Misdiagnosis in fibromyalgia: a multicentre study

M. Di Franco[1], C. Iannuccelli[1], L. Bazzichi[2], F. Atzeni[3], A. Consensi[2], F. Salaffi[4], M. Pietropaolo[1], C. Alessandri[1], S. Basili[5], M. Olivieri[1], S. Bombardieri[2], G. Valesini[1], P. Sarzi-Puttini[3]

[1]*Department of Internal Medicine and Medical Specialities, Sapienza University of Rome, Rome, Italy;*
[2]*Rheumatology Unit, University of Pisa, Pisa, Italy;*
[3]*Rheumatology Unit, L. Sacco University Hospital, Milan, Italy;*
[4]*Rheumatology Unit, Polytechnic University of Marche, Italy;*
[5]*Department of Internal Medicine and Medical Specialities, Sapienza University of Rome, Rome, Italy.*

Manuela Di Franco, MD
Cristina Iannuccelli, MD
Laura Bazzichi, MD
Fabiola Atzeni, MD
Arianna Consensi, MD
Fausto Salaffi, MD
Mario Pietropaolo, MD
Cristiano Alessandri, MD
Stefania Basili, MD
Marta Olivieri, MD
Stefano Bombardieri, MD, PhD
Guido Valesini, MD, PhD
Piercarlo Sarzi-Puttini, MD

Please address correspondence to:
Manuela Di Franco, MD,
Dipartmento di Medicina Interna e Specialità Mediche,
Sapienza Università di Roma,
Via del Policlinico 155,
00161 Roma, Italy.
E-mail: manuela.difranco@uniroma1.it

Received on December 20, 2011; accepted on December 21, 2011.

Clin Exp Rheumatol 2011; 29 (Suppl. 69): S104-S108.

Key words: fibromyalgia, misdiagnosis, underdiagnosis

Funding: This study was supported by the Fondazione Umberto Di Mario, Rome.

Competing interests: none declared.

ABSTRACT

Background. *Fibromyalgia (FM) is the second most common cause of visits to rheumatologists after osteoarthritis, and may be difficult to diagnose in many patients. It is associated with various rheumatic disorders such as rheumatoid arthritis, spondyloarthropathies (SpA) and connective tissue disease (CTD), and a late diagnosis or misdiagnosis is a common and underestimated problem.*

Objectives. *The aim of this study was to investigate the "underdiagnosis" of FM, and which rheumatic diseases tend to be confused with it.*

Methods. *The following data were collected at baseline: symptoms, disease duration, physical examination findings, previous and current investigations and management, laboratory tests, tender point count, tender and swollen joint counts, and spinal pain. The clinimetric evaluation included the Fibromyalgia Impact Questionnaire (FIQ) and Fibromyalgia Assessment Status (FAS).*

Results. *The study population consisted of 427 outpatients (418 females and 9 males; mean age 49.3 years; mean disease duration 8.5 years). Fifty-seven patients (13.3%) had been previously misdiagnosed as having other musculoskeletal disorders (MSDs); 370 patients had been previous correctly diagnosed as having FM, or were diagnosed as having it during the course of the study. The FM and MSD groups were comparable in terms of demographic data and referral patterns. Disease duration was longer and the erythrocyte sedimentation rate was higher in the MSD patients, who also had less severe FIQ and lower pain visual analogue scale scores. Moreover, the FIQ and FAS scores correlated in the MS group.*

Conclusions. *The findings of this study suggest that, although FM is a well-known clinical entity, differential diagnosis with SpA, CTD and inflammatory arthritis can still be a challenge for rheumatologists and general practitioners.*

Introduction

Fibromyalgia syndrome (FM) is a chronic multi-symptom disease characterised by widespread pain (1, 2) that affects approximately 2–3% of the general population; more than 90% of the patients are female (3). It is the second most common cause of visits to rheumatologists after osteoarthritis, and is associated with substantial morbidity and disability (4), which means that it is also a substantial economic burden for national health systems. One recent study has estimated that total FM-related costs are €7900 per patient year (€910 in direct and €6990 in indirect costs) in France, and €7256 (direct €1765, indirect €5491) in Germany; furthermore, as these costs increase with the severity of the disease, there is a difference of more than 200% in the costs of mild and severe FM (5). In addition to avoiding further stress for patients and frustration for physicians, a precise and early diagnosis would therefore reduce national healthcare costs.

