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Fibromyalgia Syndrome – a multidisciplinary approach

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Summary

According to *American College of Rheumatology* fibromyalgia syndrome (FMS) is a common health problem characterized by widespread pain and tenderness. The pain and tenderness, although chronic, present a tendency to fluctuate both in intensity and location around the body. Patients with FMS experience fatigue and often have sleep disorders. It is estimated that FMS affects two to four percent of the general population. It is most common in women, though it can also occur in men. FMS most often first occur in the middle adulthood, but it can start as early as in the teen years or in the old age. The causes of FMS are unclear. Various infectious agents have recently been linked with the development of FMS. Some genes are potentially linked with an increased risk of developing FMS and some other health problems, which are common comorbidities to FMS. It is the genes that determine individual sensitivity and reaction to pain, quality of the antinociceptive system and complex biochemistry of pain sensation. Diagnosis and therapy may be complex and require cooperation of many specialists. Rheumatologists often make the diagnosis and differentiate FMS with other disorders from the rheumatoid group. FMS patients may also require help from the Psychiatric Clinic (Out-Patients Clinic) due to accompanying mental problems. As the pharmacological treatment

options are limited and only complex therapy gives relatively good results, the treatment plan should include elements of physical therapy.

Key words: fibromyalgia, rehabilitation, pain

Introduction

Fibromyalgia Syndrome (FMS) belongs to the group of rheumatic disorders of the soft tissues. A generalized and local form can be distinguished [1, 2]. Local FMS can present with: myofascial pain syndrome, enthesopathies, tendonitis, bursitis, soft tissue disease with the peripheral nerve compression (carpal tunnel syndrome). The generalized form presents with multifocal, chronic pain, leading to chronic stress and resulting in anxiety, sleep disturbances or even depression.

Aim

The aim of the study is to present the current state of knowledge on fibromyalgia and the proposal of a multidisciplinary treatment therapy of this syndrome.

Definition

According to the *American College of Rheumatology* FMS is a common health problem that causes widespread pain and tenderness. The pain and tenderness tend to come and go, and move about the body. Patients with FMS experience fatigue and often have sleep disorders [2].

Epidemiology

It is estimated, that FMS affects two to four percent of the general population. It is most common in women, though it can also occur in men. FMS most often first presents in the middle adulthood, but it can start as early as in the teen years or later in the old age. Though uncommon, it is also possible for younger children to develop widespread body pain and fatigue [1]. Patients with rheumatic diseases such as: osteoarthritis, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), or ankylosing spondylitis are at higher risk of developing FMS. FMS occurs with higher frequency in ambitious, busy individuals, living under constant stress and also in the unemployed. The studies show that incidence of FMS increases with age and with education level [3].

Classification

Fibromyalgia can be divided into primary form, with very pronounced psychogenic background, and secondary e.g. to RA, SLE, Sjögren syndrome (SS), as well as inflammatory bowel disease (IBD) [4-8]. Physical trauma (various forms) have been implicated as triggering events in the pathogenesis of FMS and some patients report

the initiation or exacerbation of their symptoms followed a traumatic event such as a whiplash injury [9].

