Spasmophilia comorbidity in fibromyalgia syndrome

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ABSTRACT

Objectives. *To evaluate the role of spasmophilia (SP) in fibromyalgia syndrome (FM).*

Methods. *Three hundred and fourteen patients (280 F, 34 M) with a diagnosis of FM or FM and spasmophilia (FM+SP) were recruited. Clinical assessment of patients and controls included the Questionnaires FIQ, HAQ and the tender point (TP) count. Lifetime or ongoing psychiatric aspects were evaluated by trained psychiatrists by means of the classic scales: Structured Clinical Interview (SCID) for DSM-IV. The following analysis were evaluated: cytokine (IL1, IL2, IL6, IL8, IL10), TNF-α, cortisol, GH, ACTH, IGF1, 5HT, intracellular Mg, plasma calcium p(Ca), PTH, (25(OH)D) and thyroid functionality. Some typical symptoms were investigated.*

Results. *Eighty-one patients resulted positive for spamophilia (FM+SP), while 233 resulted negative for spasmophilia (FM). The mean TP number resulted higher in the FM group (15.33±3.88) with respect to FM+SP (12.88±6.17, p=0.016), while FIQ and HAQ did not differ between the two studied groups.*

FM patients exhibited a higher frequency of psychiatric disorders with respect to FM+SP patients (72% FM vs. 49% FM+SP, p<0.01). In particular the frequency of depression was 65.5% FM vs. 35% FM+SP (p<0.01).

Conclusions. *The presence of spasmophilia seems to influence psychiatric comorbidity which was less prevalent in FM+SP patients. FM is indeed characterised by an abnormal sensory processing of pain that seems to result from a combination of interactions between neurotransmitters, stress, hormones and the nervous system; spasmophilia would seem to be more linked to a dysfunction at the neuromuscular level.*

Introduction

Fibromyalgia syndrome (FM), is a chronic, generalised pain condition (1) with characteristic tender points on physical examination (regions of the body that evoke severe pain upon gentle digital palpation), often accompanied by a number of associated symptoms such as fatigue, sleep disturbance, headache, irritable bowel syndrome, temporomandibular joint disorder and mood disorders (2). It has a high prevalence in the general population (2–3%) and the condition is more common amongst women than in men, representing in women 30% of all rheumatic diseases. Moreover, FM may be associated with other rheumatic diseases (rheumatoid arthritis, lupus, Sjögren's syndrome) which aggravate the clinical picture.

The pathogenesis is still not clear, but emerging data suggest a neuro-hormonal (3) and neuro-transmitter dysregulation (4) and a central sensitisation of the nervous system (5-9) .

FM is often accompanied by the presence of latent tetany or spasmophilia. The term spasmophilia was proposed in 1874 by Wilhelm Heinrich Erb although two French researchers, Dauce in 1831 and Corvisart in 1852, had laid the foundations for an independent classification called "tetany morbid events in spontaneous muscle contractions". In the early 1900s, Mac Callum discovered that the cause of tetany in the course of hypoparathyroidism was hypocalcemia, and in 1940 Lerique identified frameworks of neuromuscular hyperexcitability that were not hypocalcemic defined as "latent tetany". Finally, in 1959 Scarlett and De Coucker discovered that the spasmophilia normocalcaemia could also be secondary to hypomagnesaemia (10).

Two types of tetany have been distinguished: manifest and latent (spasmophilia); the latter requires provocative tests to be highlighted. The former,