According to the 1990 American College of Rheumatology classification criteria (1), a diagnosis of FM requires the presence of widespread pain, and tenderness in at least 11 out of 18 tender points (TPs) for at least three months, and new diagnostic criteria have recently been proposed that include cognitive problems and somatic symptoms that were not even considered in the 1990 ACR criteria. However, with the exclusion of TP counts, these criteria are not always adopted by primary care physicians and or even rheumatologists (6).

Diagnosing FM can be difficult because it encompasses a very wide range of symptoms that can be confused with

those of other rheumatic and non-rheumatic diseases, including fatigue, sleep disturbances, psychological and cognitive alterations, headache, muscle stiffness, migraine, variable bowel habits, diffuse abdominal pain and urinary frequency (1,2). It therefore requires differential diagnoses with a number of medical conditions. Interestingly enough, the 1990 ACR criteria specifically state that FM is not a diagnosis of exclusion, and the same is true of the 2010 diagnostic criteria: "patients do not have a disorder that would otherwise explain the pain" (6).

On the other hand, the finding of abnormal serology or radiographic changes does not rule out a diagnosis of FM. This is an important point because FM may accompany rheumatic disorders such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and Sjögren's syndrome (SS) (7) and, in this context, a late diagnosis or misdiagnosis is a common and underestimated problem. One recent study found that referring physicians were disturbingly inaccurate in diagnosing FM and that this mainly led to over-diagnosis (8).

The aim of this study was to investigate the "underdiagnosis" of FM, and which rheumatic diseases tend to be confused with it. We examined the characteristics of previously misdiagnosed FM patients, and tried to identify the clinical, clinimetric and/or laboratory characteristics that might help to distinguish the patients finally diagnosed as having FM from those with other musculoskeletal diagnoses.

Methods

Patients

The study involved a total of 427 consecutive outpatients complaining of chronic widespread pain with a previous or new diagnosis of FM (418 females and 9 males; mean age 49.3 years; mean disease duration 8.5 years) referred to the Fibromyalgia Clinics of the Rheumatology Departments of the Sapienza University of Rome, the University of Pisa, the L. Sacco Hospital in Milan, and the Polytechnic University of Marche in Ancona, between March 2009 and December 2010. The diagnosis of FM was based on the American College of Rheumatology (ACR) 1990 classification criteria (1). Patients with concomitant FM and other confirmed diagnosis were excluded from this study.

All the patients underwent a predetermined protocol of investigations that included recording their demographic data and medical history, symptoms, disease duration, previous and current investigations and management, physical and rheumatological examination findings, laboratory test results, and the results of clinimetric tests validated for FM. The physical examination included a TP count according to the ACR criteria, tender and swollen joint count, and a spinal examination for presence of pain. The baseline laboratory tests included the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), anti-citrullinated protein antibodies (ACPAs), and antinuclear antibodies (ANAs) The clinimetric evaluation included the Fibromyalgia Impact Questionnaire (FIQ) (9), the Health Assessment Questionnaire (HAQ) (10) and 100 mm patient-rated pain, fatigue, anxiety and depression (Fatigue, anxiety and depression VAS).

A subgroup of 245 patients also completed the Fibromyalgia Assessment Status (FAS) (11).

It was recorded if the patients had undergone previous instrumental investigations in order to identify the musculoskeletal disease such as plain radiography, ultrasonography (US), scintigraphy, computed tomography (CT), magnetic resonance imaging (MRI), nailfold capillaroscopy, electroneurography/electromyography, computerised bone mineralometry, and salivary gland biopsy. All previous and current pharmacological treatments were also recorded as non-steroidal anti-inflammatory drugs (NSAIDs), steroids, disease-modifying anti-rheumatic drugs (DMARDs), or biological agents.

The study was approved by the ethics committees of the participating centres, and written informed consent was obtained from all of the subjects.

