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Fibromyalgia — new horizons

ABSTRACT

Fibromyalgia (FM) is a chronic non-inflammatory disease characterised by generalised pain and soft tissue tenderness, muscle stiffness, insomnia, fatigue, depression and cognitive impairment. There are still many hypotheses for the aetiopathology of FM and pathophysiological mechanisms of FM are not yet well-understood. This article presents the current reports on the difficult diagnosis options and challenges in the treatment of this disease.

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KEY WORDS: fibromyalgia; epidemiology; aetiopathogenesis; chronic non-inflammatory disease

WHAT IS FIBROMYALGIA?

Fibromyalgia (FM) is a chronic non-inflammatory disease characterised by generalised pain and soft tissue tenderness, muscle stiffness, insomnia, fatigue, depression and cognitive impairment. Until 2018, the World Health Organisation (WHO) classified FM as a musculoskeletal and connective tissue disease (ICD-10: M60-M79 Soft tissue disorders, M79.7 Fibromyalgia). The latest proposed International Classification of Diseases (ICD-11), which will take effect in 2022, changes the previous view of FM by classifying it as „chronic generalised pain" (MG30.01) in the „chronic primary pain" category.

EPIDEMIOLOGY

Epidemiological data collected by the Centre for Disease Control and Prevention (CDC) show that approx. 2% of the general population is affected by this disease [1]. The highest incidence of FM was reported in the USA (2013 — 6.4%) and Scotland (2013 — 5.4%) while in other countries, the percentage is half as large: Italy (2.22%), Germany (2013 — 2.1%), Spain (2008 — 2.4%), Japan (2014 — 2.1%), and Iran (2013 — 2.31%) [2]. Fibromyalgia is more common in women than men [3]. The disease usually develops in people aged 30–60, but can also affect children and elderly people. Differences in criteria and methods of diagnosis contribute to different estimates of the number of fibromyalgia cases in the general population or incidence by gender. Häuser et al. found that the prevalence of fibromyalgia can vary by up to 73%, depending on the diagnostic criteria applied [4].

Documented risk factors for FM include middle age, systemic lupus erythematosus and rheumatoid arthritis. Possible risk factors involve female sex, negative (stressful or traumatic) experiences, repeated trauma, infections, mainly viral (viral hepatitis, EBV, HPV, HIV, parvovirus, coxsackie B), Lyme disease, obesity, positive family history [1].

ETIOPATHOGENESIS

The pathophysiological mechanisms of FM are not yet well-understood, and many studies are still being conducted in this area. FM appears to be associated with a disordered pain modulation in the brain.

There are still many hypotheses for the aetiopathology of FM, including the slow-wave sleep disorder hypothesis, the serotonin hypothesis, the genetic basis hypothesis and the neuropathological hypothesis [5].

The **slow-wave sleep disorder hypothesis** assumes the presence of extra delta waves in

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the EEG of stage IV slow-wave sleep in patients diagnosed with FM. The „alpha-delta" sleep pattern characteristic of patients with FM, mood disorders or chronic pain is an abnormal interference of alpha activity with delta activity [6]. Abnormal, superficial and interrupted sleep can result in impaired synthesis of growth hormone (GH). As a consequence, the reduced insulin-like growth factor (IGF) concentration causes the feeling of exhaustion and increases the intensity of pain. Abnormal GH secretion seems to increase the predisposition to muscle fibre microtrauma and regenerative mechanisms defects as well [7]. This theory is supported by the feeling of general, permanent fatigue and total exercise intolerance in patients diagnosed with FM. However, it is still unclear whether FM is caused by these anomalies, or FM and sleep disorder both result from a different, yet unknown aetiological factor.

The **serotonin hypothesis** is the most commonly accepted theory of FM aetiopathogenesis. Deficits in serotonin and its precursor — tryptophan (as indicated by their reduced concentrations in serum, plasma and cerebrospinal fluid) are responsible for abnormal neurotransmission. Causes of serotonin deficiency include the action of anti-serotonin antibodies (which can be found in the serum of patients with FM) and increased density of serotonin receptors in synapses. This hypothesis is supported by numerous symptoms, mainly pain and mood disorders, as well as comorbidities such as depression [8].