due to hypocalcemia, is relatively rare and usually postoperative (parathyroid tetany), while the mechanism of the much more common latent tetany or spasmophilia involves hyperventilation and magnesium deficiency. Latent tetany particularly affects young women (11). There are many signs of spasmophilia, but none is specific, so this pathology is difficult to diagnose (12).
Chvostek and Trousseau signs are easily evoked to manifest a latent tetany (13, 14). Chvostek is a sign of the involuntary contraction of facial muscles caused by light repeated percussions of the facial nerve immediately anterior to the external auditory meatus. It is present in 10% of healthy individuals and is often absent in chronic hypocalcemia. Trousseau's sign consists of triggering a carpo-pedal spasm by reducing the blood supply to the hand with a tourniquet or sphygmomanometer applied to the forearm for 3 minutes. The Trousseau sign is also seen in alkalosis, hypomagnesemia, hypokaliemia, and in about 6% of individuals without any identifiable electrolyte disturbances. Latent tetany may become overt with the further reduction of ionised calcium after hyperventilation or somministration of NaHCO3 or diuretics that cause depletion of calcium.
Normocalcemic tetany may be defined as a pathologic state attributable to a deficit of magnesium, and characterised by signs and symptoms typical of neuromuscular excitability (painful muscle cramp) and psychosomatic manifestation.
Because we observed that some of the patients clinically diagnosed as fibromyalgic in our Division of Rheumatology presented also spasmophilia the aim of the present work is to evaluate the influence of this comorbidity in fibromyalgia syndrome.

Materials and methods

Subjects and methods

We retrospectively studied a cohort of 314 patients (280 F, 34 M) affected by fibromyalgia (FM) or fibromyalgia and spasmophilia (FM+SP). The patients were recruited and clinically classified at the Division of Rheumatology, University of Pisa (S. Chiara Hospital). FM patients were classified according to the 1990 American College of Rheumatology criteria (ACR criteria) (1). Exclusionary criteria for patients were the presence of any additional rheumatic or neoplastic disease.
The diagnosis of spasmophilia was based on clinical and electromyographic criteria. At least 4 of the following symptoms had to be present: cramps and/or titanic crisis, paresthesia, tachycardia and/or dyspnea, asthenia and dizziness. Electromyography, carried out on the first interosseus of the hand had to be positive.
All patients were drug-free or had a drug wash-out period of at least 2 weeks before clinical evaluation and blood sampling.
The Ethics Committee of the University of Pisa approved the study protocol.

Evaluation of clinical parameters

Tenderness at tender points was evaluated in each subject by digital pressure (1). The pain threshold was calculated for 18 points, and the tender point (TP) count was determined by the number of tender points that had a threshold of ≤4 kg/cm^2. The total fibromyalgic tender point score (right + left) was used in the statistical analysis.
To estimate the impact of fibromyalgia on the quality of life, all the patients received a "Fibromyalgia Impact Questionnaire" consisting of 10 items (15) as well as the Health Assessment Questionnaire (HAQ) (16). The FIQ total score, which indicates the impact of the disease on life, ranged from 0 (no impact) to 100 (maximum impact). HAQ varies between 0 and 3. Each patient was asked if they had frequently suffered from any of the following symptoms (17, 18) in the past 12 months: fatigue, non-restful sleep, anxiety, depression, irritable bowel syndrome, constipation, diarrhoea, fingers turning blue/white in the cold (Raynaud's phenomenon), paresthesiae (tingling in arms/legs), articular stiffness, muscular stiffness, dry eyes, dry mouth, temporomandibular disorders (TMD), muscle spasms, tension headache, allergy, low back pain, restless leg syndrome, gastroesophageal reflux disease, burning/pain with urination, dizziness, allodynia, traumatic event, blurred vision, sore throat, tachycardia and dyspnea.
Also disease duration (years) was taken into consideration.
Spasmophilia was evaluated by surface electromyography (SEMG) with surface electrodes as reported subsequently in the text.

Evaluation of psychiatric comorbidity

Lifetime or ongoing psychiatric aspects were evaluated by trained psychiatrists by means of the classic scales: Structured Clinical Interview (SCID) for DSM-IV (19).

Analytical measures

Blood samples were taken early in the morning and after an overnight fast. The following analysis were measured: thyroid stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3), antithyroglobulin (TgAb) and antithyroid peroxidase (TPOAb) antibodies, routine laboratory chemistry (ESR and CRP), cytokine (IL1, IL2, IL6, IL8, IL10), tumour necrosis factor α (TNF-α), cortisol, growth hormone (GH), adreno-cortico-tropic-hormone (ACTH), insuline-like growth factor (IGF1), serotonin levels (5HT), red blood cell magnesium (intracellular Mg, iMg), plasma calcium p(Ca), parathormone (PTH).