Statistical analysis

The results were analysed using a commercially available statistical software package (SPSS, version 11.5; SPSS Inc, Chicago, IL). Student's unpaired *t*-test and Pearson's product-moment correlation analysis were used for the normally distributed continuous variables, and appropriate non-parametric tests (the Mann-Whitney U-test and Spearman's rank correlation test) for all of the other variables. Categorical variables were reported as counts and percentage and the indipendence was tested by chi-square test. Multiple linear regression analyses were used to quantify the relationships between variables further. The differences between baseline and post-treatment values were analysed using Wilcoxon's signed rank test. An α-value of 0.05 was considered statistically significant; all the given *p*-values are two-tailed.

Results

The study population consisted of 427 outpatients (418 females and 9 males; mean age 49.3 years; mean disease duration 8.5 years), 57 of whom (13.3%; mean age 51.7 years; mean disease duration 10.8 years) had been referred with other uncorrected diagnosis (UD); the others had been previously correctly diagnosed as having FM or were diagnosed as having it during the course of the study. Table I and Figure 1 summarise the study results. The previous diagnoses in the referral group with UD were arthritis (RA, or undifferentiated arthritis (UA); 13 cases), connective tissue diseases (CTDs: SS, undifferentiated connective tissue disease (UCTD), SLE; 15 cases), spondyloarthropathies (psoriatic arthritis (PsA), ankylosing spondylitis (AS), Behçet's disease; 16 cases), and other diseases (osteoarthritis (OA), low back pain, arthralgia, hepatitis C virus (HCV) infection; 13 cases).

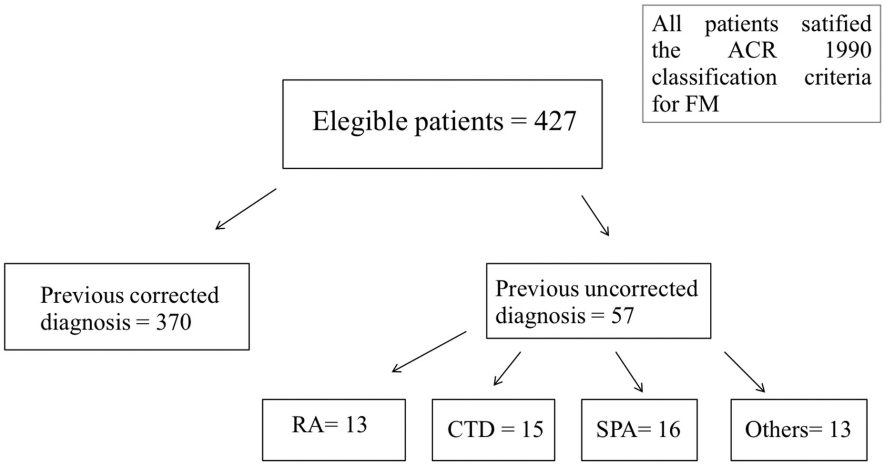
The FM and UD groups were comparable in terms of demographic data and referral patterns, but disease duration was longer and ESR higher in the UD patients, who also had less severe FIQ and pain VAS scores (Fig. 2).

The patients in the UD group had significantly more frequent ANA and RF positivity at low titres (<1:160 and <20 U/L) (p=0.02) with respect to the FM

Table I. Characteristics of the 427 FM patients and the UD patients included in this study.

	FM patients (n=370)	UDG patients (n=57)	*p*-value
Age	49.3 ± 8.5	51.7 ± 10.8	NS*
Disease duration (years)	8.05 ± 6.9	11.07 ± 7.04	$p<0.0001$*
RA (n. of pts)	0	13	$p<0.0001$#
CTD (n. of pts)	0	15	$p<0.0001$#
SpA (n. of pts)	0	16	$p<0.0001$#
Other misdiagnoses (n. of pts)	0	13	$p<0.0001$#
Diagnostic investigations (n.)	75	155	$p=0.006$#
ESR	13.4 ± 12.2	16.21 ± 12.5	$p<0.01$*
CRP	0.01 ± 0.1	0.05 ± 0.2	NS*
Autoantibodies	0.09 ± 0.2	0,19 ± 0.3	$p=0.02$*
Clinical examinations (n.)	75	155	$p=0.006$*
TP	14.4 ± 7.1	15 ± 3.2	NS*
FIQ	65 ± 18.2	60 ± 18.6	$p=0.04$*
HAQ	1.25 ± 0.8	1.23 ± 0.8	NS*
Pain VAS	7.27 ± 2.3	6.7 ± 2.2	$p=0.04$*
Fatigue VAS	8.01 ± 2.4	7.5 ± 2.5	$p=0.05$*
Stiffness VAS	7.59 ± 2.4	6.95 ± 2.7	NS*
Anxiety VAS	6.34 ± 2.9	6.31 ± 2.5	NS*
Depression VAS	5.77 ± 3.3	6.08 ± 2.8	NS*

