

# Chronic widespread pain and fibromyalgia: could there be some relationship with infections and vaccinations?

G. Cassisi<sup>1</sup>, P. Sarzi-Puttini<sup>2</sup>, M. Cazzola<sup>3</sup>

<sup>1</sup>Rheumatology Branch, Specialist Outpatient Department, Belluno, Italy;

<sup>2</sup>Rheumatology Unit, Luigi Sacco University Hospital, Milan, Italy;

<sup>3</sup>Unit of Rehabilitation Medicine, Ospedale del Circolo, Saronno, Italy.

Gianniantonio Cassisi, MD  
Piercarlo Sarzi-Puttini, MD  
Marco Cazzola, MD

Please address correspondence and reprint requests to:

Gianniantonio Cassisi, MD,  
Head of Rheumatology Branch,  
Specialist Outpatient Department,  
ASL 1 – Veneto,  
Via Feltre 57,  
32100 Belluno, Italy.

E-mail: cassisi.agordo@libero.it

Received on November 29, 2011; accepted in revised form on December 13, 2011.

Clin Exp Rheumatol 2011; 29 (Suppl. 69): S118-S126.

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2011.

**Key words:** fibromyalgia, chronic widespread pain, infection, vaccination, chronic pain, pathogenesis

## ABSTRACT

Chronic widespread pain (CWP) is a common symptom within the community, and may be part of or arise as a result of various diseases or conditions. Fibromyalgia (FM) is probably the most common and best known disease whose cardinal symptom is CWP. Many authors, however, indistinctively describe pain as “widespread”, “diffuse” or “generalised”, and this may lead to misunderstandings about true clinical or scientific significance. Widespread pain has been variously defined, over the years, beginning from the American College of Rheumatology (ACR) classification criteria for FM in 1990, and the CWP Manchester definition in 1996. A comprehensive and brief core sets for CWP was developed in 2003, by the WHO International Classification of Functioning Consensus Conference, and finally, the ACR proposed new preliminary diagnostic criteria for FM in 2010. Research into CWP and/or FM is therefore difficult and can lead to conflicting results. CWP and (particularly) FM are multifactorial disorders. There is increasing evidence that they may be triggered by environmental factors, and many authors have highlighted a relationship with various infectious agents and some have suggested that vaccinations may play a role. This review analyses the available data concerning the relationships between FM and widespread pain (in its various meanings) with infections and vaccinations, from the earliest report to the most recent contributions. Considering all scientific papers, various levels of possible associations emerge. There is no clear-cut evidence of FM or CWP due to infections or vaccinations, no correlations with persistent infection, and no proven relationship between infection, antimicrobial therapies and

pain improvement. A higher prevalence of FM and chronic pain has been found in patients with Lyme disease, and HIV or HCV infection, and, perhaps, also in patients with mycoplasmas, HBV, HTLV I, and parvovirus B19 infections. Some unconfirmed evidence and case reports suggest that vaccinations may trigger FM or chronic pain.

## Chronic widespread pain and fibromyalgia: doubts and confusion

Chronic widespread pain (CWP) is a common symptom within the community, with an estimated prevalence of between 10.7 and 13.2% (1, 2).

CWP has been variously described over the years. The 1990 fibromyalgia (FM) classification criteria of the American College of Rheumatology (ACR) defined CWP as pain on at least four days of the week for at least three months, above and below the waist, and on the left and right side of the body, as well as in the back and neck (3). Although this definition is still useful in clinical settings, it was too vague to study widespread pain in the community. A more stringent definition (the Manchester definition of CWP) was thus proposed in 1996 (4) and subsequently developed (5) with the aim of identifying patients whose pain is truly widespread.

In the Manchester definition of CWP, pain must be reported in at least two sections of two contralateral limbs and in the axial skeleton, and have been present for at least three months. This contrasts with the ACR definition, which only requires pain in any part of the contralateral body quadrants, in addition to axial pain.

In 2003, a WHO-ICF (International Classification of Functioning) Consensus Conference was held with the aim of developing internationally accepted and evidence-based compre-

Competing interests: none declared.

hensive and brief ICF core sets for CWP, and defining the spectrum of symptoms and functional limitations in CWP patients for clinical practice, research, and teaching (6). Subsequent validation of these core sets from the perspective of FM patients confirmed many of the ICF categories, but also led to the emergence of a number of categories not included in the core set (7). Furthermore, FM appears to be associated with more severe symptoms, consequences on daily life, and higher pain levels than CWP (8).

The recent proposal of ACR preliminary diagnostic criteria for FM represents the latest attempt to improve (but not replace) the 1990 ACR criteria by identifying non-tender point diagnostic criteria that may be useful for an alternative diagnostic method exclusively based on the numerical evaluation of patient-reported symptoms (9).

Many authors describe pain as "widespread", "diffuse" or "generalised", and this may lead to misunderstandings about true clinical or scientific significance. What kind of pain is CWP? Does it originate from muscles, skin, joints, bone or other places? The most frequently used terms are myalgia or arthralgia, muscle aches, and muscle or joint or skeletal pain, but it is not easy to understand the relationships between symptoms and a specific disease.

CWP may be part of, or arise as a result of various diseases or conditions, including chronic inflammatory rheumatic disease, functional or organic central sensitisation syndromes, infections, neoplasms, endocrine or metabolic affections, or the adverse effects of drugs. A recent large Swedish population-based study using the ACR classification criteria found a considerable overlap between CWP and other symptom-based conditions: joint pain, headache, chronic fatigue, irritable bowel, psychiatric disorder (major depression, but also generalised anxiety and disordered eating) (10).

Patients whose symptoms include widespread, diffuse musculoskeletal pain are commonly referred for rheumatological evaluation, although the underlying cause may not be rheumatological. A diagnosis of FM often seems to be

highly probable from the referral letter or after a few leading questions have been asked during the consultation. However, the lack of specificity of the many symptoms associated with widespread pain means that other diagnoses have to be considered. When examining or taking the history of a patient, it is necessary to bear in mind alternative and concomitant musculoskeletal disorders, such as mild systemic lupus erythematosus, polyarticular osteoarthritis, rheumatoid arthritis, polymyalgia rheumatica, hypermobility syndromes, and even osteomalacia. Non-rheumatological diseases may also have symptomatic similarities to FM, including neoplastic and neurological diseases, hypothyroidism and other endocrine disorders, chronic infections, and a variety of psychiatric conditions (11-13).

