Review

One year in review: fibromyalgia

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ABSTRACT

Fibromyalgia (FM) syndrome is a chronic disease with unknown aetiology, characterised by widespread pain, fatigue and other functional symptoms. We reviewed the literature of the past year to underline the recent progress in the etiopathogenesis, assessment and therapies of this syndrome, evaluating the articles published between January 2015 and January 2016.

Etiopathogenesis

In the last year, several hypotheses on the pathogenesis of fibromyalgia (FM) have been formulated.

In a Cochrane review, Wallit *et al*. evaluated the use of selective serotonin re-uptake inhibitors (SSRIs) in FM, and found a low level of efficacy of these drugs at every outcome, suggesting a poor link between serotonin and FM (1).

Park (2) and Ablin (3), in two reviews focused on the genetic aspects of FM, such as specific gene polymorphisms involved in the serotonergic, dopaminergic, and catecholaminergic pathways, underlined the role of these genes in the development of FM. In a large cohort of FM patients, Inanir *et al*. (4) found a link between angiotensin converting enzyme and methylenetetrahydrofolate reductase gene MTHFR C677T polymorphisms and the development of FM, and a further correlation between MTHFR C677T gene mutation and dry eyes and feelings of stiffness.

Genetic involvement was also studied by Rodriguez-Rodriguez *et al*. (5), who evaluated the genetic risk factors associated with the presence of related symptoms and with disease severity in FM patients. A genetic array composed of 320 single nucleotide polymorphisms (SNPs) was analysed in a discovery cohort comprising 564 patients, and the most suggestive variants were genotyped in a replication cohort of 397 subjects. The main finding of this paper has been the role of the tachykinin receptor 1 (TACR1) mutation gene in the development of sicca syndrome in subjects affected by FM.

Littlejohn (6) studied the link between fibromyalgia and complex regional pain syndrome (CRPS) and showed that, although these syndromes have distinct clinical phenotypes, they do share many other features. Pain, allodynia and dysaesthesia occur in each condition and seem to exist on a similar spectrum and share similar trigger factor.

The link between the immune system and FM has been studied by Staud (7), who evaluated the presence of sickness response as well as pain and analgesia. This "sickness response", which has frequently been attributed to inflammatory cytokines, strongly resembles the core symptoms of fibromyalgia, suggesting the role of cytokine abnormalities in its development.

Truini *et al*. (8), using laser evoked potentials (LEPs) and paired laser stimuli, studied the excitability in the pain matrices in FM patients. They found a significantly higher Aδ-LEP amplitude, conditioned by a preceding C-LEP, in FM patients compared to healthy subjects. This data suggests hyperexcitability in the pain matrices in FM, and provides diagnostically useful information and a therapeutic option.

An interesting study on sleep alterations was published by Segura-Jiménez *et al*. (9) using SenseWear Pro Armband (SWA) to assess sleep over the last week in FM and healthy subjects. The authors found a higher frequency of sleep disturbances and average duration of wakefulness after sleep onset in FM women compared with healthy women. Furthermore, people with FM had reduced bedtime with a comparable increase in sleepiness compared to rheumatoid arthritis (RA) patients (10).

Oxidative stress has been taken into account in a study on skin biopsies in which the skin biopsies from patients showed a significant mitochondrial dysfunction with reduced mitochondrial chain activities and bioenergetic levels and increased levels of oxidative stress, suggesting peripheral nerve damage. These findings may support the role of oxidative stress, mitochondrial dysfunction and inflammation as interdependent events in the pathophysiology of FM with a special role in the peripheral alterations (11).

Kim *et al*. (12) acquired functional magnetic resonance (fRM) and electrocardiography data on FM during rest phase and during sustained mechanical pressure-induced pain over the lower leg (the pain phase). They reported that FM patients showed decreased connectivity between multiple ipsilateral and cross-hemispheric S1 subregions, which was correlated with pain severity.