*Mann-Whitney U-test; #Chi-squared test.
FM: Fibromyalgia; UDG: Uncorrected diagnosis group; RA: Rheumatoid Arthritis; CTD: Connective Tissue Disease; SpA: Ankylosing Spondylitis; ESR: Erythro sedimentation rate; CRP: C- reactive protein; TP: Tender Points; FIQ: Fibromyalgia Impact Questionnaire; HAQ: Health Assessment Questionnaire; VAS: Visual Analogue Scale.



RA= rheumatoid arthritis; CTD= connective tissue diseases;
SPA= spondiloarthropaties,

Fig. 1. Newly referred rheumatology patients with chronic muskoloskeletal pain.

group. None of the patients in either group was ACPA positive.

Moreover, there were significant differences in the use of NSAIDs, steroids, DMARDs and biological agents ($p<0.0001$ for each class of drugs) between the FM and UD group.

The FIQ and FAS scores correlated in the UD group (Fig. 3): this was expected because the FAS index is a valid three-item instrument (pain, fatigue and sleep disturbances) that performs at least as well as the FIQ in FM patients (12).

Thirty-three patients (58%) in the UD group had undergone one or more previous instrumental investigations such as spine or hands x-rays, sacroiliac joint MRI or joint ultrasonography.

The ESR was out of the normal range in 16 patients, but almost all of the patients had nearly normal CRP levels.

Discussion

Musculoskeletal pain is a common symptom in patients with rheumatic diseases, but it is not always easy to discover its cause. Pain is certainly a cornerstone for a diagnosis of FM, but it is accompanied an array of multi-system symptoms (such as fatigue, Raynaud's phenomenon, sleep disturbances, muscle stiffness, sicca syndrome, irritable bowel disease, depression and anxiety) that act as confounding factors because they are common to various musculoskeletal conditions, and the absence of specific laboratory findings for FM can easily lead to a misdiagnosis. Furthermore, FM may be confused with a wide spectrum of rheumatic and non-rheumatic conditions, and can also be associated with other inflammatory rheumatic diseases or co-exist with them (13).

Only two studies have investigated the overdiagnosis of FM by general practitioners and rheumatologists. Fitzcharles and Boulos found that 59% of the patients referred with a diagnosis of FM had some other primary rheumatic process to account for symptoms, and that inflammatory rheumatic conditions accounted for almost one-half of the misdiagnoses (8, 14). It is therefore not always easy to diagnose FM and, in order to avoid the mistakes that lead to overdiagnosis, it is important that other diagnostic possibilities are considered, especially by the primary care physicians who mainly manage patients with widespread musculoskeletal pain.

Wolfe et al. found that approximately 25% of the patients diagnosed as having FM by their primary care physicians did not satisfy the ACR classification criteria (1). However, neither the ACR classification criteria nor the diagnostic criteria suggested by the Authors in the paper can provide a solution for this classification open issue, which probably arises because a diagnosis of FM is often based on severity assessments (6), and the absence of a gold standard or case definition for FM may explain the misdiagnosis.

The aim of this open multicentre study was to estimate the underdiagnosis of FM and highlight the principal reasons for it: 13.3% of our patients were initially not diagnosed as having FM.

