following correlations between the aspecific biochemical marker of inflammation ESR and the total FIQ score and the FIQ subscores were found: ESR *vs* pain ($r = 0.242$, $P = 0.046$), ESR *vs* stiffness ($r = 0.339$, $P = 0.004$), and ESR *vs* fatigue ($r = 0.278$, $P = 0.021$), and ESR *vs* morning tiredness ($r = 0.298$, $P = 0.012$).

The specific marker of inflammation IL-6 was correlated with the pain score ($r = 0.305$, $P = 0.016$), the total FIQ score ($r = 0.298$, $P = 0.010$), and IL-10 levels ($r = 0.354$, $P = 0.003$). TNF-α levels correlated with the total FIQ score ($r = 0.234$, $P = 0.05$). IL-10 was positively correlated with IL-6, and also with IL-1 ($r = 0.492$, $P = 0.0001$) and TNF-α levels ($r = 0.472$, $P = 0.0001$). No correlations were found between cytokine determination and the parameters of the psychiatric evaluation.

There were no differences in the biochemical or clinical data between patients with a longer (> 2 yrs.) or shorter (< 2 yrs.) duration of symptoms.

Twenty-four patients had FIQ values lower than 50 (9-49), while 56 patients had FIQ values higher than 50 (50-98.5). The FM patients with an FIQ < 50 had a lower TP (12 ± 5 *vs* 15 ± 4), TPi (1.8 ± 0.7 *vs* 2.2 ± 0.6) and ESR (9.4 ± 6.9 *vs* 15.5 ± 9.5) than the FM patients with an FIQ > 50.

Discussion

The activation and regulation of cytokine patterns is implied in a variety of disease states, e.g., sepsis rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, multiple sclerosis and skin diseases (19). The hypothesis that cytokines may be involved in the generation of pain and hyperalgesia in inflammatory and neuropathic conditions (20) has been proposed based on recent evidence that cytokines establish communication between the immune system and the nervous system.

One recent development in medicine is the concept of sickness behaviour (12), a set of behavioural and physiological changes that patients undergo during the course of an infection; these are considered to be adaptive responses designed to maintain homeostasis during infection. It has now been demonstrated that the behavioural changes are due to the effects of pro-inflammatory cytokines on brain cellular targets. Upon stimulation, the immune system secretes pro-inflammatory cytokines that convey a message to the brain and re-organize behavioural priorities. The systemic or central injection of IL-1β, IL-6 and TNF-α in animals has been shown to induce sickness behaviour (21).

Since FM patients refer some symptoms similar to those of sickness behaviour, regarding physiological and emotional changes, we hypothesized that cytokines might play a role in linking the immune and the neural systems in FM. We carried out a study, to examine the plasma levels of IL-1, IL-6, IL-8, TNF-α, IL-10 and the levels of the aspecific markers of inflammation ESR and CRP in a group of 80 FM patients in order to determine whether there is a link between these analyses and FM.

Levels of plasma IL-10, IL-8 and of TNF-α were higher in a large percentage of our patients. These molecules play an important role in inflammation: IL-8 promotes sympathetic pain and is also involved in the hypothalamic-pituitary axis (HPA) and the sympathetic nervous system (SNS); TNF-α recruits peripheral blood mononuclear cells (PMNs), monocytes and natural killer cells. TNF-α has been reported to promote degeneration of the blood-brain-barrier and may also have adverse effects on brain cell function. Among the neuropsychiatric effects of TNF-α are fatigue and anorexia (22). The higher levels of IL-8 and TNF-α found in our FM patients suggest the presence of potential inflammation.

IL-6 and IL-1 levels were apparently lower, but not significantly different between patients and controls, with the exception of the finding of a significant correlation between IL-6 and pain. This data is consistent with other studies in the literature that have reported no great differences in serum and plasma IL-6 levels in FM patients compared to controls (6, 23, 24).

IL-10 levels were higher in FM patients than in controls. It is possible that IL-10 is released as a compensatory mechanism because of its reported role as an anti-inflammatory cytokine, although this mechanism could be inefficient given the observed persistence of symptoms in our patients. However, it

