

# Fibromyalgia as a neuropathic pain syndrome<sup>(\*)</sup>

## *Fibromilgia como síndrome de dor neuropática*

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### ABSTRACT

This article discusses scientific evidence supporting the notion that all fibromyalgia (FM) features can be explained on the basis of autonomic (sympathetic) nervous system dysfunction. Also suggests that FM main features (widespread pain and tenderness at palpation on specific anatomic points) are manifestations of painful neuropathy. On these bases, a holistic approach for FM treatment is proposed.

**Keywords:** fibromialgia, sistema nervoso simpático, sistema nervoso parassimpático, dor neuropática.

### INTRODUCTION

My first argument is that FM is a multi-system illness. This means that FM symptoms are not limited to the muscles (as the name *fibromyalgia* may suggest). It is obvious that this illness also produces dramatic manifestations in different organs and systems of the body. According to the multicenter study that lead to the 1990 ACR criteria<sup>(1)</sup> besides its defining features, FM also produces dramatic manifestations in different organs and systems of the body, such as: Fatigue, sleep disorders, morning stiffness, headache, paresthesias, sicca syndrome, (pseudo) Raynaud's phenomenon, irritable bowel, headache and anxiety.

All these features are more prevalent in FM subjects when compared with patients with similar rheumatic syndromes. So, any valid theory attempting to explain FM mechanisms should first give a coherent explanation for the presence of these disparate symptoms in the same patients. When we started our FM research in the National Institute of Cardiology of Mexico a decade ago, our working hypothesis was that all of the above-mentioned features could be explained on the basis of autonomic nervous system dysfunction.

### RESUMO

*Este artigo discute as evidências científicas que justificam a proposição de que todas as características da fibromialgia (FM) possam ser explicadas como disfunção do sistema nervoso (simpático). Sugere também que as características principais da FM (dor difusa e à pressão de pontos anatómicos específicos) são manifestações de neuropatia dolorosa. Como conclusão, propõe a aproximação holística para o tratamento da FM.*

**Palavras-chave:** fibromialgia, sympathetic nervous system, parasympathetic nervous system, neuropatic pain.

### WHAT IS THE AUTONOMIC NERVOUS SYSTEM (ANS)?

The ANS is the portion of the nervous system that controls the function of the different organs and systems of the body. For instances, it regulates body temperature, blood pressure, heartbeat rate, bowel and bladder tone among many other variables. It is "autonomic" because our mind does not govern its performance, rather it works below the level of consciousness. One striking characteristic of this system is the rapidity and intensity of the onset of its action and its dissipation. Centers located in the central nervous system (brain stem, hypothalamus and thalamus) and in the spinal cord activate the ANS. These centers also receive input from the limbic system and other higher brain areas. This means that the ANS is the interface between mind and body functions. These connections enable the ANS as the main component of the stress response system in charge of the *fight-or-flight* reactions.

The ANS works closely with the endocrine system, particularly with the hypothalamic-pituitary-adrenal axis. Another endocrine axis closely related to the ANS involves growth hormone secretion.

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The peripheral autonomic system is divided into two branches; sympathetic and parasympathetic. These two branches have antagonistic effects on most bodily functions and thus their proper balance preserves equilibrium. Thus the ANS represents the *Ying-yang* concept of ancient eastern cultures. Sympathetic activation puts the whole body ready to *fight or flight*, in contrast parasympathetic tone favors digestive functions and sleep. The sympathetic autonomic branch extends from the brain stem to the spinal cord. There are rich sympathetic nerve tissue at the neck and pelvic areas (important facts for FM research). From the spinal cord the sympathetic nervous system goes to our internal organs and to the extremities. At the skin level sympathetic activity induces cold clammy hands, mottled skin and *piloerection* (goose skin).

The action of the two branches of the ANS is mediated by *neurotransmitters*. *Norepinephrine* is the predominant sympathetic neurotransmitter whereas *acetylcholine* acts in the parasympathetic periphery<sup>(2)</sup>.

Until recently, the action of this extremely dynamic ANS has been difficult to assess in clinical practice. Changes in breathing pattern, mental stress or even posture, alters immediately and completely the sympathetic/parasympathetic balance. Nevertheless, with the introduction in recent years of a new powerful cybernetic technique named *heart rate variability analysis*, the outlook changed dramatically.