FM is probably the most common and best known disease whose cardinal symptom is CWP. It is a complex multifactorial disorder currently classified as chronic widespread pain with widespread hyperalgesia/allodynia to pressure pain, and categorised as one of the large group of soft-tissue pain syndromes. However, it is also an elusive condition of unknown etiology and, as patients not only report CWP but also a variety of other complaints similar to those of commonly overlapping syndromes (14), it is also recognised as one of the central pain syndromes and is included in central sensitivity syndromes (15). It is important to underline that, in the case of differential diagnosis, although FM may explain the symptoms itself and should be diagnosed on the basis of its own characteristic features, it may also be concomitant or associated with, or secondary to other diseases: for example, 20-30% of patients with rheumatoid arthritis or systemic lupus erythematosus have associated FM (16). Research into CWP and/or FM is therefore difficult and can lead to conflicting results.

#### **The role of infections and vaccinations**

CWP and (particularly) FM are multifactorial disorders, and there is increasing evidence that they may be triggered by environmental factors (17). Many

authors have highlighted the relationship between various infectious agents and widespread pain on the basis of general symptoms such as myalgia or arthralgia, and more specific references to FM or similar conditions (11, 17-23). Patients with infectious diseases often have myalgia and arthralgia, and the onset of CWP may be characterised by fever or flu-like symptoms; there is also a subset of FM patients whose symptoms begin after a febrile illness (24, 25). For example, Lyme disease (LD) causes diffuse arthralgia, cognitive difficulties (such as impaired concentration and memory) and fatigue, and some patients with FM have been diagnosed as having chronic Lyme disease (20).

Of the 2596 people with FM interviewed on an internet survey, approximately 21% could not identify any triggering event, over 26% indicated an acute illness as triggering event, and 43% perceived infections as worsening FM symptoms (26). Furthermore, FM has also been found in patients who meet the criteria for chronic fatigue syndrome (CFS), which over the years has been associated with infectious agents (27).

Other authors have discussed the relationship between vaccinations and the onset of CWP and/or FM (20, 21) because the most reactions to vaccination are arthralgia, myalgia, pain, musculoskeletal symptoms, chronic fatigue, general malaise and cognitive impairment. However, the association (if any) has not been established and remains obscure.

#### **Infectious agents**

Various infectious agents have been linked to the development of FM and the closely related CFS; both bacterial and viral agents were implicated as triggers of CWP, some more frequently than others (and some are only anecdotal).

##### *Bacterial agents*

##### *– Lyme disease*

Lyme disease (LD), a multisystem illness caused by *Borrelia burgdorferi*, has various manifestations, particularly prolonged fatigue, widespread arthralgia and myalgia, cognitive difficulties such as impaired concentration and

**Table I.** Studies evaluating relationships between bacterial agents and chronic pain.

Author (reference)	Infective agent	Year of publication	Type of study	Correlation	Disease
Sigal LH (28)	<i>Borrelia burgdorferi</i>	1990	Observational	Yes	FM
Dinerman H <i>et al.</i> (29)	<i>Borrelia burgdorferi</i>	1992	Observational/prospective	Yes	FM
Lightfoot RW Jr <i>et al.</i> (30)	<i>Borrelia burgdorferi</i>	1993	Retrospective	Yes*	§
Steere AC <i>et al.</i> (31)	<i>Borrelia burgdorferi</i>	1993	Observational/retrospective	Yes	FM, CFS <sup>^</sup>
Hsu VM <i>et al.</i> (32)	<i>Borrelia burgdorferi</i>	1993	Retrospective	Yes	FM
Gaudino EA <i>et al.</i> (33)	<i>Borrelia burgdorferi</i>	1997	Controlled	No	PLDS <sup>°</sup>
Cairns V <i>et al.</i> (34)	<i>Borrelia burgdorferi</i>	2005	Meta-analysis	No	PLDS <sup>°</sup>
Nasralla M <i>et al.</i> (36)	<i>Mycoplasma spp</i>	1999	Non-controlled	Yes	FM, CFS <sup>^</sup>
Vernon SD <i>et al.</i> (37)	<i>Mycoplasma spp</i>	2003	Controlled	No	CFS <sup>^</sup>
Endresen CK (38)	<i>Mycoplasma spp</i>	2003	Review	Yes	FM, CFS <sup>^</sup>
Bennett RM (39)	<i>Brucella spp</i>	1989	Case report		FM
Machtey I (40)	<i>Chlamydia pneumoniae/trachomatis</i>	1997	Personal data		§
Fiore D (41)	<i>Bordetella pertussis</i>	2006	Personal data		FM

\*Not primary endpoint; §Myalgia, arthralgia, fatigue and other similar or associated symptoms; °Post-Lyme Disease Syndrome; ^Chronic Fatigue Syndrome.

memory, tenderness, hyperalgesia and dysesthesia.

The earliest observational report of an association between LD and FM indicated that LD was causally related to the symptoms of only 37 of 100 consecutive patients referred to a LD clinic, whereas 25 met the criteria for FM. It was underlined that overlapping symptoms such as malaise and mild fatigue may be incorrectly related to the chronic evolution of LD, and may lead to unnecessary antibiotic therapy due to the persistence of infection (28).

The need to differentiate chronic LD and FM was highlighted by an observational cohort study describing clinical and laboratory findings, and the results of treatment. Two hundred and eighty-seven patients with LD were observed over 3.5 years: 22 of the prospectively evaluated patients (8%) were diagnosed as having FM, 15 of whom (5%) were followed up for a mean period of 2.5 years. Nine developed the symptoms of FM soon after antibiotic therapy was started for early LD, and six during the course of Lyme arthritis but before they were treated. None of them had any symptoms of FM before LD. A further parenteral antibiotic course was given to each patient but led to no improvement, and it was concluded that antibiotic treatment usually fails to resolve symptoms (29).

A retrospective cost-analysis study of patients who complained of symptoms similar to those of FM (myalgia and chronic fatigue) and had positive LD serology (but without the classic mani-

festation) showed that the risks and costs of antibiotic therapy in endemic areas exceeded the benefits, except for the cost-effective empirical treatment of a patient with a high value of anxiety about the positive LD test (30).

Regarding the overdiagnosis of LD, a report from a Boston LD clinic showed that 156 of 788 patients with previous LD had another illness, usually diagnosed as FM or CFS. The symptoms of 49 of them began soon after the manifestations of LD (31).

In a retrospective analysis of 800 patients with persistent, non-specific symptoms of possible chronic LD, the myalgia, fatigue and neuropsychological disturbances were explained by FM in 77 cases. Two-thirds of these patients had prior or current LD; one-third never had LD nor serology evidence or prior infection. The onset of FM most frequently coincided with that of LD; only 17% of the patients developed FM with an average delay of 7.5 months. The authors concluded that FM must be considered in LD refractory to repeated courses of antibiotics (32).