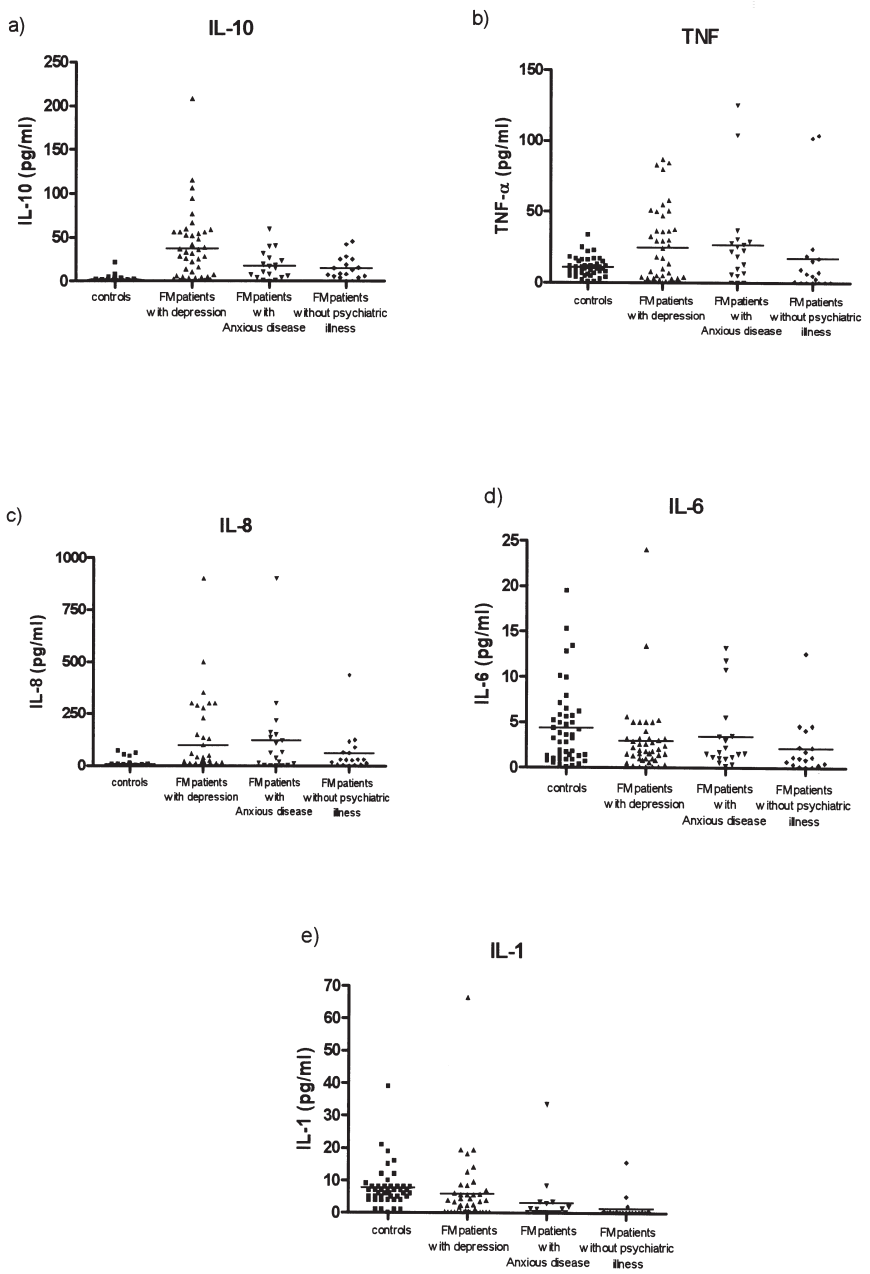

Fig. 1. Concentration of cytokines in FM patients with depression, FM patients with anxiety disorders (panic disorder, generalized anxiety disorder), FM patients without any psychiatric illness, and healthy controls.

should be noted that the increase in IL-10 levels was correlated with increased levels of IL-6 and TNF-α, and the IL-10 could, in this case, lead to chronic disease rather than having a positive effect. IL-10 has not been evaluated in previous studies so this hypothesis remains to be verified.

We did not find any differences in the cytokine levels concerning the duration of symptoms (< 2 years or > 2 years), in contrast to Wallace (6) who reported differences in IL-8 levels. We did find interesting correlations between the aspecific marker of inflammation ESR and some of the cardinal symptoms of FM such as pain, stiffness, fatigue, morning tiredness. These results highlight a parallelism between the clinical symptoms and biochemical data.

One of the main symptoms of inflammation is pain, which is also a primary symptom of FM. Recent evidence has shown that cytokines are involved in the generation of generalized pain and hyperalgesia in inflammatory and neuropathic conditions. Our results suggest that chronic sub-inflammation and an impaired response of the immune system to stressors may be present in FM.

The majority (54%) of our FM patients showed symptoms of depression, a result that is in accordance with the strong comorbidity observed between fibromyalgia and major depression (25).

The recent theory that cytokines transmit messages from the periphery to the brain by means of humoral and neural pathways may explain the mood disorders (anxiety, depression) observed in FM patients. Other studies have linked the activation of this system to the mood disorders observed in patients suffering from chronic inflammatory disorders including autoimmune disease, coronary earth disease and asthma (26), as well as in patients with psychiatric disorders (27-29).

Our data revealed higher levels of IL-10 and IL-8 in all FM patients, irrespective of the presence or absence of psychiatric disturbances, compared to controls. Therefore, it may be concluded that the cytokine pattern in FM patients with psychiatric symptoms is similar to that of FM patients taken as a whole.

In conclusion, our study shows the presence of a mechanism of sub-inflammation activated by increased IL-8 levels in FM patients and confirmed by consensual feedback, the negative production of IL-10, and by the correlation between IRS and rheumatological clinical features. The similar cytokine patterns found in FM patients with depressive symptoms, those with anxiety disorders, and those without any psychiatric disease suggest that IRS impairment itself may play a specific role in fibromyalgia.

Evaluations of IL-10 levels and the FIQ could be useful instruments to make a correct diagnosis and evaluate the severity of fibromyalgic disease.

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