Moreover, in FM patients, sustained pain-altered S1(leg) connectivity to the anterior insula was correlated with clinical/behavioural pain measures and autonomic responses.

The link between FM and peripheral neuropathy is interesting, since it affected about 50% of patients diagnosed with FM. Levin suggests the use of punch skin biopsy to diagnose small fiber neuropathy in a simple and non-invasive manner (13). Early detection of neuropathy provides a prompt diagnosis, increases the treatment options and encourages further pharmacological studies.

The link between FM and emotional sphere emerging another time from a work by Dell'Osso *et al*. (14).

In a brief paper published by Skare *et al*., the authors evaluate the levels of pentraxin 3 in FM. This protein could be linked to an nonspecific immune response in FM (15). Pernambuco *et al*. evaluate the urine levels of melatonin in FM. They found levels of melatonin significantly lower in FM respect to healthy (16).

Assessment

Recent research in understanding FM mechanisms have shown that there is a significant peripheral neuropathic component to this disorder and this is demonstrated by the finding of reduced epidermal nerve fiber density (ENFD) in FM (17). Reduced ENFD is considered the sine qua non of "small fiber neuropathy (SFN)", a disorder of the peripheral nerves that mainly affects small sensory fibers and sympathetic fibers, resulting in pain, paresthesias and autonomic dysfunction. The diagnosis of small fiber neuropathy is based on functional tests (quantitative sensory or autonomic reflex testing) showing altered skin sensory or autonomic response, plus a skin biopsy examination, which demonstrates decreased small nerve fiber density. Corneal confocal microscopy is a new non-invasive method to evaluate small nerve fiber morphology; in fact, the cornea receives the densest small fiber innervations of the body. Ramirez *et al*. investigated corneal stromal nerve fiber morphology in 17 patients affected by fibromyalgia compared to healthy controls using confocal microscopy and correlated corneal nerve microscopic features, and used validated questionnaires to measure fibromyalgia severity (including a neuropathic pain survey and an autonomic symptom questionnaire) (18). They showed that women who suffer from fibromyalgia have thinner/smoother corneal stromal nerves and decreased corneal sub-basal nerve plexus density when compared to healthy controls, but no correlation was found with neuropathic symptoms. The authors concluded that SFN may play a role in the pathogenesis of fibromyalgia pain and that corneal confocal microscopy could become a useful test in the study of patients with fibromyalgia, but further studies are needed. In conclusion, these new studies highlight the concept of fibromyalgia as a sympathetically maintained neuropathic pain illness, which diverges from the widely held view of fibromyalgia as a "centralised" pain syndrome.

Another important aspect in FM is the presence of highly debilitating sleep disturbances, but little is known about the contribution of polysomnographic (PSG) parameters determining subjective sleep quality. Diaz-Piedra *et al*. compared sleep variables (PSG parameters and subjective sleep quality) between women affected by FM and healthy controls (19). FMS patients showed objective alterations in sleep quality, sleep depth and sleep continuity compared to controls, but no differences were found in sleep duration, thus confirming the tendency to perceive nightly sleep as unrefreshing regardless of its duration. Moreover, the authors demonstrated that time spent awake seems to be the best predictor of subjective sleep quality and that depression level is a predictor of subjective sleep quality, which is probably related to the fact that depression may be exacerbated by, or contribute to, sleep disturbances.

Another study by Mundt *et al*. (20), evaluated the utility of actigraphy in detecting changes in sleep following a cognitive behavioural therapy for insomnia in a group of patients affected by insomnia and fibromyalgia, relying on the fact that when chronic pain co-occurs with insomnia, sleep is more fragmented with more movement and arousals.

Salaffi *et al*. evaluate the efficacy of a multicomponent intervention, evaluate the feasibility and user acceptance of an internet-based home telemedical surveillance system for the evaluation of pain and other key health outcomes in patients with fibromyalgia, with good results in term of surveillance, data acquisition and compliance (21).