A recent meta-analysis compared the prevalence of fatigue, musculoskeletal pain and neurocognitive difficulties in patients who had had LD and control subjects without LD. The symptoms were significantly more prevalent in the first group, particularly fatigue, joint or muscle pain, muscle aches, swollen joints and, among the neurocognitive symptoms, memory problems, poor concentration, and difficulties in formulating ideas and word finding. The

authors stated that this pattern, which in some patients with LD may last for years despite antibiotic therapy, seems to be different from that seen in patients with FM, depression or CFS, thus strengthening the developing idea of a post-LD syndrome, especially with regard to cognitive impairment (33, 34).

It can be concluded that LD may trigger FM, may even co-exist with it in a chronic form but may frequently be confused with it: however, FM is actually most frequently associated with the overdiagnosis of LD. As no correlations have been found between FM and persistent infection, antibiotic therapy is not useful (18).

Some authors say that the development of FM as a consequence of *Borrelia burgdorferi* infection is the worst complication of LD (31).

The anxiety of patients regarding LD and seropositivity may in itself have deleterious effects, leading to the exacerbation of other symptoms and making it difficult for physicians to refuse requests for antibiotic treatment (20). It is probably for these reasons that some authors have suggested that chronic LD becomes a part with "Medically unexplained symptoms" syndromes, such as FM, CFS and multiple chemical sensitivity (35).

#### – Other bacterial agents

Some studies have investigated *Mycoplasma*, a bacterial genus responsible for chronic diseases in humans, as a possible candidate infectious trigger of FM and CFS. As a matter of fact, the

majority of attempts have been made for CFS. One study of 91 patients with an overlapping diagnosis of FM and CFS found a high prevalence of infection (using PCR on peripheral blood) due to multiple *Mycoplasma* species, and more than 50% showed at least dual infection. The authors did not indicate if the patients were symptomatic for infection. Multiple *Mycoplasma* infections were associated with more protracted FM or CFS, but no control group was indicated (36).

This finding was not confirmed by another similar study of 34 patients with CFS and control group, in tertiary care clinics (37).

A subsequent review indicated that *Mycoplasma* blood infections have been detected by means of PCR in about 50% of FM and CFS patients, but in only 10% of healthy subjects. Most of the patients seem to recover and return to their pre-illness state after prolonged antibiotic therapy. The authors concluded that it is not clear whether *Mycoplasma* infections are associated with FM and CFS as causal agents, co-factors or opportunistic infections (38).

Most important from a practical point of view is the usefulness of antibiotic treatment in these cases (20).

Concerning other bacterial agents,

chronic brucellosis has been mentioned as a possible trigger of FM (39), and positive serology for *Chlamydia pneumoniae* (78%) and *Chlamydia trachomatis* (57%) has been found in personal data relating to myalgia of unknown cause, including FM (40). Finally, there are some data indicating the presence of *Bordetella Pertussis* antibodies in patients with FM, but the scientific validity of these findings is questionable (41).

#### Viral agents

##### – Hepatitis C virus

Evidence of correlations between HCV infection and musculoskeletal symptoms emerged at the end of the 1990s in the form of extra-hepatic rheumatic manifestations, including FM (42).

A higher prevalence of HCV antibodies (15.2%) was found in 112 FM patients compared to a control group of rheumatoid arthritis patients (5.3%). Of the 58 patients with chronic HCV infection, 53% suffered from diffuse musculoskeletal pain and 10% fulfilled the criteria for FM. There was no association with liver damage or autoimmune markers. The authors concluded that HCV infection should be considered in FM patients even if their liver enzymes were normal (43).

In the same period, another study compared 90 patients with HCV infection with 128 healthy patients and 32 patients with non-HCV-related cirrhosis. A diagnosis of FM was established in 14 of the patients with HCV (16%), only one of the patients with non-HCV related cirrhosis (3%), and in none of the healthy controls (44). The highest prevalence (24%) was observed in the patients with advanced HCV cirrhosis, and the HCV patients had higher tender point counts than the controls. The authors found no significant difference between the male patients with non-HCV-related cirrhosis and those with HCV-related cirrhosis among men, but FM was significantly more prevalent among the women with HCV-related cirrhosis. It was concluded that care should be taken not to misinterpret FM symptoms in patients infected with HCV.

Another study confirmed the frequent occurrence of musculoskeletal pain and fatigue in patients with chronic HCV infection: of the 239 HCV-positive patients, 81% complained musculoskeletal pain (as opposed to 56% who were HCV-negative), regardless of the severity of liver disease, the route of infection, or interferon therapy (45). Fatigue (frequent in both FM and HCV infection) has been found to be asso-

**Table II.** Studies evaluating the relationships between viral agents and chronic pain.

Author (reference)	Infective agent	Year of publication	Type of study	Correlation	Disease
Lovy MR <i>et al.</i> (42)	Hepatitis C	1996	Observational	Yes*	FM, §
Rivera J <i>et al.</i> (43)	Hepatitis C	1997	Controlled	Yes	FM, §
Buskila D <i>et al.</i> (44)	Hepatitis C	1997	Controlled	Yes	FM
Barkhuizen A <i>et al.</i> (45)	Hepatitis C	1999	Controlled	Yes	§
Poynard T <i>et al.</i> (46)	Hepatitis C	2002	Observational/prospective	Yes	FM, §
Narvæz J <i>et al.</i> (47)	Hepatitis C	2005	Controlled	No	FM
Palazzi C <i>et al.</i> (48)	Hepatitis C	2008	Controlled	No	FM
Mohammed RH <i>et al.</i> (50)	Hepatitis C	2010	Cross-sectional	Yes	FM, CFS <sup>^</sup> , §
Buskila D <i>et al.</i> (52)	Human Immunodeficiency	1990	Controlled	Yes	FM
Simms RW <i>et al.</i> (53)	Human Immunodeficiency	1992	Observational/controlled	Yes	FM, §
Marquez J <i>et al.</i> (54)	Human Immunodeficiency	2004	Observational/prospective	Yes	FM
Cruz BA <i>et al.</i> (55)	Human T cell lymphotropic	2005	Controlled	Yes	FM
Adak B <i>et al.</i> (56)	Hepatitis B	2005	Controlled	Yes	FM, §
Buckwald D <i>et al.</i> (57)	Epstein-Barr	1987	Controlled	No	FM
Moldofsky H (58)	Epstein-Barr	1989	Case report		FM
Nash P <i>et al.</i> (59)	Coxsackie B	1989	Case report		FM
Leventhal LJ <i>et al.</i> (60)	Parvovirus B 19	1991	Case series		FM
Berg AM <i>et al.</i> (61)	Parvovirus B 19	1993	Controlled	No	FM
Buyukkose M <i>et al.</i> (62)	Parvovirus B 19	2009	Controlled	Yes	FM

\*Not primary endpoint; §Myalgia, arthralgia, fatigue or other similar or associated symptoms; ^Chronic Fatigue Syndrome.



ciated with female gender, an age of more than 50 years, cirrhosis, depression and purpura. It has also been associated with arthralgia, myalgia, paresthesia, sicca syndrome and pruritus; the prevalence of FM was 19% (46).

