REVIEW ARTICLE

Fibromyalgia: pathogenetic, diagnostic and therapeutic concerns

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ABSTRACT

Musculoskeletal pains are one of the most common complaints reported by patients. In 1972, Smythe described the generalized pain and tenderness on palpation at specific points and, 4 years later, the term fibromyalgia was introduced for determining the disease syndrome.

The etiology and pathogenesis of fibromyalgia are still unknown. This disease appears probably multi-factorial. It is considered that the changes in the neuronal activity in the central nervous system, abnormal metabolism of biogenic amines and immunological disorders may among other things, contribute to the development of the disease. The complaints are non characteristic and highly sujective, which makes it substantially difficult to differentiate between fibromialgia and both chronic fatigue syndrome and psychosomatic diseases. The treatment of fibromyalgia is complex and long-term. The antidepressants and psychotherapy is of vital importance. The effectiveness of locally used agents is also being emphasized.

Fibromyalgia has become a serious social problem in the well developed countries in the recent years. Therefore, of importance are efforts to appropriately diagnose fibromyalgia and to implement its appropriate treatment that resolves disease symptoms in a possibly maximum degree.

The term fibromyalgia appeared relatively recently, in 1976. It was defined as a disease syndrome characterized by a generalized musculoskeletal pain, a feeling of stiffness, sleep disorders associated with awaking feeling unrefreshed, fatigue and the presence of points which are tender during palpation.[1] The frequency of its occurrence in the American population is estimated at 3.4% in women and 0.5% in men. In addition, the frequency increases with age and it is assessed that 7.4% of women aged >70 years suffer from this disease. Lower morbidity is observed in the European population where fibromyalgia affects about 1% of the whole population.[2]

There have been a number of hypotheses that made attempts to explain the mechanism of fibromyalgia. However, there is no concept that provides full explanation of the pathogenesis of the disease. It is claimed that the disease is multi-factorial and develops mainly in predisposed subjects.

In the light of the latest research by Williams and Gracely, the phenomenon of central sensitization seems to be particularly intriguing. It consists in a more intense pain sensation associated with spinal and supraspinal enhancement of the nervous impulsation originating from nociceptors.[3] The authors confirmed that by using the identical pain stimulus in patients with fibromyalgia the increased neural activity leading to a stronger pain sensation was evoked. However, the pain experienced by patients with fibromyalgia and by healthy individuals in an identical manner is associated with a similar neuronal activity increase in the contralateral sensory cortex, the superior temporal gyrus, putamen, insula, and on the ipsilateral part of the cerebellum. Moreover, Williams and Gracely have observed disturbed blood flow within the central nervous system as a potential vital pathogenic factor. They found using single photon emission computed tomography that the patients at rest

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have a lower regional cerebral flow that follows a decreased neural activity which was observed in the right and the left thalamus and both caudate nuclei. This leads to prolonged nociceptive impulsation.

Katz has explained muscular pain in a different way by assuming that the pain is produced as a result of regional vascular dysregulation in muscles[4] and might be induced by reduced nitric oxide levels and oxidative stress[5]. The beneficial effect of vasodilatation and the nature of pain which is similar to myalgia appearing during anaerobic metabolism associated with intense physical exercise support this concept. Moreover, the nocturnal fall in saturation, which might also underlie other disease symptoms, also suggests that muscle hypoxia contributes to the pain etiology.[6] Lower night minimum saturation values, more frequent episodes of the saturation decrease <92% and the longer total period of saturation persisting <92% were observed in fibromyalgia patients.

Maes has postulated a different etiology of the pain. He showed that patients suffering from fibromyalgia had significantly lower levels of certain amino acids such as valine, leucine, isoleucine and fenyloalanine, by examining the amino acid level in their plasma.[7]

Since amino acids take part in providing energy to muscles and in the regulation of protein synthesis, he put forward a hypothesis that decreased levels of amino acids could contribute to pain.

Moreover, a sleeping disorder has also been recognized as a pathogenic factor. The electroencephalographic examinations of patients with fibromyalgia showed the 4th phase of sleep disorders (non-REM sleep – NREM) which involve overlap of many recurrent α waves. The study findings, in which the symptoms of fibromyalgia developed after the interruption of the 4th phase of sleep by artificially produced α waves in healthy subjects, seem to confirm this hypothesis. Under the physiological conditions, the NREM phase stimulates synthesis of insulin-like growth factor-1 (IGF-1), the substance responsible for keeping the correct state at the muscles and muscular strength. The disorders of this phase of sleep lead to decreased production of IGF-1, which can then slow down the muscle regeneration and be responsible for the prolonged time of exercise-induced pain feeling. The results of some studies indicate that sleeping disorders play a primary role as the causative factor in fibromyalgia relapses.[8]