Myoelectric measurement

Electromyography measures the electrical potentials that are formed in a muscle during its contraction. The individual potentials reflect the activity of a group of motor units in the case of surface electrodes. Compared to more established needle electromyography, SEMG provides more comprehensive information relating to the muscle (metabolic state) and avoids the risk of using needles.
Surface electrodes were applied to the opposing muscle of the thumb, then using a sphygmomanometer cuff, a pressure greater than 20 mmHg of the patient's systolic blood pressure was applied to the arm, and the spontaneous activity within 10 minutes of ischemia was recorded as well as after ischemia, and then during hyperpnea for 3 minutes. Surface electromyogra-

Table I. Demographic data and clinical characteristics of the patients.

Patients	Age	Sex	Disease duration (years)	FIQ	HAQ	TP
FM (n=233)	47.52 ± 12.19	210F, 23M	6.8 ± 7.4	59.75 ± 18.68	0.81 ± 0.59	15.33 ± 3.88*
FM+SP (n=81)	44.44 ± 10.75	70F, 11M	7.5 ± 7.0	60.0 ± 9.89	0.91 ± 0.61	12.88 ± 6.17*

(FM: fibromyalgic patients; FM+SP: fibromyalgic patients with spasmophilia comorbidity). Results are expressed as mean±SD.
*Tender point, FM *vs*. FM+SP; p=0.016 (Mann-Whitney U-test).

phy (SEMG) was considered positive for spasmophilia in the presence of doublets, triplets and multiplets at baseline and/or after the application of an ischaemic stimulus.

Statistical analysis was performed by the non-parametric Mann-Whitney U-test and the Pearson's chi-square test.

Results

The demographic data and clinical characteristics of the fibromyalgic patients are shown in Table I. All the patients studied resulted normocalcemic. Eighty one patients resulted positive for spamophilia (FM+SP), while 233 resulted negative for spasmophilia (FM). There are no differences in age and disease duration between the two study groups, while sex ratio (M/F) was slightly different between the two groups of patients: 1/7 in FM+SP patients, 1/9 in FM patients. FIQ and HAQ did not differ between the two studied groups.

The mean TP number resulted higher in the FM group (15.33±3.88) with respect to FM+SP (12.88±6.17, p=0.016). Symptoms comparison evidenced some differences between FM+SP and FM patients (Table II): restless leg syndrome (59% FM+SP *vs*. 44% FM), and tachycardia (46% FM+SP *vs*. 31% FM) were more frequent in FM+SP patients with respect to FM patients, instead allergies (23% FM+SP *vs*. 38% FM) resulted less frequent in FM+SP patients. Other symptoms more represented in the FM+SP group of patients, even if not reaching significant values, were the following: articular stiffness, dry mouth, muscle spams and gastro oesophageal reflux disease.

We found high levels of IL2 (10.76±21.40 pg/ml) and IL10 (19.53±31.06 pg/ml) in both the groups of patients. However, cytokine plasma levels did not differ between FM+SP and FM patients, except for TNF-α plasma levels with higher results at nearly significant values, in the FM+SP group of patients (FM: 14.28±39.34; FM+SP: 23.07±53.88 pg/ml, p=0.06). FM+SP patients showed the following concentrations significantly different with respect to FM patients: growth hormone levels (FM: 2.13±3.20, FM+SP: 3.95±4.76 ng/ml, p=0.002) were higher while intracellular Mg concentrations resulted lower (FM: 4.35±0.58; FM+SP: 3.95±0.56 MEq/L, p=0.0001) even if in the normal range.

The other laboratory parameters measured did not differ between the two groups of patients studied.

The percentage of positive AbTPO and AbTg and the values of TSH, fT3 and fT4 were similar between FM and FM+SP patients (data not shown).