Two recent studies led to different conclusions: the first found no increase in the prevalence of hepatitis C among patients with FM in comparison with healthy controls (47); the second, which evaluated the prevalence of HCV infection in 152 patients with FM and 152 patients affected by non-HCV related rheumatic degenerative disorders (peripheral osteoarthritis and radicular compression syndrome), did not find any statistically significant difference in anti-HCV antibodies in the three groups, and concluded that HCV does not play a significant pathogenetic role in FM (48).

Other authors have tried to elucidate the mechanism by which HCV infection can trigger FM or musculoskeletal symptoms: alterations in cytokines can produce hyperalgesia and other neurally mediated symptoms as a result of central nervous system aberrations and hypothalamic-pituitary-adrenal axis down-regulation (49).

In a very recent cross-sectional study carried out in Egypt, 306 patients with HCV chronic infection (excluding decompensated liver disease, interferon therapy, end-stage renal disease, co-existing viral infection) were interviewed over a period of one year with the aim of assessing the prevalence of rheumatological manifestations, which was estimated to be 16.3%; CFS was diagnosed in 9.5% and FM in 1.9% (similar to the current prevalence of FM); and arthralgia and myalgia were present in respectively 6.5% and 1.3%. FM was significantly present in female population (50).

#### – Human immunodeficiency virus

Higher rates of FM have been reported in patients with HIV infection. Among the various clinical manifestations of HIV infection, the rheumatological aspects have been clearly defined. The prevalence of FM and FM-like symptoms is increased, and widespread myalgia is a prime symptom of many in-

fections ranging from the common cold to HIV infection (51).

In the first report on this issue, 15 of 51 patients with HIV infection (29%) met criteria for FM; in this controlled study the prevalence of FM among patients with psoriatic arthritis was similar (24%), but much higher among patients with rheumatoid arthritis (57%). FM was significantly associated with myalgia and arthralgia, but no correlation was found with age, duration of infection, stage of disease, or therapy (52).

In another series of 140 patients, FM was found in 41% of those who reported musculoskeletal symptoms, and about 11% of all of the patients fulfilled the criteria for FM. Compared with 301 controls, known HIV-infected patients with FM were more commonly male and reported current depressed mood more frequently. The FM patients had a longer duration of HIV infection (53).

Over ten years later and despite the introduction of highly active anti-retroviral therapy, which greatly improved treatment and prognosis, FM affected 13 out of 75 study patients (17%) (54). There are three possible connections between HIV and FM (20). Alterations in the function of the hypothalamic-pituitary-adrenal axis are well documented in patients with HIV infection, as well as in those with FM. Sleep disturbances associated with level of pain and stress have been observed in HIV-infected patients, and disturbed sleep patterns are classical manifestations of FM. Finally, depression is very common among patients infected with HIV and also frequent in chronic pain conditions, particularly FM.

#### – Other viral agents

A higher prevalence of FM (38%) was found in 100 subjects infected with human T cell lymphotropic virus type I compared to only 4.8% in 62 negative controls (55).

One study of 50 hepatitis carriers, who had been serum anti-HBs negative for at least six months, and 50 age- and gender-matched HBs Ag-negative controls suggested that chronic hepatitis B carriage increases the risk of FM and many of its associated symptoms. Approximately 50% of the former had

diffuse musculoskeletal symptoms, and FM was diagnosed in 25%, a significantly higher prevalence than in the control group (56).

Other viral agents have also been considered, but there is no firm evidence or there are only anecdotal reports. One study described 50 FM patients with symptoms resembling chronic Epstein-Barr virus infection; however, serology for antibodies against Epstein-Barr virus antigens showed no differences in comparison with a control group (57). Another described the effect of acute viral infection on the development of sleep disorders and symptoms after a febrile illness, and the author hypothesised a relationship between the infection and the onset of fibrositis and CFS (58). Evidence of chronic infection with coxsackie B virus over a 4-year period was an associated myalgic syndrome that fulfilled Smythe's diagnostic criteria for FM (59).

A possible relationship between parvovirus B19 and the onset of FM was proposed after three patients developed FM following a serologically proven acute infection (60). In a subsequent study, 15 FM female patients who recalled a viral prodrome preceding the onset of their symptoms and 11 FM patients who did not recall any such illness were assessed for signs of infection with human parvovirus B19 by means of IgM and IgG antibody testing and using PCR. Twenty-six females served as control. No patient or control had positive IgM levels or persistent viremia. No increase in the prevalence of positive IgG serology was observed in comparison with patients without an acute onset (61). This hypothesis has a new hype for a recent study that checked the presence of anti-B19 IgM and IgG antibodies in 75 patients with FM and 75 healthy controls: anti-B19 IgM antibodies showed no difference, whereas the anti-B19 IgG seropositivity was significantly higher in FM patients compared to the controls (81.3% vs. 64%). There were no differences in the clinical features of the anti-B19 IgG positive and negative FM patients. The author suggested that Parvovirus B 19 infection may play a role in the etiopathogenesis of FM or act as a triggering factor (62).

**Table III.** Studies evaluating the relationships between vaccinations and chronic pain.

Author (reference)	Type of vaccination	Year of publication	Type of study	Correlation	Disease
Allen AD (63)	Rubella	1988	Observational/retrospective	Yes	FM, CFS <sup>^</sup>
Weibel RE <i>et al.</i> (64)	Rubella	1996	Observational/retrospective	Yes	FM, §
Tingle AJ <i>et al.</i> (65)	Rubella	1997	Randomised/controlled	No	§
Lathrop SL <i>et al.</i> (66)	<i>Borrelia burgdorferi</i>	2002	Retrospective	Yes	§
Nancy AL <i>et al.</i> (67)	Hepatitis B	2008	Case report		FM, CFS <sup>^</sup>
Cassisi G (68)	Hepatitis B e C / <i>Clostridium tetani</i>	2010	Case report		FM, §
Gherardi RK <i>et al.</i> (69)	Different	1998	Retrospective	Yes	§
Ryan AM (70)	Unknown	2006	Case report		§, MMS <sup>°</sup>
Exley C <i>et al.</i> (71)	Hepatitis B e C / <i>Clostridium tetani-diphtheriae</i> Poliomyelitis	2009	Case report		§, MMS <sup>°</sup> , CFS <sup>^</sup>
Unwin C <i>et al.</i> (76)	Multiple (Gulf syndrome)	1999	Cross-sectional	Yes*	§
Hotopf M <i>et al.</i> (77)	Multiple (Gulf syndrome)	2000	Cross-sectional	Yes*	§
Hotopf M <i>et al.</i> (78)	Multiple (Gulf syndrome)	2004	Prospective	Yes*	§

\*Not primary endpoint; §Myalgia, arthralgia, fatigue or other similar or associated symptoms; <sup>^</sup>Chronic Fatigue Syndrome; <sup>°</sup>Macrophagic Myofasciitis Syndrome.