Therapies

FM therapy requires a multidimensional approach, such as a physical, pharmacological and cognitive one. An important problem in FM patients is the low compliance rate which, in the case of most patients, depends on an inadequate clinical response and on the difficulty in making a correct clinical characterisation of patients. For example, in a cohort FM patients, van Middendorp *et al*. evaluated by phone interview the percentage of distressed (Type D) personality, combining high negative affectivity and social inhibition, which is linked to poor health in various populations, in cohort FM patients by a phone interview. They found a high percentage of type D personality

that may have specific treatment implications (22). Another innovative study that showed the importance of clinical characterisation in leading to a tailored therapy was proposed by Vilalta-Abella *et al*. Using a virtual environment they studied the representation of pain and absence of pain. The patients used different colours and different physical states to depict pain (red, motionless) and the absence of pain (blue, in motion). The statistical analysis showed that the degree of anxiety and depression influenced the perceived characteristic of movement (23).

Pharmacological therapies

Regarding therapy, during the last year several drugs have been evaluated. Wallit *et al*. evaluated the safety and efficacy of selective serotonin reuptake inhibitors (SSRI) (24). In a cohort of 383 subjects, they evaluated the superiority of SSRI with respect to placebo to reduce the key symptoms of FM without any serious adverse events. An interesting observation emerged from a study by Lee *et al*. (25) which was that they did not observe an improvement of widespread pain in RA patients treated with milnacipran. In FM, milnacipran was used with contrasting results as reported by Cording *et al*. (26). The main results emerging from six randomised trials indicate a lower clinical response in FM with pain relief efficacy of 40% compared to 30% of placebo. Another trial designed to investigate the efficacy of milnacipran, reported a low level of efficacy in ameliorating sleep (27). Another antidepressant drug used in FM is amitriptyline. From an interesting review published by Rico-Villademors *et al*., low doses (10-75 mg/day) of amitriptyline are effective for the treatment of FM and, despite the limited quality of the data, they do not seem to be associated with relevant tolerability or safety issues (28).

In a retrospective observational study published by Del Giorno *et al*., palmitoylethanolamite was added to a combination therapy of pregabalin and duloxetine as an anti-inflammatory therapy, with interesting results in terms of improvement of pain relief (29).

Murakami *et al*. evaluated the efficacy and safety of duloxetine in Japanese patients with fibromyalgia. They assessed a cohort of 393 patients who were randomised to receive either duloxetine (n=196) or placebo (n=197) and reported that duloxetine treatment could be associated with improvements in both pain relief and in quality of life in Japanese patients with FM (30).

In a feasibility study, the authors evaluated the effects of transdermal magnesium chloride in FM, with interesting results in terms of quality of life (31).

Pregabalin is a commonly used drug in FM, and Roth *et al*. investigated the effect of this drug on wake and sleep bout parameters with the result that pregabalin improved sleep parameters characteristic of disturbed sleep in FM by preventing awakenings and increasing the duration of sleep (32).

Pregabalin was used in another trial in which the safety and efficacy of pregabalin was evaluated in patients with concomitant depression who were taking antidepressants (33). The main results of this trial was that compared with placebo, pregabalin statistically significantly improved FM pain and other symptoms in patients taking antidepressant medication for depression comorbidity.

Some authors have hypothesised that testosterone deficiency may play a role in FM. In a pilot study, White et al. evaluated pharmacokinetics and the clinical response of testosterone gel in FM (34). They gave 12 FM patients a daily dose for 28 days with transdermal testosterone gel and observed a decrease in muscle pain, stiffness, and fatigue, and increased libido during study treatment.

Another study on an antidepressant was published by Leombruni *et al*. who compared duloxetine and acetyl L-carnitine in FM patients (35), and observed that both drugs had a positive effect on the physical component of the quality of life, but only duloxetine improved the psychological component.