We found that there was a significant difference in ESR values between the FM and UD groups: the patients with

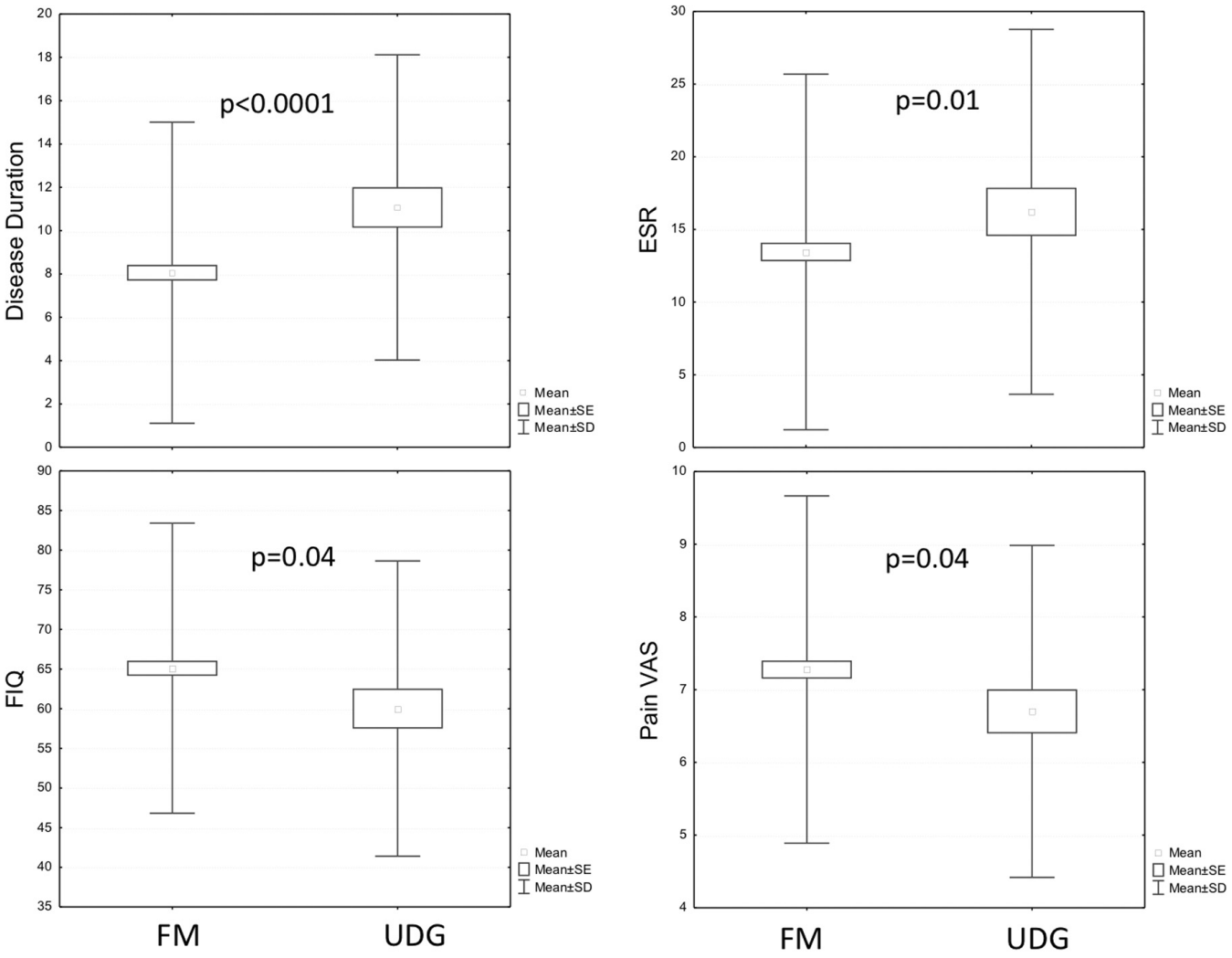


Fig. 2. Clinical and laboratory significant differences between the two study groups.
ESR: Erythrosedimentation rate; FIQ: Fibromyalgia Impact Questionnaire; VAS: Visual Analogue Scale; FM: Fibromyalgia; UDG: Uncorrected diagnosis group.

out-of-range values were more frequently judged to be suffering from a condition other than FM although ESR is considered to be a relatively unspecific test.

Another possible reason for misdiagnosis may have been autoantibody positivity, which was misinterpreted in our UD patients. On the other hand, some studies of ANA positivity in FM patients have shown a prevalence of 11.5–30% (15, 16). Furthermore, a recent study of a large group of FM patients and healthy controls by Kötter *et al*. found that there was no significant difference in the frequency of ANA or the risk of CTD in the former, and the detection of ANAs did not predict the later development of CTD (17).

