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## Editorial

### Physiopathology of fibromyalgia<sup>☆</sup>

### Fisiopatología de la fibromialgia

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Fibromyalgia is a disease that is characterised by generalised pain, with increased responses to stimuli perceived as nociceptive as well as somatic symptoms; the pain is chronic and may or may not be associated with joint rigidity. It is usually associated with fatigue, sleep disorders, cognitive dysfunction and depression. It develops with biochemical, metabolic, immunoregulatory and genetic abnormalities, and it lacks a biomarker and evidence of alterations in the functional and chemical connectivity of the pain processing system of the brain.<sup>1</sup>

The disease was reported in 1592 in the *Liber de reumatismo*, in which Guillaume de Baillou described muscle pains that he termed “rheumatism”; in 1815 William Balfour mentioned a “special pain in muscles and joints” and called it “fibrositis”. In 1880, the psychologist Beard described the combination of fatigue, generalised pain and psychological disorders and coined the term “neurasthenia”. In 1904 the pathologist Ralph Stockman described inflammatory processes in which the fibrous and intramuscular walls in biopsies from patients affected by what was known as chronic rheumatism. More recently, Gowers W. Stated that he agreed with the term “fibrositis” to refer to what he characterised as “inflammation of the fibrous tissue” in his description of lumbago secondary to rheumatic fibrositis. The term “fibromyalgia” was first used by Hench in 1976, because there was no evidence of inflammation. Lastly, in 1990, the American College of Rheumatology established criteria for its classification and diagnosis, and these were modified in 2010, 2011 and 2016.<sup>2</sup>

The International Association for the Study of Pain defines this symptom as an “unpleasant sensorial and emotional experience associated with real or potential tissue damage”.<sup>3</sup> It defines inflammation as a necessary defensive process for life, in which without

inflammation the response to endogenous or exogenous attacks and tissue repair would not be possible.<sup>4</sup> In fibromyalgia the sensory “volume control” has a lower pain threshold, and this is also the case for other stimuli (heat, noise and strong odours), as well as hypervigilance.<sup>5</sup> Prevalence varies (from 0.4% to 11%), with a predominance of the female sex (of from >90% to <61%).<sup>6</sup>

Some factors are identified with fibromyalgia: these are a) genetic; b) environmental, c) hormonal, d) neural and e) immunological, as well as certain infections such as Epstein-Barr virus, parvovirus, brucellosis and Lyme’s disease. No specific cause is identified in the vast majority of patients.<sup>7</sup>

Primary and secondary fibromyalgia behave in similar ways.<sup>8</sup> There are abnormalities in pain processing, with an excess of excitatory neurotransmitters such as substance P (with levels that are 2 to 3 times higher in the cerebrospinal fluid)<sup>9</sup> and glutamate, with low levels of inhibitor neurotransmitters such as serotonin and norepinephrine in descending spinal antinociceptive pathways, and with alterations in endogenous opioids in some brain regions that participate in pain modulation and dopamine deregulation.<sup>10–13</sup> There are higher levels of norepinephrine and lower levels of dopamine, 5-HT, 5-HIAA and 5-HTP in women with fibromyalgia. Higher levels of norepinephrine are associated with poorer physical health. It is also possible that plasma norepinephrine levels >694,69 pg/ml may be a fibromyalgia predictor, with an area under the curve of >0.75 (CI 95%: 0.660–0.978).<sup>14</sup> It is also known that there is a reduction in binding of opioid receptor  $\mu$  in areas of the brain that process pain, with an increase in basal endogenous opioid activity, favouring opioid-induced hyperalgesia.<sup>15</sup>

Some fibromyalgia patients experience cognitive disorders, such as difficulty in concentrating, lack of memory or problems with planning and decision-making. These are attributed to interference between nociceptive and cognitive processing: the experience of pain associated with low intensity somatosensory stimulation associated with attention, memory and executive functions in fibromyalgia, compared with traditional levels of pain threshold and tolerance.<sup>16</sup>