Etiology and pathophysiology

The etiology of FMS remains unclear. Various infectious agents have recently been linked with the development of FMS. Viral agents as hepatitis C [10], HIV [11] and hepatitis B [12] have been associated with FMS on epidemiological and clinical grounds. FMS occurrence in families suggests a possible link between genes and an increased risk of developing FMS together with some other health problems which are common co-morbidities to FMS. There are three genes already identified as potentially associated with the risk of FMS. Their presence is found in 35% of FMS cohort and is associated with higher levels of inflammatory cytokines [13]. It is the genes that determine individual sensitivity and reaction to pain, quality of the antinociceptive system and complex biochemistry of pain sensation [14]. Heightened sensitivity to pain could be of central origin and originate from the central augmentation of sensory input and decreased activity of the central pain inhibitory function. A single nucleotide polymorphism (SNP) in serotonin transporter (5-HTT) coding gene is a good candidate for a common heritable factor, as it is more common in patients with FMS, depressive disorders and irritable bowel disease (IBD) [15]. Patients with FMS share the dysfunction of the central monoaminergic systems with patients with affective or anxiety disorders. Lower concentrations of metabolites, such as serotonin, noradrenalin and dopamine, reported in the cerebrospinal fluid, may be indicative of this dysfunction [16]. Diminished regulatory response of the serotonergic and noradrenergic systems to the transmission of the pain signals results in central augmentation of sensory input [17]. The involvement of other neurotransmitter systems is also postulated, such as neurokinin, opioid and glutaminergic [18]. The derangement of these systems can be partially responsible for the heightened perception of the pain stimuli as they affect the transduction of pain stimuli to the central nervous system (CNS) as well as for the central pain perception, resulting from the excessive activation of CNS. In this regard FMS would be similar to some other disorders, termed together – central sensitivity syndromes (CSS)[18], which share a lot of clinical features e.g. pain, fatigue, sleep disturbances, allodynia, problems with the psychosocial functioning and poor coping with stress. CSS group includes a wide range of disorders, presenting with both mental and somatic disorders and, at least in some of them, including FSM, with changed reaction to stress, which is partially related to the disturbances in the functioning of the hypothalamo-pituitary-adrenal stress axis (HPA). Disturbances in the activity of this axis are also found in FMS [19]. In contrast to major depression (MDD), especially the melancholic type, fibromyalgia patients present with hypocortisolemia, and suppression, sometimes even excessive, of the cortisol production in dexamethasone suppression test (DST) [20, 21]. The response to stress is decreased and results in inadequate psychobiological work-through. Hypocortisolemia results in decrease in inhibitory feedback effect of cortisol on the noradrenergic and immune system together with increased production of proinflammatory cytokines [22]. Similar abnor-

malities within the stress axis are noted in other CSS or affective spectrum disorders (ASD) disorders e.g. posttraumatic stress disorder (PTSD), atypical depression (AD), chronic fatigue syndrome (CFS), IBS and many others.

Clinical picture

FMS is a chronic health problem presenting with pain all over the body and with other symptoms, such as: tenderness to touch or pressure of the affected joints, muscles fatigue, sleep problems (especially waking up unrefreshed), problems with memory or clear thinking [22, 23]. Some patient may also complain of depression or also of migraine or tension headaches, digestive problems e.g. IBS or gastroesophageal reflux disease, irritable or overactive bladder, pelvic pain or temporomandibular disorder (TMJ) which is a set of symptoms including face or jaw pain, jaw clicking and ringing in ears [2]. People with FMS often suffer from Reynaud's syndrome, xerophtalmia and addiction to alcohol [24]. FMS symptoms and related problems vary in intensity and may wax and wane over time, they are often worsened by stress [4]. FMS is most often set off by some triggering factors, such as spine problems, arthritis, injury or other type of physical stress. Emotional stress may also act as a triggering factor [4, 25]. Chronic pain is the leading symptom of FMS. Clinical practice shows that while acute pain can be alleviated by most medications and methods, almost nothing helps with chronic pain [26]. Pain causes hypersensitivity which disarrays the relation between the stimulus, conduction, perception and response. Chronic pain affects the biochemical structure and blood flow in a brain leading to neuronal loss in the cerebral cortex and the thalamus. It is directly related to mental and emotional disturbances, problems in family/partner relations, and impairment of cognitive functions [26].

Additional tests

No additional tests (e.g. imaging studies, biochemical assessments) are currently available for diagnosing FMS. Some tests need to be performed to rule out other health problems, which can be misinterpreted as FMS.

Diagnosis

The current recommendations indicate that FMS should be diagnosed on the basis of the comprehensive analysis of all symptoms the patient presents with. The number of tender points is no longer regarded as the key diagnostic criterion. A physical examination is helpful to detect tenderness and allows exclusion of other possible causes of the muscle pain. As generalised pain is the main feature of FMS, it is very important for the patient to precisely describe the nature, intensity, location and time frame of the pain. Analysis of the pain pattern helps to differentiate between FMS and other diseases presenting with similar symptoms. For instance, hypothyroidism or rheumatic polymyalgia may mimic FMS. FMS can also be confused with RA or SLE.