Experiments performed in the recent years have demonstrated that immunologic disorders might also cause fibromyalgia. Higher levels of interleukin-10, interleukin-8 and tumor necrosis factor α have been observed. It suggests a contribution of the inflammation response to the pathogenesis of this disease.[9] Of note, there has been a significant correlation between cytokine levels and the intensity of clinical symptoms, particularly the pain complaints. Moreover, Wallace showed that patients with fibromyalgia have increased levels of interleukin-6 which induces hyperalgesia, symptoms of fatigue and depression.[10]

Serotonin deficiency and increased P substance levels in the cerebrospinal fluid play an important role in the pathogenesis of the disease.[11]

It has also been claimed that genetic factors may predispose to fibromyalgia. In the carriers of the allele responsible for the formation of more active monoaminoxidase A (MAO-A) appears to confer increased risk for morbidity. In addition, the allele carriers present more intense disease symptoms.[12] This observation might confirm a role of serotonin deficiency in the development of fibromyalgia.

Features of personality, the mood changeability and cognitive disorders have an impact on the pathogenesis of fibromyalgia. The results of the studies have shown that mild or moderate cognitive disorders occur in 83% of patients, however, lower mood in 80% of patients suffering from fibromyalgia.[13] Moreover, these individuals often present increased anxiety sensitivity and features of emotional liability to a variable level. As already mentioned, the generalized pain, combined with the stiffness of the trunk and hip and shoulder girdles are the leading clinical symptoms. The pain is burning, biting or blunt, appears even after a mild compression and is long-lasting, although its intensity varies during the day. Apart from the typical pain location in the muscles and the tendons, the patient may also experience arthralgias. Numbness of hands and feet, and Raynaud's symptom are commonly diagnosed. The symptoms are usually followed by weakness, chronic fatigue, dizziness, and sleeping disturbances in the form of difficulties in falling asleep and keeping sleep.[14] The disease symptoms exacerbate in stress, fear, cold, humidity and fatigue. It should be emphasized that fibromyalgia can also be induced by emotional stress, surgery, trauma or hypothyroidism. The diagnosis might be harder to be established for diseases associated with fibromyalgia which symptoms can dominate in the clinical presentation, including irritable bowel syndrome, irritable bladder syndrome, headaches (including migraine), menses disorders, premenstrual syndrome, restless leg syndrome and sicca syndrome.[15]

From the diagnostic point of view, fibromyalgia often poses considerable problems.[16] The most essential issue is to obtain information about the generalized pain and to indicate tender points. According to the American College of Rheumatology criteria (TABLE), there are 18 tender points, however recognition of at least 11 tender points is necessary to establish the diagnosis of fibromyalgia. Additionally, there have been reports in which a lower number of tender points was used in the diagnostic process of fibromyalgia.[17] Among additional examinations, determination in serum and cerebrospinal fluid the levels of serotonin and its metabolites, tryptophan, IGF-1 and

TABLE Classification criteria for fibromyalgia according to the 1990 American College of Rheumatology

A. generalized pain in interview (all conditions below fulfilled):
1. Pain of the left side of the body,
2. Pain of the right side of the body,
3. Pain above the waist,
4. Pain below the waist,
5. Pain in the axial skeleton area (cervical spine, the anterior part of the chest, thoracic spine or in the lumbosacral region)
B. Pain induced by digital palpation pressure at tender points in at least 11 out of the following 18 locations:
1. occiput: both sides, suboccipital muscle insertions,
2. lower part of the cervical spine: both sides, anterior aspects of C5–C7 inter-transverse spaces,
3. trapezius muscle: both sides, midpoint of upper border
4. supraspinatus muscle: both sides, origins, above the spatula spine, near medial border,
5. the 2nd rib: both sides, upper lateral surface of second costochondral junction,
6. lateral epicondyle: both sides, 2 cm distal from to the epicondyles,
7. gluteal muscle: both sides, upper outer buttock, anterior fold of the muscle,
8. greater trochanter: both sides, posterior to the trochanter prominence,
9. knee joint: both sides, medial fat pad, just proximal to medial condyle.
For the classification purposes A and B criteria must be fulfilled and the generalized pain should persist for at least 3 months.
Digital palpation should be made with a pressure of about 4 kg. In order to determine the tender point as a positive one, the patient must state that to palpation was painful.

P substance, seem to be helpful if fibromyalgia is suspected. However, laboratory tests which would confirm the diagnosis of fibromyalgia in the explicit way are not available. Sphygmomanometry can be a simple screening test for fibromyalgia.[18] It appears that the sphygmomanometer cuff pressure to 180 mmHg or until the pain sensation (at lower pressure) is a good, and effective initial test to differentiate between fibromyalgia and rheumatologic or psychosomatic diseases.