### Vaccinations

A number of intriguing lines of evidence suggest that vaccinations may play a role in triggering CWP and/or FM, but the specific effects of antigens and adjuvants, or environmental and personal context are still elusive.

#### Rubella vaccine

It was first suggested that rubella vaccination may be etiologically involved in CFS and fibrositis more than 20 years ago (63), when an apparently epidemiological association with the 1979 introduction of a new rubella vaccine was noted in the USA. In the three years following, in fact, the first reports of patients developing CFS appeared. A retrospective study of the outcomes of 124 claims of chronic arthropathy associated with rubella vaccine and submitted to the National Vaccine Injury Compensation Program found a causal relationship between this vaccine and the post-vaccination onset of chronic arthropathy and various conditions including arthritis, arthralgia, FM and myalgia (64).

However, a subsequent randomised, placebo-controlled trial failed to demonstrate a statistically significant increase in the frequency of chronic arthralgia, arthritis or persistent myalgia (65).

#### Other vaccines

A study of the adverse events linked to Lyme vaccination in the USA over a period of 18 months found that arthralgia, myalgia and non-specific pain together accounted over 66% of the total (66).

CFS, FM and demyelization were diagnosed in a 56-year-old woman after the second dose of hepatitis B vaccine, and worsened with the third vaccination, but the possible role of a previous exposure to silicone to augment the immune response was discussed (67).

Diffuse arthralgia and myalgia, fatigue, cognitive and psychological disturbances, and overload phenomena were observed in a 53-year-old woman who met the 1990 ACR criteria for FM; the illness began three days after the first dose of a polyvalent hepatitis B-C-tetanus vaccine, and it was still present after one year (68).

Atypical arthralgia, myalgia and fatigue were described as adverse reactions to vaccine adjuvant experienced by a patient who developed macrophagic myofasciitis syndrome (MMS) (69). The persistence of vaccine-derived aluminium hydroxide at the site of the intramuscular injection is believed to be the cause of this uncommon inflammatory disorder, whose onset may be delayed by up to 10 years (70). Finally, another case report indicated previous vaccination with a polyvalent hepatitis-B-C-polio-tetanus-diphtheria vaccine (given over four weeks) as a concomitant trigger of MMS and CFS (71).

#### Combined vaccines and vaccination against exotic agents (the Gulf war syndrome)

The Gulf war syndrome, known to be strictly associated to vaccination against various biological agents, has many

similarities with FM and CFS as a functional disorder included in the so-called “Medically unexplained symptoms” (72). This unique clinical entity was first described after the military conflict in the Persian Gulf that took place in the early 1990s, and is characterised by chronic fatigue, musculoskeletal symptoms, general malaise, irritability and cognitive disturbances (73, 74); it also frequently overlapped post-traumatic stress disorder (75). This constellation of symptoms was reported by about 10–15% of the 700,000 US troops deployed during the war, to whom multiple standard vaccinations (against plague, anthrax, typhoid, tetanus, cholera) and vaccinations against biological agents were administered. Studies of the association between the symptoms, multiple vaccinations and specific environmental exposure showed that the prevalence of symptoms such as fatigue, and post-traumatic and psychological stress was higher than that observed in servicemen participating in other military conflicts (76).

One cross-sectional study indicated stress as a risk factor, pointing out that the administration of multiple vaccinations during deployment closely correlated with fatigue, psychological distress, health perception, physical function and the presence of “multi-symptom illness”, whereas the administration before deployment was only associated with post-traumatic stress reaction (77). A subsequent follow-up study showed that the severity of the

initial symptoms and psychological distress were the most important risk factors for the chronic persistence of the illness (78).

### Discussion

Many scientific papers concerning the possible relationship between infections and chronic pain (mainly FM) have been published over the last 30 years (Tables I and II). However, none of them was based on the Manchester definition of CWP (4, 5) and, as they usually considered non-specific symptoms such as myalgia, arthralgia, fatigue and musculoskeletal pain, it is not always clear whether FM refers to a defined illness or a group of different symptoms similar to the cardinal symptom of FM.

The more stringent Manchester definition conflicts with the ACR definition of CWP, and myalgia or arthralgia, muscle aches, or muscle, joint or skeletal pain cannot always be included in the diagnosis of FM. It is therefore likely that FM is only the tip of the CWP iceberg. The diagnosis of FM is confounding, and it is not clear whether the FM groups in the studies described in this paper are real or as homogeneous as they should be. Some reports refer to diagnostic or classification criteria incorrectly; others used the 1990 ACR criteria (3), previous criteria that are not universally recognised (79, 80), or simple clinical definitions (81). Even the description of chronic pain is itself uncertain, although there is common agreement that it must last for at least three months.

One further complication is that the relationship between chronic pain and infection is equivocal. Chronic pain may be associated with a systemic infection, or caused by the spread of the infectious agent, or, lastly, be a consequence of it, particularly in subjects with specific risk factors. Increasing evidence supports the fact that environmental and genetic factors play an important role in the pathogenesis of FM, and many stressors can induce or modulate its development (17, 22, 23). It is therefore often difficult to analyse the available literature in a consistent manner.

Nevertheless, it can be seen from Tables I and II that first reports of a relationship

between FM and infections go back to the end of the 1980s, and the latest are very recent. For some agents, the initial interest was followed by no further reports, whereas the interest in others is still alive or very new. For example, the relationship between LD and FM was first noted at the beginning of the 1990's, but no specific report followed. On the other hand, the interest in HCV aroused at the end of the 1990s is still topical; furthermore, HIV and parvovirus B19 infections were studied twenty years ago but its relationship with FM has only recently been confirmed. Mycoplasma infection was first studied only about ten years ago, and reports of HBV and HTLV I as possible agents in the development of FM or musculoskeletal pain are even more recent. The studies themselves include controlled and uncontrolled trials, observational and retrospective studies, case reports and case series. There is one meta-analysis relating to LD, whereas the reports concerning *Chlamydia*, *Brucella*, *Bordetella*, Epstein-Barr and coxsackie viruses are only anecdotal.

Evaluating the relationship between vaccination and chronic pain is more complicated as only one of the studies was a randomised controlled trial. With the exception of those concerning the rubella vaccine, the reports have all been published in the last ten years (Table III). Furthermore, although there are sometimes specific references to FM or CFS, the words generally used to describe the symptoms are myalgia, arthralgia, non-specific pain, fatigue, malaise and cognitive disturbances (Table III).