Disease duration was longer in our UD group, possibly because of the delay in correctly diagnosing these patients. The FIQ and pain VAS scores were more severe in the FM patients than in those with UD, and this may have put physicians on the wrong track and is one of the possible causes of underdiagnosis.

The absence of any significant difference in TP count between the two groups is not surprising as all of the patients met the 1990 ACR criteria, but it does raise the question as to whether such counts are useful. In our case, they seemed to be useful for diagnosing FM, but it is well known that the counts are not always very precise. Wolfe *et al*. have recently pointed out that they are rarely used by the primary care physicians responsible for most diagnoses of FM and, when they are used, they are often incorrect (6). Our data confirm that the 1990 ACR classification criteria perform well in specialised clinics such as those involved in our study, but it is likely that they not widely used in primary care settings. Moreover, changes in the map or an improvement in pain may lead to the possible loss of a tender point. As Wolfe *et al*. pointed out, FM differs from RA or SLE (conditions that do not involve a diagnosis based on symptom severity) and patients may continue to be affected even if they subsequently fail to meet the classification criteria (6).

The results of our study indicate that the most frequent misdiagnoses were SpA (including PsA, AS and Behçet's disease) even though all of the performed examinations showed spine OA and there were no MRI signs of sacroiliitis. This is because low back pain is

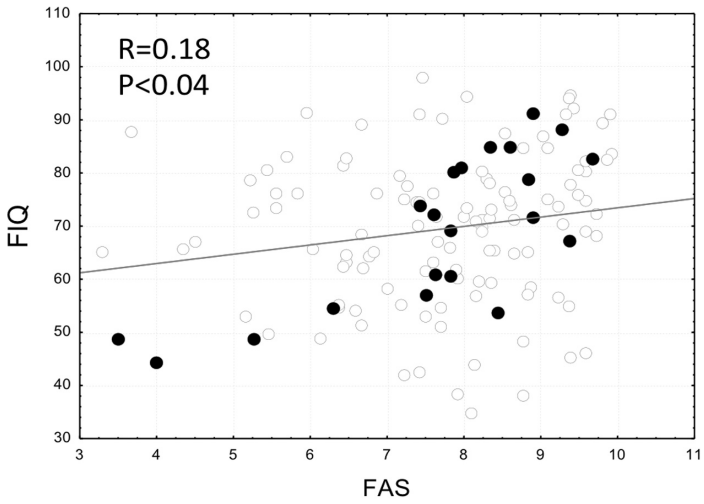


Fig. 3. Correlation between FIQ and FAS in the UD group.
FIQ: Fibromyalgia Impact Questionnaire;
FAS: Fibromyalgia Assessment Status.

Open circles: FIQ
Closed circles: FAS

widespread in FM patients even in the absence of any significant disease of the axial skeleton.

Our data support the possibility that the report of pain may be due to other reasons. The FIQ score was higher in the FM group than in the UD group. The FIQ is an extensively validated FM-specific instrument that captures the overall effect of FM symptoms (9) and is not useful for diagnosis. It can be hypothesised that the previously misdiagnosed patients had milder disease (as also confirmed by their lower pain VAS scores) and that the physicians were misled.

What are the consequences of these misdiagnoses? First of all, FM patients often undergo extensive and unnecessary investigations before their diagnosis is finally confirmed, but the most important aspect is the use of incongruous, ineffective and sometimes dangerous therapies. The most striking and serious finding of this study is that the misdiagnosis meant that some patients underwent treatment with NSAIDs and steroids and/or DMARDs (glucocorticoids, hydroxychloroquine, methotrexate, leflunomide, cyclopsorine, sulfasalazine) and/or biological agents. As FM symptoms generally respond poorly to various treatments, the consequences of the misdiagnoses and mistreatment are a later diagnosis and a longer disease duration, which can worsen the patients' quality of life and increase the economic burden on society.