Psychiatric comorbidity, calculated according to the psychiatric evalua-

Table II. Self reported symptoms of patients without spasmophilia (FM) and patients with fibromyalgia and spasmophilia (FM+SP). Values are expressed in percentages.

	Patients without spasmophilia (n=233)	Patients with spasmophilia (n=81)	p-value
Fatigue	90	90	0.836
Non-restful sleep	69	75	0.414
Anxiety	60	61	0.958
Depression	38	42	0.977
Irritable bowel syndrome	67	60	0.943
Constipation	43	37	0.495
Diarrhoea	24	22	0.958
Fingers turn blue/white in the cold	31	22	0.240
Paresthesiae	63	65	0.869
Articular stiffness	75	81	0.333
Muscular stiffness	77	74	0.783
Dry eyes	50	43	0.394
Dry mouth	44	54	0.240
TMD§	49	53	0.730
Muscle spasms	44	55	0.157
Tension headache	50	54	0.684
Allergy	38	23	0.034*
Low back pain	58	57	0.972
Restless leg syndrome	44	59	0.049*
Gastroesophageal reflux disease	49	57	0.336
Burning/pain with urination	23	26	0.641
Dizziness	49	45	0.659
Allodynia	57	49	0.307
Traumatic event	42	36	0.520
Blurred vision	41	43	0.917
Sore throat	32	35	0.783
Tachycardia	31	46	0.042*
Dyspnea	55	48	0.754

(§TMD: Temporomandibular disorders).

tions, was different between the two subgroups and FM patients exhibited a higher frequency of psychiatric disorders with respect to FM+SP patients (72% FM *vs*. 49% FM+SP, $p<0.01$). In particular the frequency for depression was 65.5% in FM patients *vs*. 35% in FM+SP patients ($p<0.01$) and panic disorder was 47.2% in FM patients *vs*. 39% FM+SP patients.

Discussion

There are no relevant data in the literature that analyse the characteristics of patients with spasmophilia. In our study some significant differences emerged between the group of patients affected by fibromyalgia and the group of fibromyalgic patients positive for spasmophilia.

Male sex was slightly more represented in fibromyalgic patients positive for spasmophilia (FM+SP) than in fibromyalgic patients negative for spasmophilia (FM).

There was no difference regarding the quality of life (FIQ), fatigue, pain and other evaluated symptoms, while we found a lower mean TP number in FM+SP patients. Restless leg syndrome and tachycardia were more frequent in FM+SP patients, while allergies were less frequent. As far as restless leg syndrome, there are controversial results in the literature regarding the role of Mg: Popoviciu *et al*. (20) indicated that serum Mg is low in restless leg syndrome (RLS), and Hornyak (21) and Bartel (22) found that intravenous Mg in pregnancy was therapeutic to RLS. On the contrary, Walters (23) did not confirm these results, finding no statistically difference between RLS patients and controls in either serum or cerebrospinal fluid Mg.

We revealed high values of IL2 and IL10 in both the group of patients studied. In particular 65% of the FM-patients and 59% of FM+SP patients had elevated levels of IL2, 30% of FM patients and 41% of FM+SP patients had elevated levels of IL10.

Unlike the results found in the literature (24, 25), our study did not reveal high values of IL-8 in either FM+SP or FM patients, but we confirmed the presence of high levels of IL-10 in both the studied groups (25, 26). In particular, IL10 plasma levels in the FM+SP patients resulted higher with respect to FM patients, even if not reaching statistic significance. Moreover, TNF-α plasma levels resulted higher in the FM+SP patients.

The possibility that the activation and regulation of the cytokine pattern might be involved in the genesis of pain and hyperalgesia was recently proposed (27, 28) based also on the development of the concept of "sickness behaviour" (29). In particular it has been suggested that cytokines may act as a link between the immune and nervous system in FM (25, 30), given the fact that FM patients have symptoms similar to sickness behavior. Given our results a role for cytokines might be hypothesized for the genesis of spasmophilia symptoms.