MMS has been associated with vaccinations in three reports that describe similar symptoms, but it is the Gulf war syndrome that can be considered a paradigm of the possible relationship between chronic pain and vaccinations. In this regard, a possibly new called autoimmune/inflammatory syndrome induced by adjuvants (ASIA) has recently been described (82). The authors provocatively suggest that silicosis, Gulf war syndrome, MMS and post-vaccination phenomena share the common link of adjuvants, which may induce autoimmune/inflammatory disease in humans.

Finally, a few reviews have considered the possible role of infections and vaccinations in triggering FM (18, 20, 21), thus underlining its importance in everyday practice, but there is no review of chronic pain or CWP. The relevance of infections in triggering FM has been indicated in a number of reviews of its pathogenesis or diagnosis (11, 17, 19, 22, 23).

### Conclusions

There is no evidence that either FM or CWP is caused by infections and vaccinations, but there does seem to be a significant relationship between them and infections. FM (and probably CWP) may appear or worsen after infections or vaccinations, probably because the antigens act as the trigger in a self-maintaining process in the presence of a genetic (17) or/and behavioural predisposition (18). However, the level of the available evidence varies widely: the reports are often anecdotal, the control studies are not always confirmed, and there are very few studies for the different kind of agents. Furthermore, many authors refer to FM or CFS, but their terminology is often confused.

No relationship has been demonstrated between persistent infection and FM or CWP, nor any relationship between infection therapies and improvements in pain. However, musculoskeletal symptoms and FM can be generated by LD, and there is some evidence regarding the developing concept of post-Lyme syndrome. A higher prevalence of FM and chronic pain has been found and confirmed in patients with HIV or HCV infection and, although not always confirmed, a higher prevalence of FM and musculoskeletal pain has been found in patients with *Mycoplasma*, HBV, HTLV I, and parvovirus B19 infection. The data concerning other infectious agents (*Brucella*, *Chlamydia*, *Bordetella*, Epstein-Barr and Cocksackie virus) are very poor and insufficient.

Some unconfirmed evidence and case reports suggest that vaccinations may trigger FM or chronic pain, but the specific roles of antigens and adjuvants, or environmental and personal contexts is still unclear.



In line with the conclusion of the first review analysing the relationships between FM and infections (18), and extending its meaning, it needs to be kept in mind that some patients with infections or undergoing a vaccination program may develop FM or chronic musculoskeletal symptoms. It is therefore important to define CWP-related infections in order to avoid repeated, uncorrected and exaggerated diagnostic testing, and essential to steer clear of inappropriate antibiotic or antiviral therapies, excessive bedrest and disability. Finally, chronicity needs to be prevented by means of education, reassurance, active rehabilitation, and the correct treatment of syndromic symptoms.