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Characteristically in fibromyalgia there is dysfunction of the hypothalamus-hypophysis-suprarenal axis. This affects the adaptive response, with alterations in the levels of corticotrophin-releasing hormone, over-production of adrenocorticotrophic hormone (ACTH) and a fall in cortisol level.<sup>17</sup> Melatonin secretion falls during the night, and this may contribute to poor sleep quality, daytime fatigue and increased perception of pain.<sup>18</sup> Recently a urinary metabolite associated with the melatonin secretion known as urinary 6-sulfatoxymelatonin (aMT6s) was found in greater quantities during daytime hours in subjects with major depression and fibromyalgia in comparison with healthy subjects. This shows how interruption of melatonin secretion is positive correlated with clinical symptoms.<sup>19</sup> Sleep alteration commonly occurs with fibromyalgia, affecting more than 90% of patients<sup>20</sup>: The slow waves are reduced during sleep,<sup>21</sup> and  $\alpha$  intrusion has been identified, together with a prominent  $\alpha$  frequency rhythm (7-12 Hz) in patients with fibromyalgia during NREM sleep.<sup>22</sup> Restricted sleep is an important factor in the development of somatic symptoms, while exercise is extremely important in a positive sense.<sup>23</sup> Sleep alterations in fibromyalgia are prevalent and must be properly evaluated.<sup>24</sup>

The central nociceptive processing by C fibres towards the spine causes abnormal recovery in the dorsal horn neurone, forming part of the central sensitisation secondary to active amplification, increasing the response to pain and recruiting low threshold sensory inputs which are able to activate the pain circuit.<sup>25</sup> Moreover, the injection of substance P into the central nervous system of rats reduces sleep and causes awakenings; patients with fibromyalgia have altered memory and concentration (termed “fibrofog”), with poor performance in cognitive tests.<sup>26</sup>

Small nerve fibre neuropathy is associated with pain in fibromyalgia, with an isolated small magnitude impact on dysfunction in the descending pain modulator system. In a transversal study of 41 women with fibromyalgia and 28 healthy women, the patients with fibromyalgia had lower sensitivity and pain thresholds, and serum brain derived neurotrophic factor are associated with the thermal heat threshold and conditional pain modulator system capacity (CPM-Task). This indicates that the de-inhibition of the descending pain modulator system correlates positively with dysfunction of the periphery sensory neurons and inversely with the serum brain derived neurotrophic factor.<sup>27</sup> Histopathological findings in the smaller fibres cannot be detected in all of the patients who fulfil fibromyalgia criteria<sup>25</sup> or in tests of small fibre disease involvement: the prevalence of this entity in fibromyalgia stands at 49% (CI 95%: 38%-60%) with moderate heterogeneity ( $I^2=68\%$ ). When prevalence was estimated using skin biopsy it amounted to 45% (CI 95%: 32%-59%;  $I^2=70\%$ ), and for corneal confocal microscopy it was 59% (CI 95%: 40%-78%;  $I^2=51\%$ ).<sup>28</sup> In one study the anaesthesiologists Oudejans et al. reported that half of the population with fibromyalgia had signs of small fibre disease measured using corneal confocal microscopy; this is compatible with what Ramírez et al. had reported beforehand when they studied 17 patients with fibromyalgia and compared them with 17 healthy controls using corneal confocal microscopy; the patients with fibromyalgia had thinner stromal nerves ( $5.0 \pm 1.0 \mu\text{m}$ ) than the controls ( $6.1 \pm 1.3$ ;  $P=.01$ , as well as a less dense sub-basal plexus nerve in  $\text{mm}^2$  ( $85 \pm 29$ ) compared with  $107 \pm 26$  in the controls ( $P=.02$ ). This reduction in nerve size is associated with neuropathic pain descriptors (Fisher's exact test  $P=.007$ ).<sup>29,30</sup> In electromyographic and neuroconduction studies in patients with fibromyalgia, the electrodiagnostic characteristics of polyneuropathy, muscle enervation and CIDP are common and often coincide with small fibre neuropathy (63%), independently of whether or not they were associated with rheumatoid arthritis, with presentation in up to 90%.<sup>31</sup>

Dysfunction of the autonomous nervous system at central cardiovascular level is characteristic.<sup>32</sup>

Several studies of fibromyalgia have shown high levels of oxidative stress markers; the accumulation of damaged mitochondrial DNA in cells leads to an innate inflammatory response; the mitochondrial DNA content in fibromyalgia correlates inversely with TNF levels. Oxidative stress may be part of its aetiology: the thiol group acts as an antioxidant, as was shown in a study of 80 women with fibromyalgia that showed a correlation between the reduction in thiol level and increase in disulfur level with FIQ scores, as this did not occur in the healthy control group.<sup>33</sup>