The complaints in subjects with fibromyalgia, largely subjective and thus difficult to verify by a physician, hamper the objective assessment of clinical activity of the disease. The Pittsburgh Sleep Quality Index tests that have been used and the Fibromyalgia Impact Questionnaire[19] (questionnaire evaluating the effect of fibromyalgia on everyday life), are burdened with mistakes resulting from the subjective patient's assessment. However, they are helpful in determining the stage of the disease and the effectiveness of the treatment.[20] The most recent study conducted by Denko and Malemuda has brought a definite hope for gaining a more objective assessment of the disease. They showed that in patients in which carbohydrate metabolism disorders are not observed, fasting levels of the growth hormone and insulin[21] might be valuable activity markers for the clinical disease. Of note, disorders of sexual hormone levels have not been observed in patients of that group.[22]

In differential diagnosis, amongst a number of diseases, the chronic fatigue syndrome should be first of all considered.[23] Both pathological syndromes are characterized by musculoskeletal pain, sleeping disorders, fatigue and psychiatric disorders (mild fear and depression). The symptoms suggesting a viral infection, a sudden onset of complaints, as well as impaired memory and concentration ability additionally lead to the suspicion of chronic fatigue syndrome. Some researchers distinguish a primary and secondary form of fibromyalgia coexisting with other diseases. Then, it can be accompanied by symptoms of various diseases such as systemic connective tissue disease, ankylosing spondylitis, bone inflammation, arthritis, soft tissue pain syndrome, polymialgia, polymyalgia rheumatica, sarcoidosis, ulcerative colitis, and the endocrine disorders e.g. hypothyroidism, hyperthyroidism.[24-26] The symptoms and the laboratory tests typical of these diseases constitute the basis for the differentiation between the primary and secondary fibromyalgia. Fibromyalgia also requires distinguishing from depression, however, the presence or absence of tender points helps to distinguish both entities.

Fibromyalgia poses major diagnostic and therapeutic problems. Since the pathogenesis of the disease is not fully understood an effective causal treatment cannot be administered. Therefore, the therapy is based on the multidirectional symptomatic treatment involving various methods. Pharmacotherapy with antidepressants (tricyclic antidepressants – TCA), selective serotonin reuptake inhibitors (SNRI) and selective serotonin norepinephrine uptake inhibitors prevail. The SNRI are considered the most effective and, at the same time, the safest class of medications, particularly duloxetine[27] used in a 30–60-mg dose twice a day. They relieve a number of disease symptoms, in addition, they are much safer than the popular TCA in prolonged therapy. The findings published in 2007 indicate that gabapentin is also efficacious in relieving the pain[28] (improvement was recorded in >50% of patients). Moreover, it decreases the frequency of sleeping disorders and relieves other symptoms. Milnacipran in a daily dose of 25–100 mg[29] is also used in treatment. Tramadol in a 50–100 mg dose 3 times daily is important in the therapy. Nonsteroidal anti-inflammatory treatment is also

used. However, glucocorticosteroids appear to be ineffective despite previous encouraging reports. Local medications, that is massage, warmth, and steroids or lidocain injections to tender points are also efficacious in relieving pain.[30] Stretching and therapeutic rehabilitation are recommended. Moreover, attention is paid to the need of psychotherapy and particularly cognitive therapy.[31] Despite this variety of therapeutic options, a percentage of recovery or rather regression of symptoms is assessed by several investigators at about a few tens of percent. Anticonvulsants, i.e. pregabaline[32] and lacosamid, recently used in patients with fibromyalgia, are promising drugs[33] (the first results of Phase IIa are encouraging). Of note, under the auspices of EULAR 2008 (The European League Against Rheumatism) another study on therapeutic options in patients with fibromyalgia has been published.

Fibromyalgia represents an important social problem. It is assumed that 10–25% of patients is not capable of working anywhere, while in others modifications in working conditions or the profession itself are necessary. Spontaneous remissions in this disease are rare. Pains, depressive states, sleeping disorders significantly worsen the patients' life quality. Hence, given the prognosis minimizing the severity of disease symptoms is uncertain.

A higher prevalence of fibromyalgia observed in the United States compared to the European countries may suggest lower morbidity in Europe. It can also result from insufficient knowledge in this field, e.g. that of recognizing criteria and treating the problems reported by a patient such as symptoms of chronic fatigue syndrome or psychosomatic complaints. The poorly understood etiology of the disease, still constituting a challenge for investigators, does not allow a more effective treatment of fibromyalgia. Therefore, a range of various measures should be used in therapy in order to relieve the complaints and improve the patients' life quality.

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