### WHAT IS HEART RATE VARIABILITY ANALYSIS?

This technique is based on the fact that the heart rate is not uniform, but varies continuously from beat to beat by few milliseconds. The periodic components of this endless heart rate variation are dictated by the antagonistic impulses that the sympathetic and parasympathetic branches have on the heart. Cybernetic recording of this constant variability is able to estimate both sympathetic and parasympathetic activity. The elegance of this method resides on the fact that all measurements are derived from electrocardiograms, so patients are subjected to no discomfort whatsoever<sup>(3)</sup>.

### OUR RESEARCH ON FIBROMYALGIA

We used heart rate variability analysis to estimate ANS function in patients with FM. We found that such patients have changes consistent with relentless hyperactivity of their sympathetic nervous system during the 24 hours of the

day<sup>(4)</sup>. Very interestingly, in a different study FM patients were subjected to a simple stress test (to stand-up), their overworked sympathetic nervous system became unable to further respond meaning that the system was already exhausted<sup>(5)</sup>.

It is known that as we stand-up blood tends to pool in the lower parts of the body. In normal circumstances there is an immediate sympathetic surge that compensates this blood shift and maintains normal blood circulation to the head. People with FM clearly have an abnormal response, their sympathetic nervous system fails to respond properly.

It is pertinent to mention that researchers from different parts of the world have confirmed these abnormal heart rate variability findings in patients with FM<sup>(6-9)</sup>.

Based on this research we proposed that *dysautonomia* is frequent in patients with FM. Such *dysautonomia* can be characterized as a sympathetic nervous system that is persistently hyperactive but hypo-reactive to stress. Furthermore we propose that such *dysautonomia* explains all FM features<sup>(10)</sup>.

Our ANS findings in no way contradict prior groundbreaking research on sleep disorders and hormonal abnormalities in FM, rather they are integrated in a coherent holistic model.

### DYSAUTONOMIA EXPLAINS ALL FM FEATURES

Sympathetic *hyporeactivity* provides a coherent explanation for the constant fatigue and other symptoms associated to low blood pressure such as dizziness, foggy and faintness. This phenomenon can be compared to what would happen to a constantly forced engine that becomes unable to speed-up as response to further stimulation.

Relentless sympathetic *hyperactivity* explains the sleep disturbances. It is known that parasympathetic tone predominates during deep sleep stages and that seconds before awakening episodes there is a sympathetic surge. Our concurrent studies of polysomnography and heart rate variability analyses have shown that FM people have relentless nocturnal sympathetic hyperactivity associated to constant arousal and awakening episodes<sup>(11)</sup>.

This sympathetic *hyperactivity* may also explain the cold-clammy hands (pseudo Raynaud's phenomenon) and the constant dryness in the mouth.

Interestingly, investigators that directly studied irritable bowel syndrome and interstitial cystitis have reported alterations consistent with sympathetic hyperactivity.

Special mention deserves the relationship of FM with anxiety and depression. It is clear that FM patients frequently have associated anxiety and/or depression. It hardly could be any other way with persons suffering from chronic intense pain. Unfortunately, the psychological component associated to the multisystem FM features has led some physicians to diagnose these patients with pejorative labels such as hypochondriacs or hysterics. New labels have been used in recent years such as persons with “health seeking behavior” or “somatizers”. In my opinion these labels are totally misplaced and do not help by any means in understanding the causes that lead to FM. The fact that there is a psychological component in FM does not diminish the validity of the diagnosis nor make patients guilty for their own suffering. The key issue in FM research is not whether or not there is a psychological component, the key issue is to find out why these persons have so much pain. There is ample evidence to sustain the fact that FM pain is real as attested by different studies demonstrating very high levels of the powerful pain-transmitting *substance P* in the cerebrospinal fluid of these patients.

According to our model anxiety could be either the cause or the effect of sympathetic hyperactivity. It should be noted that any normal person injected with norepinephrine becomes jittery and anxious.