Opioids continue to be used by many FM patients even though they are not a recommended treatment option. Argoff *et al*. evaluated the efficacy of pregabalin with prior opioid use (36) using the data from four clinical trials. The results emerging from these indicate that pregabalin is effective in pain relief irrespective of prior opioid use.

The use of herbal medicine has great resonance in FM. Collado Mateo *et al*. evaluated the efficacy of ganoderma lucidium, a type of mushroom, in FM (37). Their study included sixty-four women with fibromyalgia who took 6 grams of ganoderma lucidium over a 6-week period, at the end of which, a positive result was observed in the level of physical fitness of these patients.

Complementary and alternative therapies

Another important point of view regarding FM therapy is represented by complementary and alternative therapies (CAM). Dias *et al*. evaluated three classical traditional Chinese medicine (TCM) therapies: acupuncture (AC), electroacupuncture (EAC) and moxibustion (MX) in the management of pain and promotion of quality of life in a relatively small cohort of FMS patients (38). Unfortunately, they do not show a significant improvement in pain or reduction of tender points in any of the groups studied. Salehi *et al*. made an exhaustive review of the efficacy of chiropractice in FM, and reported interesting results in conditions such as neck pain, shoulder and neck trigger points, and sport injuries, but not in FM (39).

Vayvay *et al*. investigated the effects of Laser and taping applications on pain, flexibility, anxiety, depression, functional status and quality of life in patients with FM. The results yielded by the Laser group were: a decrease in pain severity in activity (p=0.028), in anxiety level (p=0.01) and an improvement in general health status, quality of life (p=0.01) (40).

Music therapy has been analysed by Alparslan *et al*. in a randomised study. The authors underline the capability of music to relief of pain from 1 to 14 days (41).

Larsson *et al*. evaluated the effects of a progressive resistance exercise programme on muscle strength, health status, and current pain intensity in a cohort of 130 FM patients (42) and concluded that the exercise programme improved

muscle strength, health status, and current pain intensity when assessed immediately after the intervention.

An innovative approach to FM is the administration of hyperbaric oxygen. In a prospective, active control, crossover clinical trial, the authors evaluated this approach and showed that this therapy can improve the symptoms and quality of life of FM patients. Moreover, it showed that hyperbaric oxygen therapy can induce neuroplasticity and significantly rectify abnormal brain activity in pain-related areas of FM patients (43).

Wang *et al*. (44) set up a clinical trial of a large fibromyalgia population to evaluate Tai Chi versus aerobic exercise, which is a recommended component of the current standard of care, to explore the potential of exercise in the management of FM.

The importance of exercise was underline in a study on 22 women with FM exposed to 6 month of aerobic physical program. The training induced changes in cardiac autonomic nervous system modulation in FM and these changes were accompanied by changes in anxiety and depression (45).

Another study underlines the effects of a 16-week hydrotherapy program on 20 FM patients. The authors showed interesting results in ameliorating symptoms, aerobic functional capacity and cardiac autonomic control (46).

An emerging treatment for FM, transcranial direct current stimulation (tTDC), was analysed in a randomised trial in which the patients were randomised to an active or sham tTDC group. A difference was observed in the active group with respect to the sham treatment, but small effect sizes indicate that this treatment is unlikely to reflect clinically important changes (47). The authors underline the power of tTDC to improve quality of life and relieve pain and gave this method a 1b level of evidence.

Conclusion

During the past year there have been no substantial changes in the management of fibromyalgia. It seems well established that genetics plays a role in the development of the disease as well as in the serotonin and noradrenaline system. As regards therapies, studies proposed with alternative therapies have the bulk of the study design, but are often limited with regard to the sample size, and the lack of appropriate control groups. However, improvements have been made with regard to studies on complementary and alternative therapies. As regards drug therapies are concerned, new drugs have not been proposed.

In conclusion, FM is a clinical condition that is difficult to manage and results in poor quality of life. Many efforts have yet to be made to understand, assess and treat this disease.

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