## References

- ANDERSSON HI, EILERTSSON G, LEDEN I, ROSENBERG C: Characteristics of subjects with chronic pain, in relation to local and widespread pain report. A prospective study of symptoms, clinical findings and blood tests in subgroups of a geographically defined population. *Scand J Rheumatol* 1996; 25: 146-54.
- CROFT PR, RIGBY AS, BOSWELL R, SCHOLLUM J, SILMAN AJ: The prevalence of chronic widespread pain in the general population. *J Rheumatol* 1993; 14: 41-5.
- 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.
- MACFARLANE GJ, CROFT PR, SCHOLLUM J, SILMAN AJ: Widespread pain: is an improved classification possible? *J Rheumatol* 1996; 23: 1628-32.
- HUNT IM, SILMAN AJ, BENJAMIN S, MCBETH J, MACFARLANE GJ: The prevalence and associated features of chronic widespread pain in the community using the 'Manchester' definition of chronic widespread pain. *Rheumatology* (Oxford) 1999; 38: 275-9.
- CIEZA A, STUCKI G, WEIGL M *et al.*: ICF Core Sets for chronic widespread pain. *J Rehabil Med* 2004; (44 Suppl.): 63-8.
- HIEBLINGER R, COENEN M, STUCKI G, WINKELMANN A, CIEZA A: Validation of the International Classification of Functioning, Disability and Health Core Set for chronic widespread pain from the perspective of fibromyalgia patients. *Arthritis Res Ther* 2009; 11: R67.
- STAUD R: Chronic widespread pain and fibromyalgia: two sides of the same coin? *Curr Rheumatol Rep* 2009; 11: 433-6.
- WOLFE F, CLAUW DJ, FITZCHARLES MA *et al.*: The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res* 2010; 62: 600-10.
- KATO K, SULLIVAN PF, EVENGÅRD B, PEDERSEN NL: Chronic widespread pain and its comorbidities: a population-based study. *Arch Intern Med* 2006; 166: 1649-54.
- REILLY PA: The differential diagnosis of generalized pain. *Baillieres Best Pract Res Clin Rheumatol* 1999; 13: 391-401.
- APARICIO VA, CARBONELL-BAEZA A, ORTEGA FB, ESTEVEZ F, RUIZ JR, DELGADO-FERNÁNDEZ M: Usefulness of tenderness to characterize fibromyalgia severity in women. *Clin Exp Rheumatol* 2011 Jul 14. [Epub ahead of print].
- BAZZICHI L, ROSSI A, GIACOMELLI C, BOMBARDIERI S: Exploring the abyss of fibromyalgia biomarkers. *Clin Exp Rheumatol* 2010; 28 (Suppl. 63): S125-30.
- CASSISI G, SARZI-PUTTINI P, ALCIATI A *et al.*: (Italian Fibromyalgia Network): Symptoms and signs in fibromyalgia syndrome. *Reumatismo* 2008; 60 (Suppl. 1): 15-24.
- YUNUS MB: Central sensitivity syndromes: a new paradigm and group nosology for fibromyalgia and overlapping conditions, and the related issue of disease versus illness. *Semin Arthritis Rheum* 2008; 37: 339-52.
- YUNUS MB: Role of central sensitization in symptoms beyond muscle pain, and the evaluation of a patient with widespread pain. *Best Pract Res Clin Rheumatol* 2007; 21: 481-97.
- BUSKILA D: Developments in the scientific and clinical understanding of fibromyalgia. *Arthritis Res Ther* 2009; 11: 242.
- GOLDENBERG DL: Do infections trigger fibromyalgia? *Arthritis Rheum* 1993; 36: 1489-92.
- DAOUD KF, BARKHUIZEN A: Rheumatic mimics and selected triggers of fibromyalgia. *Curr Pain Headache Rep* 2002; 6: 284-8.
- ABLIN JN, SHOENFELD Y, BUSKILA D: Fibromyalgia, infection and vaccination: two more parts in the etiological puzzle. *J Autoimmun* 2006; 27: 145-52.
- BUSKILA D, ATZENI F, SARZI-PUTTINI P: Etiology of fibromyalgia: the possible role of infection and vaccination. *Autoimmun Rev* 2008; 8: 41-3.
- ABLIN JN, NEUMANN L, BUSKILA D: Pathogenesis of fibromyalgia – a review. *Joint Bone Spine* 2008; 75: 273-9.
- STISI S, CAZZOLAM, BUSKILAD *et al.*: (Italian Fibromyalgia Network): Etiopathogenetic mechanisms of fibromyalgia syndrome. *Reumatismo* 2008; 60 (Suppl. 1): 25-35.
- MOLDOFSKY H, SASKIN P, LUE FA: Sleep and symptoms in fibrositis syndrome after a febrile illness. *J Rheumatol* 1988; 15: 1701-4.
- BURCKHARDT CS, CLARK SR, CAMPBELL SM, O'REILLY CA, BENNETT RM: Events and co-morbidities associated with the onset of fibromyalgia. *J Musculoskeletal Pain* 1995; 3 (Suppl. 1): 71.
- BENNETT RM, JONES J, TURK DC, RUSSELL II, MATA LLANA L: An internet survey of 2,596 people with fibromyalgia. *BMC Musculoskelet Disord* 2007; 8: 27.
- GOLDENBERG DL, SIMMS RW, GEIGER A, KOMAROFF AL: High frequency of fibromyalgia in patients with chronic fatigue seen in a primary care practice. *Arthritis Rheum* 1990; 33: 381-7.
- SIGAL LH: Summary of the first 100 patients seen at a Lyme disease referral center. *Am J Med* 1990; 88: 577-81.
- DINERMAN H, STEERE AC: Lyme disease associated with fibromyalgia. *Ann Intern Med* 1992; 117: 281-5.
- LIGHTFOOT RW Jr, LUFT BJ, RAHN DW *et al.*: Empiric parenteral antibiotic treatment of patients with fibromyalgia and fatigue and a positive serologic result for Lyme disease. A cost-effectiveness analysis. *Ann Intern Med* 1993; 119: 503-9.
- STEERE AC, TAYLOR E, MCHUGH GL, LOGIGIAN EL: The overdiagnosis of Lyme disease. *JAMA* 1993; 269: 812-6.
- HSU VM, PATELLA SJ, SIGAL LH: "Chronic Lyme disease" as the incorrect diagnosis in patients with fibromyalgia. *Arthritis Rheum* 1993; 36: 1493-500.
- GAUDINO EA, COYLE PK, KRUPP LB: Post-Lyme syndrome and chronic fatigue syndrome. Neuropsychiatric similarities and differences. *Arch Neurol* 1997; 54: 1372-6.
- CAIRNS V, GODWIN J: Post-Lyme borreliosis syndrome: a meta-analysis of reported symptoms. *Int J Epidemiol* 2005; 34: 1340-5.
- SIGAL LH, HASSETT AL: Contributions of societal and geographical environments to "Chronic Lyme disease": the psychopathogenesis and aporology of a new "medically unexplained symptoms" syndrome. *Environ Health Perspect* 2002; 110 (Suppl. 4): 607-11.
- NASRALLA M, HAIRER J, NICOLSON GL: Multiple mycoplasma infections detected in blood of patients with chronic fatigue syndrome and/or fibromyalgia syndrome. *Eur J Clin Microbiol Infect Dis* 1999; 18: 859-65.
- VERNON SD, SHUKLA SK, REEVES WC: Absence of Mycoplasma species DNA in chronic fatigue syndrome. *J Med Microbiol* 2003; 52: 1027-8.
- ENDRESEN GK: Mycoplasma blood infection in chronic fatigue and fibromyalgia syndromes. *Rheumatol Int* 2003; 23: 211-5.
- BENNETT RM: Confounding features of the fibromyalgia syndrome: a current perspective of differential diagnosis. *J Rheumatol* 1989; Suppl. 19: 58-61.
- MACHTEY I: Chlamydia pneumoniae antibodies in myalgia of unknown cause (including fibromyalgia). *Br J Rheumatol* 1997; 36: 1134.
- FIGLIORE D: Fibromialgia e sindrome da fatica (stanchezza) cronica. <http://www.domenicofiore.it/fibromialgia/>
- LOVY MR, STARKEBAUM G, UBEROI S: Hepatitis C infection presenting with rheumatic manifestations: a mimic of rheumatoid arthritis. *J Rheumatol* 1996; 23: 979-83.
- RIVERA J, DE DIEGO A, TRINCHET M, GARCÍA MONFORTE A: Fibromyalgia-associated hepatitis C virus infection. *Br J Rheumatol* 1997; 36: 981-5.
- BUSKILA D, SHNAIDER A, NEUMANN L, ZILBERMAN D, HILZENRAT N, SIKULER E: Fibromyalgia in hepatitis C virus infection. Another infectious disease relationship. *Arch Intern Med* 1997; 157: 2497-500.
- BARKHUIZEN A, ROSEN HR, WOLF S, FLORA K, BENNER K, BENNETT RM: Musculoskeletal pain and fatigue are associated with chronic hepatitis C: a report of 239 hepatology clinic patients. *Am J Gastroenterol* 1999; 94: 1355-60.
- POYNARD T, CACOUB P, RATZIU V *et al.*:



- Fatigue in patients with chronic hepatitis C. *J Viral Hepat* 2002; 9: 295-303.
47. NARVÁEZ J, NOLLA JM, VALVERDE-GARCÍA J: Lack of association of fibromyalgia with hepatitis C virus infection. *J Rheumatol* 2005; 32: 1118-21.
  48. PALAZZI C, D'AMICO E, D'ANGELO S, NUCERA A, PETRICCA A, OLIVIERI I: Hepatitis C virus infection in Italian patients with fibromyalgia. *Clin Rheumatol* 2008; 27: 101-3.
  49. THOMPSON ME, BARKHUIZEN A: Fibromyalgia, hepatitis C infection, and the cytokine connection. *Curr Pain Headache Rep* 2003; 7: 342-7.
  50. MOHAMMED RH, EL MAKHZANGY HI, GAMAL A *et al.*: Prevalence of rheumatologic manifestations of chronic hepatitis C virus infection among Egyptians. *Clin Rheumatol* 2010; 29: 1373-80.
  51. MILLER RG, CARSON PJ, MOUSSAVI RS, GREEN AT, BAKER AJ, WEINER MW: Fatigue and myalgia in AIDS patients. *Neurology* 1991; 41: 1603-7.
  52. BUSKILA D, GLADMAN DD, LANGEVITZ P, UROWITZ S, SMYTHE HA: Fibromyalgia in human immunodeficiency virus infection. *J Rheumatol* 1990; 17: 1202-6.
  53. SIMMS RW, ZERBINI CA, FERRANTE N, ANTHONY J, FELSON DT, CRAVEN DE: Fibromyalgia syndrome in patients infected with human immunodeficiency virus. The Boston City Hospital Clinical AIDS Team. *Am J Med* 1992; 92: 368-74.
  54. MARQUEZ J, RESTREPO CS, CANDIA L, BERMAN A, ESPINOZA LR: Human immunodeficiency virus-associated rheumatic disorders in the HAART era. *J Rheumatol* 2004; 31: 741-6.
  55. CRUZ BA, CATALAN-SOARES B, PROIETTI F: Higher prevalence of fibromyalgia in patients infected with human T cell lymphotropic virus type I. *J Rheumatol* 2006; 33: 2300-3.
  56. ADAK B, TEKEOĞLU I, EDIZ L *et al.*: Fibromyalgia frequency in hepatitis B carriers. *J Clin Rheumatol* 2005; 11: 157-9.
  57. BUCHWALD D, GOLDENBERG DL, SULLIVAN JL, KOMAROFF AL: The "chronic, active Epstein-Barr virus infection" syndrome and primary fibromyalgia. *Arthritis Rheum* 1987; 30: 1132-6.
  58. MOLDOFSKY H: Nonrestorative sleep and symptoms after a febrile illness in patients with fibrositis and chronic fatigue syndromes. *J Rheumatol* 1989; Suppl. 19: 150-3.
  59. NASH P, CHARD M, HAZLEMAN B: Chronic coxsackie B infection mimicking primary fibromyalgia. *J Rheumatol* 1989; 16: 1506-8.
  60. LEVENTHAL LJ, NAIDES SJ, FREUNDLICH B: Fibromyalgia and parvovirus infection. *Arthritis Rheum* 1991; 34: 1319-24.
  61. BERG AM, NAIDES SJ, SIMMS RW: Established fibromyalgia syndrome and parvovirus B19 infection. *J Rheumatol* 1993; 20: 1941-3.
  62. BUYUKKOSE M, KOZANOGLU E, BASARAN S, BAYRAMOGLU O, YARKIN F: Seroprevalence of parvovirus B19 in fibromyalgia syndrome. *Clin Rheumatol* 2009; 28: 305-9.
  63. ALLEN AD: Is RA27/3 rubella immunization a cause of chronic fatigue? *Med Hypotheses* 1988; 27: 217-20.
  64. WEIBEL RE, BENOR DE: Chronic arthropathy and musculoskeletal symptoms associated with rubella vaccines. A review of 124 claims submitted to the National Vaccine Injury Compensation Program. *Arthritis Rheum* 1996; 39: 1529-34.
  65. TINGLE AJ, MITCHELL LA, GRACE M *et al.*: Randomised double-blind placebo-controlled study on adverse effects of rubella immunization in seronegative women. *Lancet* 1997; 349: 1277-81.
  66. LATHROP SL, BALL R, HABER P *et al.*: Adverse event reports following vaccination for Lyme disease: December 1998-July 2000. *Vaccine* 2002; 20: 1603-8.
  67. NANCY AL, SHOENFELD Y: Chronic fatigue syndrome with autoantibodies—the result of an augmented adjuvant effect of hepatitis-B vaccine and silicone implant. *Autoimmun Rev* 2008; 8: 52-5.
  68. CASSISI G: Poliartralgia e astenia a insorgenza acuta dopo vaccinazione polivalente, con caratteristiche assimilabili a fibromialgia. *Progressi in Reumatologia* 2010; Suppl. 1: 82.
  69. GHERARDI RK, COQUET M, CHÉRIN P *et al.*: Macrophagic myofasciitis: an emerging entity. Groupe d'Etudes et Recherche sur les Maladies Musculaires Acquises et Dysimmunitaires (GERMMAD) de l'Association Française contre les Myopathies (AFM). *Lancet* 1998; 352: 347-52.
  70. RYAN AM, BERMINGHAM N, HARRINGTON HJ, KEOHANE C: Atypical presentation of macrophagic myofasciitis 10 years post vaccination. *Neuromuscul Disord* 2006; 16: 867-9.
  71. EXLEY C, SWARBRICK L, GHERARDI RK, AUTHIER FJ: A role for the body burden of aluminium in vaccine-associated macrophagic myofasciitis and chronic fatigue syndrome. *Med Hypotheses* 2009; 72: 135-9.
  72. BINDER LM, CAMPBELL KA: Medically unexplained symptoms and neuropsychological assessment. *J Clin Exp Neuropsychol* 2004; 26: 369-92.
  73. FUKUDA K, NISENBAUM R, STEWART G *et al.*: Chronic multisymptom illness affecting Air Force veterans of the Gulf War. *JAMA* 1998; 280: 981-8.
  74. LANGE G, TIERSKY LA, SCHARER JB *et al.*: Cognitive functioning in Gulf War Illness. *J Clin Exp Neuropsychol* 2001; 23: 240-9.
  75. FORD JD, CAMPBELL KA, STORZBACH D, BINDER LM, ANGER WK, ROHLMAN DS: Posttraumatic stress symptomatology is associated with unexplained illness attributed to Persian Gulf War military service. *Psychosom Med* 2001; 63: 842-9.
  76. UNWIN C, BLATCHLEY N, COKER W *et al.*: Health of UK servicemen who served in Persian Gulf War. *Lancet* 1999; 353: 169-78.
  77. HOTOPF M, DAVID A, HULL L, ISMAIL K, UNWIN C, WESSELY S: Role of vaccinations as risk factors for ill health in veterans of the Gulf war: cross sectional study. *BMJ* 2000; 320: 1363-7.
  78. HOTOPF M, DAVID A, HULL L, NIKALAOU V, UNWIN C, WESSELY S: Risk factors for continued illness among Gulf War veterans: a cohort study. *Psychol Med* 2004; 34: 747-54.
  79. YUNUS MB, MASIAT ALDAG JC: Preliminary criteria for primary fibromyalgia syndrome (PFS): multivariate analysis of a consecutive series of PFS, other pain patients, and normal subjects. *Clin Exp Rheumatol* 1989; 7: 63-9.
  80. SMYTHE HA: Non-articular rheumatism and psychogenic musculoskeletal syndromes. In MCCARTY DJ (Ed.): *Arthritis and Allied Conditions*, 9th Ed. Philadelphia, Lea & Febiger 1979: 881-91.
  81. KRAFT GH, JOHNSON EW, LABAN MM: The fibrositis syndrome. *Arch Phys Med Rehabil* 1968; 49: 155-62.
  82. SHOENFELD Y, AGMON-LEVIN N: 'ASIA' – autoimmune/inflammatory syndrome induced by adjuvants. *J Autoimmun* 2011; 36: 4-8.