

## Is fibromyalgia a generalized reflex sympathetic dystrophy?

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### ABSTRACT

*Fibromyalgia and reflex sympathetic dystrophy share defining characteristics, namely chronic pain and allodynia, as well as other important clinical features such as onset after trauma, female predominance, paresthesias, vasomotor instability, response to sympathetic blockade and anxiety/depression. Recent research using heart rate variability analysis demonstrated that patients with fibromyalgia have changes consistent with relentless circadian sympathetic hyperactivity.*

*I propose that fibromyalgia is a sympathetically maintained pain syndrome in which ongoing sympathetic hyperactivity sensitises the primary nociceptors and induces widespread pain and allodynia.*

Fibromyalgia (FM) is a common syndrome characterised by two major features: chronic widespread pain and tenderness at palpation in well defined anatomical points. These two defining features are invariably accompanied by an array of multisystem symptoms (1). We have shown by means of heart rate variability analysis that patients with fibromyalgia have changes consistent with relentless circadian sympathetic hyperactivity (2) associated with hypo-reactivity to orthostatic stress (3). These disturbances have been confirmed by other groups of investigators (4-6). This type of dysautonomia may explain the multisystem manifestations of FM (7).

Through the years different terms have been used for clinical conditions in which pain is likely to be maintained by ongoing sympathetic hyperactivity such as reflex sympathetic dystrophy (RSD) and causalgia (8). The International Association for the Study of Pain introduced the term 'complex regional pain syndromes' (CRPS) to denominate these conditions in view of the inconstant evidence of increased sympathetic traffic in the affected limbs of some of these patients and also their variable response to sympathetic blockade (9). Nevertheless, the term CRPS has gained little acceptance among clinicians. The traditional term RSD

remains in vogue and will be used in this discussion.

The group of experts of the International Association for the Study of Pain defines RSD (also known as CRPS type I) as a syndrome that develops after an initiating noxious event. It is characterised by spontaneous pain or allodynia not limited to the territory of a single peripheral nerve and disproportionate to the inciting event. There is or has been evidence of edema, skin blood flow abnormality, or abnormal sudomotor activity in the region of pain since the inciting event (9).

Pain induced by sympathetic hyperactivity has experimental foundations (8). In a rodent model, after nerve damage sympathetic stimulation and nor-epinephrine are excitatory for primary skin C-fiber nociceptors (10). On the other hand, peripheral nerve injury triggers noradrenergic sprouting within the dorsal root ganglia and the formation of basket-like structures around large-diameter axotomized sensory neurons; sympathetic stimulation can activate such neurons repetitively. These unusual connections may give rise to a vicious cycle of sympathetic hyperactivity and pain (11). Furthermore, it has been demonstrated that following nerve injury, the nociceptor phenotype undergoes important changes as it starts to express adrenoceptors and becomes responsive to catecholamines (8, 12).

I find several points of coincidence between the clinical features of FM and RSD which lead me to propose that FM could be a generalised form of RSD. These similarities are outlined in Table I and are further discussed below.

**Table I.** Similarities between reflex sympathetic dystrophy syndrome and fibromyalgia.

Onset after trauma
Female predominance
Chronic pain
Allodynia
Paresthesias
Vasomotor instability
Response to sympathetic blockade
Emotional response to chronic pain

**Onset after trauma.** Historically RSD and causalgia have been related to precedent gunshot wounds and other types of injuries, especially Colles's fracture of the wrist (8). Post-traumatic onset has been also demonstrated in FM. This is particularly true in cases of trauma to the neck area. Buskila *et al.* in a controlled study reported that FM was 13 times more frequent following neck injury than following lower extremity injury (13).