The **genetic basis hypothesis** — potential candidate genes associated with fibromyalgia include the serotonin transporter gene (*SLC64A4*), transient receptor potential vanilloid 2 channel (*TRPV2*), gene encoding the MYT1L protein (*MYT1L*), neurexin 3 (*NRXN3*), catechol-O-methyltransferase (*COMT*) and serotonin receptors. Most frequently, their variability is studied at the level of the most common genetic variation in the human genome, i.e. the single nucleotide polymorphism (SNP). There is also a number of genome-wide association studies (GWAS). The ongoing research focuses on finding the FM marker in microRNA [9]. Recent studies have concentrated on the epigenetic basis of FM, but they are conducted on small groups of probands, which is why it is too early to draw any conclusions. The hypothesis of a genetic basis is supported by the occurrence of FM in the patients' families.

The **neuropathological hypothesis** is a relatively new theory based on observational studies. In 2018, Grayston et al. proposed conducting a meta-analysis on the incidence of small fibre neuropathy in FM. It evaluated 935 scientific reports, which highlighted the prevalence of small fibre neuropathy (SFN) in 49% of patients diagnosed with FM. The high number of SFN cases in FM emphasises the importance of identifying standard methods for describing neuropathy and understanding the processes leading to the development of SFN in order to achieve better diagnostic results and develop effective therapeutic strategies [10].

SYMPTOMS

The symptoms of fibromyalgia can be divided into somatic and psychopathological. Musculoskeletal somatic symptoms include generalised and chronic pain, muscle weakness and morning stiffness. Researchers and experts from the International Association for the Study of Pain (IASP) describe fibromyalgia pain as „nociceptive". After nociceptive and neuropathic, this is the third category of pain. The mechanisms underlying this type of pain are not fully understood. Nociceptive pain is defined as „pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain". Symptoms recorded in the case of nociceptive pain include multifocal pain that is more widespread and/or intense than expected, given the amount of identifiable tissue or nerve damage. Other symptoms of nociceptive pain arising from the CNS involve fatigue, as well as sleep, memory and mood disorders [11].

The remaining somatic symptoms are: fatigue, reduced tolerance to pressure (allodynia), gastrointestinal disorders (irritable bowel syndrome), headaches (migraine), dysuric symptoms, cold hands or feet, often complete intolerance to cold, dry mouth, excessive sweating, dizziness, intermittent dyspnoea and paresthesias. Psychopathological symptoms include sleep disorders, cognitive symptoms (with „brain fog" being the most commonly reported symptom), mood disorders, anxiety disorders, personality disorders and symptoms of schizophrenia [5].

Table 1. Diagnostic criteria for fibromyalgia (2016)

<table>
<tr><th colspan="3">Criteria</th></tr>
<tr><td colspan="3">1. WPI (0–19 points) *pain occurring in the past week</td></tr>
<tr><td>Left upper region (Region 1)</td><td>Right upper region (Region 2)</td><td>Axial region (Region 5)</td></tr>
<tr><td>Jaw
Shoulder
Upper arm
Lower arm</td><td>Jaw
Shoulder
Upper arm
Lower arm</td><td rowspan="3">Neck
Upper back
Lower back
Chest
Abdomen</td></tr>
<tr><td>Left lower region (Region 3)</td><td>Right lower region (Region 4)</td></tr>
<tr><td>Buttock, trochanter
Upper leg
Lower leg</td><td>Buttock, trochanter
Upper leg
Lower leg</td></tr>
<tr><td colspan="3">2. SSS (0–12 points)</td></tr>
<tr><td colspan="3">Presence and intensity of fatigue (0–3 pts), cognitive symptoms (0–3 pts), waking unrefreshed (sleep disorders) (0–3 pts)
Presence of somatic symptoms: abdominal pain, depression, headache (YES/NO, 0–3 pts)</td></tr>
<tr><td colspan="3">3. Presence of generalised pain in at least 4 out of 5 indicated body regions (WPI)</td></tr>
<tr><td colspan="3">DIAGNOSIS: acquisition of WPI ≥ 7 and SSS ≥ 5 (OR WPI 4–6 and SSS ≥ 9) in parts 1 and 2
Presence of symptoms of constant severity ≥ 3 months</td></tr>
</table>