FMS Diagnosis Criteria [2]

1. Pain and symptoms over the past week, based on the total of:
   Number of painful areas out of 18 parts of the body
   Plus level of severity of these symptoms:
- Fatigue
- Waking unrefreshed
- Cognitive (memory or thought) problems
   Plus number of other general physical symptoms
2. Symptoms lasting at least three months at a similar level
3. No other health problems that would explain the pain and other symptoms.

Treatment

Although there is no ultimate cure for FMS, some medications can alleviate symptoms of the disease. Non-drug treatments may also be helpful. It seems that the best outcomes can be achieved with a comprehensive approach [27]. Three classes of medication have been proven useful in FMS. The first two classes belong to antidepressants: tricyclic antidepressants (TCA) and serotonin and norepinephrine reuptake inhibitors (SNRI). The third group includes ligands of alpha 2-delta subunit of L-type voltage-regulated calcium channels [28]. Dual action antidepressants, which stimulate the serotoninergic and noradrenergic transmission, may augment the inhibition of the pain signals transmitted from the spinal cord to the brain. The efficacy of this approach is estimated for 30 – 50% [29]. As TCA are characterized by poorer tolerance the therapeutic doses as low as possible are recommended (70-80 mg may prove sufficient) [30]. Contraindications for this type of medication must also be taken into consideration. Amitriptyline is TCA preparation most often recommended for the treatment of FMS. SNRI (duloxetine, milnacipran, venlafaxine) are better tolerated. The doses used in FMS are comparable to those used in depression or lower. These drugs are helpful for the pain treatment, but also show efficacy against other FMS symptoms. Among selective serotonin reuptake inhibitors (SSRI) only fluoxetine and paroxetine are partially effective, which can be attributed to their action within the noradrenergic system. The above mentioned antidepressants are especially recommended when FMS coexists with depressive or anxiety disorders, when they should be the first line treatment. Pregabalin and gababentin have also be proven useful in FMS treatment [28, 29]. Both drugs are relatively well tolerated. The somnolence which is a side effect some patients complain of may be reduced by rescheduling most of the day dose for the evening. Out of the medications described above the following are approved by FDA for the treatment of FMS: duloxetine, milnacipran and pregabalin. In Europe only milnacipran has EMA approval for FMS. In general opioids are not recommended for the treatment of FMS pain, as the evidence suggests they are of little benefit to most FMS patients. In fact they may increase pain sensitivity and make the pain persistent [20]. If an opioid must be used for the pain control in FMS, tramadol seems to be the best choice. In some cases FMS pain can improve with acetaminophen or

non-steroid anti-inflammatory drugs (NSAIDs) like ibuprofen or naproxen. Yet, these drugs most likely treat the pain triggers, rather than the FMS pain itself. Thus, they are found to be most useful in patients with other underlying disorders e.g. arthritis. Some medications used as analgesics may also improve the quality of sleep. These include cyclobenzaprine, amitriptyline, gabapentin or pregabalin. It is not recommended for FMS patients to take hypnotic drugs such as zolpidem or benzodiazepines [2]. Non-pharmacological treatment methods should first of all include cognitive-behavioural therapy (CBT) or at least proper psycho-education to allow the patient to learn how to cope with stress and to establish realistic expectations. CBT improves the overall functioning of patients, but does not affect the intensity of the pain [27].

Multidisciplinary approach

A role of a rheumatologist

Although FMS is not a form of arthritis, nor does it involve inflammation or injury to the joints, muscles or other tissues, as it is related to chronic pain and fatigue, similar to arthritis, most people regard it a rheumatic disease. Thus a rheumatologist most often becomes the specialist patients are directed to and who puts the diagnosis forward (and rules out other rheumatic disorders).