In functional studies using magnetic resonance imaging to evaluate the brain response to tactile motor, visual and auditory stimulation in 35 women with fibromyalgia and 25 controls, a relationship was observed between the brain responses involving subjective hypersensitivity to daily sensory stimulation, spontaneous pain and functional disability and greater subjective sensitivity (discomfort) to multisensory stimulation; additionally, there was reduced activation in the primary and secondary auditory and visual areas, together with increased responses in the insula and anterior lingual gyrus. The reduced responses in visual and auditory areas were correlated with subjective sensory hypersensitivity and clinical measurements of severity.<sup>34</sup> We recognise a characteristic cerebral sign of fibromyalgia at neuronal level, by analysing the functional magnetic resonance imaging response in 37 patients with fibromyalgia and 35 healthy controls to painful pressure and painless multisensory stimulation (visual-auditory-tactile).<sup>35</sup> This showed changed in the excitability of the motor cortex in patients with fibromyalgia, when resting and during slow and rapid tapping with the fingers, using a functional infrared spectroscope (detecting changes in cerebral cortex metabolism in real time). Oxyhaemoglobin concentrations were lower in the patients with fibromyalgia during rapid movements, indicating that activation of the motor cortex is dysfunctional in patients with fibromyalgia.<sup>36</sup> Transcranial Doppler ultrasound scan was used to determine bilateral cerebral blood flow velocity (CBFV) in the anterior and medial cerebral arteries in 44 patients with fibromyalgia and 31 healthy individuals in a resting period lasting for 5 min. Less variability in CBFV was detected in low and high flow ranges in fibromyalgia, which indicates deficient coordination of the cerebral regulatory systems, as well as CBFV variability, which was associated with better clinical results.<sup>37</sup>

First degree family members are at 8 times greater risk of fibromyalgia, and family members have more sensitive points than controls, and they are also at higher risk of functional disorders.<sup>38</sup> Studies in twins showed that genetic factors contribute almost 50% to the risk of developing fibromyalgia.<sup>39</sup> Genetic polymorphisms in the region of serotonin 2A receptor of chromosome 13 (the region that regulates the serotonin transport gene catecholamine methyltransferase, dopamine D3 receptor and adrenergic receptor) have been linked to a higher risk of fibromyalgia.<sup>40</sup> Some genes are potentially implicated in fibromyalgia, and they stand out as possible causes of up to 50% susceptibility (*SLC64A4*, *TRPV2*, *MYT1L* and *NRXN3*), while epigenetic alterations are probably more important, there is a pattern of hypomethylated DNA in the genes that are involved in the stress response, DNA repair, the autonomous system response and subcortical neurone anomalies.<sup>41</sup> In 116 families in the Family Study of Fibromyalgia a fibromyalgia-suggestive link was found in the whole genome of the region of chromosome 17p11.2-q11.2<sup>42</sup> when the exome was sequenced in chemokine genes and functional analysis of SNP in the region of chromosome 17p13.3-q25 previously associated with fibromyalgia in the study of the family association with the complete genome. SNP rs1129844 in *CCL11* and rs1719152 in *CCL4* were associated with high levels of chemokines in the plasma of 220 patients with fibromyalgia. In transmission disequilibrium tests,

rs1129844 was transmitted unequally from parents to affected children ( $P < .0074$ ). CCL4 rs1719152 variant protein showed protein aggregation and powerful negative regulation of the associated CCR5 receptor, which is a receptor associated with hypotensive effects (and probably associated with the orthostatic hypotension seen in some patients with fibromyalgia). Fibromyalgia was also described as being associated with SNP in *MEFV*, which is a chromosome 16 gene associated with syndromes of recurring fevers and had a  $P < .008$  in transmission disequilibrium tests. In general, 36% of SNP with significant cases of transmission disequilibrium were found for CCL11 and 12% for *MEFV*, together with variant of the protein in CCL4 (41%), which affects the negative regulation of CCR5.<sup>43</sup> Genetic variations in catecholamine-O-methyltransferase (*COMT*), which produce excessive levels of catecholamines, originate chronic pain due to the stimulation of adrenergic receptors. The missense variant val158met in single nucleotide polymorphism (SNP) of the *COMT* gene causes a reduction in catecholaminergic exchange. When 60,367 participants in 237 United States of America clinics were studied retrospectively, 2,713 had fibromyalgia and fewer allelic frequencies of the *COMT* SNP; nevertheless, the *COMT* haplotypes associated with pain sensitivity were not directly associated with fibromyalgia (they were generally associated with chronic pain conditions), although they indicate the role of *COMT* in fibromyalgia.<sup>44</sup>