**Female predominance.** Chronic painful conditions are more prevalent in females. This distribution is evident in FM and in RSD. One possible explanation for this discrepancy is gender differences in the structure and function of the sympathetic nervous system that may be related to hormonal influences (14). There are fewer sympathetic preganglionic neurons in the spinal cords of female cats than male cats (15). Sprouting of sympathetic fibres into the hippocampus induced by neural injury has been shown to be more restricted in male than in female rats and to be affected by neonatal manipulation of testosterone levels (16). In the resting state, cutaneous sympathetic tone is greater in women than in men, as attested to by the lower skin perfusion in females (17).

**Chronic pain.** Both conditions are characterised by chronic, debilitating pain, disproportionate to the underlying tissue damage and unresponsive to analgesic or anti-inflammatory drugs.

**Allodynia** (pain resulting from a normal non-noxious stimulus). This type of sensory disturbance is the hallmark of RSD. One of the diagnostic criteria for FM is hypersensitivity to palpation of well-defined anatomical points. Of note is that 10 of the 18 FM tender points are located in the neck area in the proximity of the superficial sympathetic ganglia network. Nowhere else in the body are the sympathetic ganglia so adjacent to the skin. As suggested by Russell (18), tender points reflect a state of generalised allodynia since patients with FM also have generalised hypersensitivity to palpation (19).

**Paresthesias.** Burning and tingling are symptoms typically associated with neuropathic pain. The controlled study

that led to the American College of Rheumatology criteria for FM found that paresthesias are more prevalent in FM patients when compared with patients with similar rheumatic diagnoses (1).

**Vasomotor instability.** Edema and vasomotor alterations are characteristic of RSD. It is clear that FM patients have abnormal peripheral vasomotion often regarded as 'atypical' Raynaud's phenomenon (1). Vaeroy *et al.* demonstrated that such patients have an abnormal skin vasoconstrictory response to acoustic stimulation or cold pressure test (20).

**Response to sympathetic blockade.** A strong argument in favor of the participation of the sympathetic nervous system in RSD is the remarkable improvement of pain after sympathetic blockade. As a matter of fact, this procedure is the principal therapeutic intervention for RSD (21). In the only published controlled study of regional sympathetic blockade in fibromyalgia, Bengtsson and Bengtsson describe that stellate ganglion blockade with bupivacaine notably decreases regional rest pain as well as the number of tender points, compared with the lack of response to sham injection of saline solution in the neck area, thus suggesting that FM pain is responsive to sympatholytic manoeuvres (22).

**Emotional response to chronic pain.** Chronic debilitating pain is often associated with anxiety and depression. Such is the case in the two syndromes under discussion. Anxiety may be either the cause or the effect of sympathetic hyperactivity. The fact that there is a psychological component in these illnesses does not diminish the validity of the diagnoses nor does it make the patients censurable for their suffering.

Arguments against the fore-mentioned hypothesis are that FM patients do not display a vast loss of bone mineralisation nor the movement disorders nor the tissue atrophy that are sometimes seen in advanced stages of RSD. Nevertheless, it should be noted that some of these features have been reported, albeit in mild forms, in FM. Densitometry studies have found an increased

prevalence of osteoporosis in both pre and post-menopausal women with FM as compared to normal controls (23), and periodic leg movements are frequently found in FM (24).

The sympathetic nervous system forms part of the stress response system, which also has an endocrine component. There is a close interplay between these two systems. Alterations of the hypothalamic-pituitary-adrenal axis (25) and the growth hormone axis (26) have been reported in FM. The involvement and effects of the stress response system in FM seem different when compared to other rheumatic syndromes (27).

In conclusion, FM and RSD share the same defining characteristics (chronic pain and allodynia) as well as other important clinical features. RSD has the advantage of presenting localised alterations which manifest in the symptomatic limb but are absent on the opposite site. This peculiarity has facilitated the study of its pathogenesis and its recognition as a 'real' entity.

Further research into the mechanisms whereby ongoing sympathetic hyperactivity leads to chronic pain and allodynia may be pertinent to the pathogenesis of these two enervating syndromes.

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