A role of a psychiatrist

FMS patients often complain of multiple mental problems, especially sleep disturbances (including all three phases), fatigue, impairment of cognitive functions and low mood. These symptoms are so typical for FMS, that the first three are proposed by ACR (*American College of Rheumatology*) as diagnostic criteria [2]. The presence of mental problems is related to the more severe course of FMS. More and more evidence emerges suggesting that mental dysfunctions belong to the clinical image of FMS. The relation between FMS and psychiatry is highlighted by the common coexistance of psychopathological symptoms in FMS patients and high comorbidity of FMS with some mental disorders. It must also be noted, that FMS and some mental disorders, share many genetic, neuroendocrine and immune factors. Comorbidity with mental disorders includes: affective anxiety disorders, major depressive disorder (MDD) which is found in 62% of FMS patients, bipolar disorder (PB) found in 11%, panic disorder (PD) found in 29% and social fobia (SP) – in 19% [31]. PTDS is observed in 21% of patients with FMS. The mental disorders listed above are also observed more often in first degree relatives of the FMS patients [32]. On the Basis of the studies demonstrating high comorbidity of these disorders a term "affective spectrum disorders" (ASD) has been introduced. ASD include, apart from fibromyalgia and some affective and anxiety disorders (DSM-IV-TR classification): the hyperkinetic disorders, bulimia nervosa and a spectrum of somatic disorders such as IBD (Inflammatory Bowel Diseases) and migraine. All the disorders share at least one of the following genetically determined features: increased pain sensitivity, decreased

mechanism of pain inhibition, mood alterations [33]. Recently a lot of attention is drawn to the cognitive dysfunction, so called fibro fog (disorders of complex cognitive processes such as memory, concentration, attention, executive functions -ed.), which is one of the most common complaints in FMS patients. Fibro fog seems to result not only from the coexisting problems such as depression, sleep disturbances and neuroendocrine dysfunction, but shows a significant correlation with the pain. It may be presumed that increased processing of sensory signals leads to increased problems with attention span. Experimental data showed the presence of specific difficulty in cognitive inhibition in FMS patients, for which the right inferior frontal cortex might be responsible [34].

A role of a rehabilitation team

Nowadays physiotherapy can offer many methods for pain control, old and new, which, as the research proves, can alleviate the pain, decrease stiffness and improve the patients' physical function and overall quality of life [35]

Exercise program

Physical exercise play an important part in FMS treatment, as it weakens the pain, improves the mood, decreases stiffness as well as reduces the anxiety and fear, resulting in the overall improvement of the life quality [36]. The role of physical exercise in the comprehensive treatment of FMS is beyond question, but the recommendations regarding the type and intensity of exercise still bring controversies. The best is to vary the exercise program on the basis of patients' individual preferences, physical condition and comorbidities.

Physiotherapy

The preliminary results suggest that this method may find its place among the non-pharmacological treatments for FMS. Physiotherapy and magnetotherapy can significantly improve health-related quality of life [37]. Ultrasound treatment, using the mechanical wave, is a long-known method used for the treatment of myofascial pain. There is emerging evidence that ultrasound, for treating triggering pain points in FMS patients, can present a reasonable alternative to medication [20, 25]. Extracorporeal shockwave therapy (ESWT) with both radial and focused shock waves is a relatively new method of treatment. Further studies with long follow-ups are required to evaluate the efficacy and safety of ESWT [35]. The use of biostimulatory laser therapy becomes more popular in the treatment of pain, inflammation, edema and for the tissue regeneration after trauma. The pain in deep located tissues can be treated with high intensity laser (HILT), which provides both photochemical and photothermic effect. Both methods are under clinical trials [35]. Kryochamber sessions help fighting pain via the stimulation of the CNS and release of the endogenous endorphins which have analgesic action and heighten the mood [38, 39].

Hydrotherapy

Water is an ideal environment for resistance exercise, non-weight exercises, aerobic, relaxing and many other types of exercise. The therapy can be conducted in thermal basins or in the sea water (thalassotherapy), in natural or artificial pools. Hydrotherapy can be combined with other physiotherapy methods e.g. electric-water baths. Combination of physiotherapy with pharmacotherapy helps to achieve better sustainability of the symptom control [40, 41].

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