Pro-inflammatory and anti-inflammatory imbalance is found in patients with primary fibromyalgia, with more pro-inflammatory cytokines (TNF, IL-1, IL-6 and IL-8) and potential central neuroinflammation. The latter is triggered by the increase in the levels of cytokines and neurotrophic factors observed in the cerebrospinal fluid, among which substance P stands out together with brain-derived neurotrophic factor, glutamate and nerve growth factor. When the glial cells are activated they produce pro-inflammatory cytokines and neuroinflammation; there is a rise in IL-6, IL-8, IL-1 $\beta$  or TNF $\alpha$  in fibromyalgia<sup>45,46</sup>; the results of other studies are contradictory.<sup>47,48</sup> The level of IL-17 is raised in patients with primary fibromyalgia in comparison with healthy patients, with a correlation with TNF, IFN, IL-2, IL-4 and IL-10.<sup>49</sup> However, IL-4, IL-5 and IL-13 are suppressed, and some acute phase reactants are raised, although there is also evidence that shows that VSG is not altered in patients with primary fibromyalgia, so that the involvement of inflammation is not fully clear. There is a reduction in the severity of primary fibromyalgia, with stable levels of IL-10 and variability in the basal levels of CXCL8 associated with pain, rigidity and sleep.<sup>50</sup> In retrospective database analysis of 630 patients with primary fibromyalgia, 26.9% of the total and 19.2% of those younger than 50 years old had high levels of VSG, and raised PCR was also observed in 35.8% of the younger population (<50 years old); positive antinuclear antibodies were found in 185 (29.3%) and rheumatoid factor was found in 136 (21.5%), and both were positive in 6% ( $n = 38$ ), and of the total, 1.4% ( $n = 9$ ) had raised positive VSG, PCR, ANA and FR,<sup>51</sup> which sometimes functions as the forerunner of an autoimmune disease. Kottcher et al. reported a 0.0027% probability of developing a connective tissue disease within one year in a retrospective study of patients with primary fibromyalgia. This is similar to the incidence of LEG in the general population (0.005%) while having ANA+ does not predict the development of autoimmune disease.<sup>52</sup>

Intestinal dysbiosis has been described as a result rather than a cause of fibromyalgia; there is excessive bacterial growth in the small intestine (SIBO) and there is a clinical improvement after treatment.<sup>53</sup> Alteration in the intestinal microbiota affects intestinal permeability and leads to altered bacteria in fibromyalgia, such as *Faecalibacterium*, *Roseburia*, *Dorea*, *Coprococcus*, *Clostridium*, *Ruminococcus* and *Coprobacillus*. This causes an excess of tryptophan to form indole and skatole, and this brings about a reduction in tryptophan and, with this, reduced recruitment in the central

nervous system. The latter causes a reduction in melatonin and serotonin synthesis, although it has to be said that studies are needed to define the role of the microbiota in fibromyalgia.<sup>54</sup>

Studies of proteomics and fibromyalgia have found 5 dominant enriched routes: acute phase response signalling, LXR/RXR activation, FXR/RXR activation, coagulation system and complementary system. There are also 6 complementary proteins (C1S, CFAH, CO7, CO2, C1QC, CO9) with increased expression in fibromyalgia. Haptoglobin and fibrinogen have been shown to be associated with fibromyalgia, and this may be considered to be a plasma protein signature.<sup>55</sup> Other authors have used proteomics to show over-expression of 3 proteins associated with oxidative stress:  $\alpha$ 1-antitrypsin, transthyretin and retinol, binding protein 4 in fibromyalgia.<sup>56</sup> Malatji et al. reported 196 metabolites when studying urinary metabolites in 18 women with fibromyalgia. Of these, only 14 metabolites were significantly raised, from which it is inferred that energy use is relevant in fibromyalgia. The microbiota may alter brain function through the intestinal-brain axis, and the examination of urine in fibromyalgia is a route to be explored to add non-invasive clinical information for its diagnosis and treatment.<sup>57</sup>

There are reasons to believe that masked depression is of extreme importance in fibromyalgia, and that it is necessary to “reduce the excessive medication of misery”, given that the depression is expressed with a prevalence of 40%-80%.<sup>25,58</sup> As fibromyalgia and dissociative disorders are linked, patients with fibromyalgia had higher scores, and this may be connected with dissociative experiences, trauma and victimisation. Antidepressants may also play a role in dissociative symptoms: patients in antidepressant treatment have lower scores.<sup>59</sup>

## Conflict of interests

The authors have no conflict of interests to declare.

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