We observed lower intracellular magnesium (Mg) levels in spasmophilic patients, although within the normal range, and this is consistent with the pathogenesis of spasmophilia. Mg, the second most prevalent intracellular cation in the body, plays an important role in enzyme activity, membrane stability, and ion transport (31, 32). Mg deficit may be due to gastrointestinal and renal mechanisms not efficient for Mg conservation (20). Moreover there are known morbid conditions that produce body Mg loss (diabetes, alcoholism, malabsorption) and medications (diuretics, cyclosporine, aminoglycosides, cisplatin, amphotericin B) which exacerbate the problem (34).

Mg has been shown to inhibit the N-methyl-D-aspartate (NMDA) receptor (35), activation of which induces the release of neurotransmitters, such as substance P. A reduction in extracellular Mg lowers the threshold levels of excitatory amino acids (*i.e*. glutamate) necessary to activate this receptor. This neurogenic response is followed by the release of proinflammatory cytokines (TNF-α, IL-1β, IL-6) by T lymphocytes during the first week of dietary depletion (36). In fact TNF-α receptor knockout in mice reduces adverse effects of Mg deficiency on bone (37).

Exogenous and endogenous catecholamines have been shown experimentally to result in a slight drop (approximately 0.2 mEq/L) in the serum Mg concentration, and increased catecholamine secretion could be a contributing cause of hypomagnesemia in acute illness and stress (38, 39). In this context, it would be interesting to know the cathecolamine levels in spasmophilic patients.

GH levels were significantly higher in FM+SP patients with respect to FM patients, even if in the normal range. Patients had GH levels <1 ng/ml with the following percentages: FM+SP 38%, FM 54%. It is known that patients with fibromyalgia have an abnormal sleep pattern involving stages 3 and 4 of non-REM sleep (40). As growth hormone is secreted predominantly during stages 3 and 4 of non-REM sleep, it was hypothesized that fibromyalgia may be associated with impaired secretion of growth hormones (41). In fact, about one third of patients with fibromyalgia have low IGF-1 levels (42). Furthermore, the growth hormone is important in maintaining muscle homeostasis (43), and it was theorised that suboptimal levels may be a factor in the impaired resolution of muscle microtrauma in fibromyalgia (44). We observed that both the group of patients with FM+SP and FM referred non-restful sleep with no difference in incidence. We cannot explain the meaning of higher GH levels in patients with spasmophilia, we may only hypothesize a role for GH in spasmohilia which should be further investigated.

The incidence of autoimmune thyroiditis in the two studied groups is similar and in agreement with literature (45, 46). This finding leads us to suppose that in FM+SP patients, as in FM patients, it might have a role in worsening the typical symptoms.

The psychiatric comorbidity of FM patients resulted in agreement with the literature (47, 48). Interesting differences emerged from the comparison between the two groups: FM patients had a higher incidence of psychiatric disorders, in particular of depressive disorders with respect to spasmophilic patients. In the studied FM+SP patients, panic disorder unexpectedly was not representative, as panic disorder and latent tetany appear to occur concomitantly (49).

Regarding mood perception, it was probably distorted in both groups of patients because the incidence of anxiety and depression calculated from the self-reported symptoms was not similar to that calculated from the psychiatric evaluation.

In conclusion, the most peculiar differences between FM+SP and FM patients that emerged from our study were: lower levels of intracellular Mg in FM+SP patients, which confirm the typical symptoms and higher levels of TNFα in patients with FM+SP, which might be linked to the lower iMg levels. Moreover, FM+SP patients had fewer tender point numbers and a lower incidence of psychiatric disorders than FM patients.

The most interesting result, which seems to further differentiate the two diseases, is represented by psychiatric comorbidity that is clearly prevalent in FM patients.

FM is indeed characterised by an abnormal sensory processing of pain that seems to result from a combination of interactions between neurotransmitters, external causes, stress, hormones and the nervous system, while spasmophilia would seem more linked to a peripheral dysfunction at the neuromuscular level, and these considerations might be useful to differentiate the treatment.

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