So, we have to address the key FM issue, how to explain its defining features: widespread pain and tenderness at palpation on specific anatomical points. We propose that these key features can be explained by the mechanism known in Medicine as *sympathetically maintained pain*<sup>(12)</sup>. This type of pain is characterized by its frequent onset after trauma, by being independent of any tissue damage and by the presence of *allodynia* and *paresthesias*. *Sympathetically maintained pain* is a type of neuropathic pain. This means that the problem lies in the pain-transmitting nerve itself. Examples of neuropathic pains are post-herpetic neuralgia, diabetic neuropathy and reflex sympathetic dystrophy. We have suggested that FM is a generalized form of reflex sympathetic dystrophy<sup>(12)</sup>. Unfortunately these types of neuropathic pains respond poorly to the usual analgesic/anti-inflammatory medications. Neuropathic pain is characterized by three clinical features: Stimulus-independent pain, allodynia and paresthesias, these are precisely FM pain features. Our study demonstrating that practically all subjects with FM have different types of paresthesias adds evidence to the notion that FM is a neuropathic pain syndrome<sup>(13)</sup>.

*Sympathetically maintained pain* syndromes have strong experimental foundations. Studies done in animals have shown that trauma may trigger relentless sympathetic hyperactivity and that in such instances the pain-transmitting nerves are altered and abnormally activated by norepinephrine, (a phenomenon known as *norepinephrine-evoked pain*) thus starting a vicious cycle of sympathetic hyperactivity and pain. Moreover, after nerve injury there are structural changes at the dorsal root ganglia with sympathetic sprouting and also in the posterior horn with invasion of the A-beta fibers to lamina II area. Such structural changes induce stimulus-independent pain and allodynia<sup>(14-15)</sup>.

FM has clear *sympathetically maintained pain* features. As discussed before, there is relentless sympathetic hyperactivity. There is frequent onset after physical or psychological trauma. There is widespread pain without underlying tissue damage, accompanied by *allodynia* and *paresthesias*. It is interesting to notice that most FM tender points are located in the neck area, a zone with very rich sympathetic ganglia network. Nowhere else in the body are the sympathetic ganglia so near to the skin. Our recent prospective double-blind study showing that injections of tiny amounts of norepinephrine induces pain in FM patients, reinforces the notion that FM is a *sympathetically maintained pain syndrome*<sup>(16)</sup>.

## TREATMENT OF DYSAUTONOMIA IN FIBROMYALGIA

The realization of dysautonomia in FM demands a holistic approach for its treatment<sup>(17)</sup>. We are not dealing with a localized ailment, rather it is our main regulatory system that is not working properly.

Dysautonomia provides a plausible explanation for the reported beneficial effects of interventions such as cognitive-behavioral therapy and graded aerobic exercises. These disciplines improve FM symptoms and also improve resting autonomic tone.

It seems wise to ask patients to avoid the intake of adrenaline-like substances such as nicotine, caffeine-containing soft drinks and coffee. Liberal intake of mineral water may help symptoms related to low blood pressure such as fatigue, dizziness and faintness.

For this chronic illness with multiple complaints, is important to refrain from excessive use of medications. Therapy should be individualized and remain under physician's supervision. Medications should be directed to improve sleep and autonomic balance.

The main FM symptom, widespread pain should be eased with centrally acting analgesics. Anti-inflammatory medications have little beneficial effects. It is clear that current analgesic therapy is insufficient in many cases. We have to direct our attention to anti-neuropathic medications, but again, currently available compounds are not satisfactory in many instances. Different types of anti-neuropathic drugs are in the development period. There are reasons to expect that these new medications will be also effective for FM pain.

In conclusion, there are reasons to be optimistic. The FM enigma is in the process of being better understood. I am convinced that scientific evidence will eventually disprove FM non-believers. Both patients and health care providers have to be daring and move away from the decrepit medical paradigm that views any illness without obvious structural damage as non-existent or as belonging to the psychiatry realm. We as rheumatologist have to recognize the

paradox that we confront. On one hand, chronic pain is the main complaint of the overwhelming majority of our patients; on the other hand we know very little about basic mechanisms of chronic pain. This is due to an obvious deformity of our training programs. If we review Rheumatology's textbooks we will find thick chapters on the basic mechanisms of inflammation or autoimmunity, but none of the textbooks contain a chapter on the basic mechanisms of chronic pain. No wonder why when we have to take care of a patient with severe pain but without inflammatory or autoimmune manifestations, we feel totally disoriented.

We need to adopt a scientifically holistic paradigm that recognizes the tight mind-body interactions in any chronic disease state. We have to be imaginative and develop different treatments for FM based on the unfolding new knowledge.

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