Conclusions

Although FM is a well known and separate clinical entity, differential diagnosis with SpA, CTD and inflammatory arthritis may still be a challenge for rheumatologists and general praticisoners. Some of its symptoms can be confounding because they are common to other diseases, and there are no laboratory and imaging findings that can be considered diagnostic hallmarks. Even if new diagnostic criteria do not include physical examination, the TPs count remains an helpful tool in order to discriminate FM patients.

Misdiagnoses are harmful for patients and the community, and clinicians should be alerted to considering a diagnosis of FM in patients presenting with ill-defined symptoms and signs in order to prevent mistreatment.

Acknowledgements

The authors would like to thank everyone who collaborated with this study.

References

1. WOLFE F, SMYTHE HA, YUNUS MB *et al*.: The American College of Rheumatology 1990. Criteria for the Classification of Fibromyalgia: Report of the Multicenter Criteria Committee. *Arthritis Rheum* 1990; 33: 160-72.
2. MEASE PJ, CLAUW DJ, ARNOLD LM *et al*.: Fibromyalgia syndrome. *J Rheumatol* 2005; 32: 2270-7.
3. WOLFE F, ROSS K, ANDERSON J, RUSSELL IJ, HEBERT L: The prevalence and characteristics of fibromyalgia in the general population. *Arthritis Rheum* 1995; 38: 19-28.
4. MARDER WD, MEENAN RF, FELSON DT *et al*.: The present and future adequacy of rheumatology manpower. A study of health care needs and physician supply. *Arthritis Rheum* 1991; 34: 1209-17.
5. WINKELMANN A, PERROT S, SCHAEFER C: Impact of fibromyalgia severity on health economic costs: results from a European cross-sectional study. *Appl Health Econ Health Policy* 2011; 9: 125-36.
6. WOLFE F, CLAUW DJ, FITZCHARLES MA: The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res* 2010; 62: 600-10.
7. BLIDDAL H: Chronic widespread pain in the spectrum of rheumatological diseases; *Best Pract Res Clin Rheumat*. 2007; 21: 391-402.
8. FITZCHARLES MA, BOULOS P: Inaccuracy in the diagnosis of fibromyalgia syndrome: analysis of referrals. *Rheumatology* 2003; 42: 263-7.
9. BENNETT R: The Fibromyalgia Impact Questionnaire (FIQ): a review of its development, current version, operating characteristics and uses. *Clin Exp Rheumatol* 2005; 23 (Suppl. 39): S154-S162.
10. FRIES JF, SPITZ P, KRAINES RG, HOLMAN HR: Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980; 23: 137-45.
11. SALAFFI F, SARZI-PUTTINI P, GIROLIMETTI R, GASPARINI S, ATZENI F, GRASSI W: Development and validation of the self-administered Fibromyalgia Assessment Status: a disease-specific composite measure for evaluating treatment effect. *Arthritis Res Ther* 2009; 11: R125.
12. IANNUCCELLI C, SARZI-PUTTINI P, ATZENI F *et al*.: Psychometric properties of the Fibromyalgia Assessment Status (FAS) index: a national web-based study of fibromyalgia *Clin Exp Rheumatol* 2011; 29 (Suppl. 69): S49-S54. [Epub Oct 19].
13. ATZENI F, CAZZOLA M, BENUCCI M, DI FRANCO M, SALAFFI F, SARZI-PUTTINI P: Chronic widespread pain in the spectrum of rheumatological diseases. *Best Pract Res Clin Rheumatol* 2011; 25: 165-71.
14. FITZCHARLES MA, ESDAILE JM: The overdiagnosis of fibromyalgia syndrome. *Am J Med* 1997; 103: 44-50.
15. AL-ALLAF AW, OTTEWELL L, PULLAR T: The prevalence and significance of positive antinuclear antibodies in patients with fibromyalgia syndrome: 2-4 years' follow-up. *Clin Rheumatol* 2002; 21: 472-7.
16. BRIDGES AJ: Fibromyalgia, antinuclear antibodies and clinical features of connective tissue disease. *Clin Exp Rheumatol* 1993; 11: 696-7.
17. KÖTTER I, NEUSCHELER D, GÜNAYDIN I, WERNET D, KLEIN R: Is there a predisposition for the development of autoimmune diseases in patients with fibromyalgia? Retrospective analysis with long term follow-up. *Rheumatol Int* 2007; 27: 1031-9.