WPI — Widespread Pain Index; SSS — Symptom Severity Scale

DIAGNOSTIC CRITERIA

Due to the lack of biochemical, genetic or imaging markers of FM, the diagnosis of this disease is based on data obtained from a questionnaire. The first guidelines for diagnosing fibromyalgia were established in 1990 (ACR criteria) and based on the occurrence of pain, indicated as the main symptom (tender points), without taking into account psychopathological symptoms. In 2010, the ACR proposed a new version of the diagnostic criteria based on two scales — the Widespread Pain Index (WPI) and the Symptom Severity Scale (SSS). The diagnostic criteria established in 2010 were redefined twice, in 2011 and 2016, for clinical and epidemiological purposes. In addition to the WPI (0–19 points) and SSS (0–12 points) scales, the latest, 2016 version includes a „generalised pain criterion", defined as the presence of pain in 4 out of 5 possible painful body regions. The current criteria for the diagnosis of FM, developed in 2016, are shown in Table 1 [5].

TREATMENT OPTIONS

Current guidelines for the treatment of fibromyalgia unanimously advocate a multidisciplinary approach, combining pharmacological and non-pharmacological treatments, including psychotherapy, with complementary methods, such as cognitive behavioural therapy (CBT), aerobic and strengthening physical training and even meditative movement therapy. According to EULAR, the recommended first-line treatment is non-pharmacological and mainly involves physiotherapy based on aerobic and strengthening exercises [12].

Due to potential side effects and the low percentage of cooperating patients, pharmacotherapy is recommended only in special cases (e.g. in the case of sleep disorders) [8]. Due to the wide range of FM symptoms, the form of therapy should be adjusted individually, while the decision to introduce an appropriate method of treatment should be made together with the patient, depending on the severity of the symptoms (Fig. 1).

Drugs tested on several cohorts of patients included amitriptyline, pregabalin, cyclobenzaprine, growth hormone, monoamine oxidase inhibitors (MAOIs), serotonin and norepinephrine reuptake inhibitors (SNRIs) (duloxetine, milnacipran), selective serotonin reuptake inhibitor (SSRIs) (as a group), and sodium hydroxybutyrate. A summary of the said recommendations in terms of individual drugs is provided in Table 2. It is worth noting that milnacipran — a drug from the SNRI group approved in Australia for the treatment of FM — received only a weak „for" from the EULAR [12].

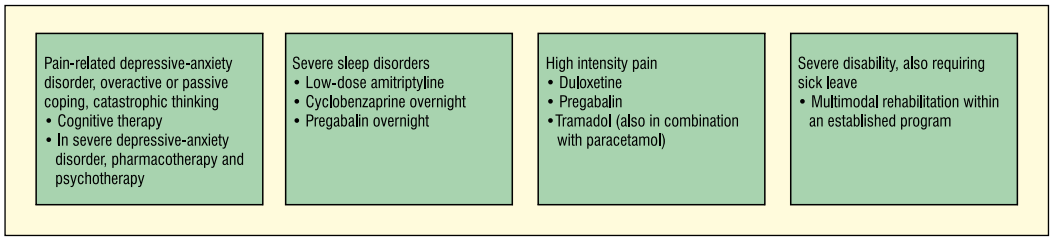

Figure 1. Treatment of specific symptoms/disorders associated with fibromyalgia in EULAR 2016 recommendations [12]

Table 2. Evaluation of drugs for the treatment of fibromyalgia according to EULAR 2016 criteria [12]

Drug or group of drugs	Strength of EULAR recommendation
Amitriptyline	Weak "for", at a low dose
Pregabalin	Weak "for"
Gabapentin	For research only
Cyclobenzaprine	Weak "for"
MAOIs	Weak "against"
SNRIs (duloxetine, milnacipran)	Weak "for"
SSRIs	Weak "against"
Sodium hydroxybutyrate	Strong "against"
Growth hormone	Strong "against"
Nonsteroidal anti-inflammatory drugs	Weak "against"
Tramadol	Weak "for"

EULAR — European Alliance of Associations for Rheumatology (formerly European League Against Rheumatism); MAOIs — monoamine oxidase inhibitors; SNRIs — serotonin and norepinephrine reuptake inhibitors; SSRIs — selective serotonin reuptake inhibitor

ARE WE FACING A CHANGE OF DIRECTION?

A large number of patients diagnosed with FM want to know the cause of their condition. Many of them have to convince doctors that it is not „a disease that exists only in their heads". In 2021, a paper by Andreas Goebel et al. describing FM as an autoimmune disease was published in the Journal of Clinical Investigation. IgG antibodies isolated from patients with FM were administered to mice, which developed a reduced cold and touch tolerance as a result. After removing the antibodies, the same group of mice no longer presented these symptoms [13]. This study appears to support the theory of a possible autoimmune basis of FM. If it is confirmed on a large cohort, this time consisting of humans, it will result in a real revolution in the perception of fibromyalgia and methods of its treatment.

References

1. https://www.cdc.gov/arthritis/basics/fibromyalgia.htm (23 May 2022).
2. Marques AP, Santo Ad, Berssaneti AA, et al. Prevalence of fibromyalgia: literature review update. Rev Bras Reumatol Engl Ed. 2017; 57(4): 356–363, doi: 10.1016/j.rbre.2017.01.005, indexed in Pubmed: 28743363.
3. Cabo-Meseguer A, Cerdá-Olmedo G, Trillo-Mata JL. Fibromyalgia: Prevalence, epidemiologic profiles and economic costs. Med Clin (Barc). 2017; 149(10): 441–448, doi: 10.1016/j.medcli.2017.06.008, indexed in Pubmed: 28734619.
4. Häuser W, Brähler E, Ablin J, et al. Modified 2016 American College of Rheumatology Fibromyalgia Criteria, the Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks-American Pain Society Pain Taxonomy, and the Prevalence of Fibromyalgia. Arthritis Care Res (Hoboken). 2021; 73(5): 617–625, doi: 10.1002/acr.24202, indexed in Pubmed: 32248629.
5. Atzeni F, Talotta R, Masala IF, et al. One year in review 2019: fibromyalgia. Clin Exp Rheumatol. 2019; 37 Suppl 116(1): 3–10, indexed in Pubmed: 30747097.
6. Vijayan S, Klerman EB, Adler GK, et al. Thalamic mechanisms underlying alpha-delta sleep with implications for fibromyalgia. J Neurophysiol. 2015; 114(3): 1923–1930, doi: 10.1152/jn.00280.2015, indexed in Pubmed: 26245315.
7. Bennett RM, Cook DM, Clark SR, et al. Hypothalamic-pituitary--insuline-like growth factor-laxis dysfunction in patients with fi bromyalgia. J Rheumatol. 1997; 24: 1384–1389.
8. Samborski W. Fibromialgia — aktualne zasady rozpoznawania choroby, nowe propozycje dotyczące patogenezy i leczenia. Forum Reumatol. 2015; 1(1): 5–11.
9. D'Agnelli S, Arendt-Nielsen L, Gerra MC, et al. Fibromyalgia: Genetics and epigenetics insights may provide the basis for the development of diagnostic biomarkers. Mol Pain. 2019; 15: 1744806918819944, doi: 10.1177/1744806918819944, indexed in Pubmed: 30486733.
10. Grayston R, Czanner G, Elhadd K, et al. A systematic review and meta-analysis of the prevalence of small fiber pathology in fibromyalgia: Implications for a new paradigm in fibromyalgia etiopathogenesis. Semin Arthritis Rheum. 2019; 48(5): 933–940, doi: 10.1016/j.semarthrit.2018.08.003, indexed in Pubmed: 30314675.
11. Kosek E, Cohen M, Baron R, et al. Do we need a third mechanistic descriptor for chronic pain states? Pain. 2016; 157(7): 1382–1386, doi: 10.1097/j.pain.0000000000000507, indexed in Pubmed: 26835783.
12. Macfarlane GJ, Kronisch C, Dean LE, et al. EULAR revised recommendations for the management of fibromyalgia. Ann Rheum Dis. 2017; 76(2): 318–328, doi: 10.1136/annrheumdis-2016-209724, indexed in Pubmed: 27377815.
13. Goebel A, Krock E, Gentry C, et al. Passive transfer of fibromyalgia symptoms from patients to mice. J Clin Invest. 2021; 131(13), doi: 10.1172/JCI144201, indexed in Pubmed: 34196305.