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Fibromyalgia and unexplained widespread pain: The idiopathic cerebrospinal pressure dysregulation hypothesis☆

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ABSTRACT

Fibromyalgia (FM) is a debilitating, widespread pain disorder that is assumed to originate from inappropriate pain processing in the central nervous system. Psychological and behavioral factors are both believed to underlie the pathogenesis and complicate the treatment. This hypothesis, however, has not yet been sufficiently supported by scientific evidence and accumulating evidence supports a peripheral neurological origin of the symptoms.

We postulate that FM and several unexplained widespread pain syndromes are caused by chronic postural idiopathic cerebrospinal hypertension. Thus, the symptoms originate from the filling of nerve root sleeves under high pressure with subsequent polyradiculopathy from the compression of the nerve root fibers (axons) inside the sleeves. Associated symptoms, such as bladder and bowel dysfunction, result from compression of the sacral nerve root fibers, and facial pain and paresthesia result from compression of the cranial nerve root fibers. Idiopathic Intracranial Hypertension, Normal Pressure Hydrocephalus and the clinical entity of symptomatic Tarlov cysts share similar central and peripheral neurological symptoms and are likely other manifestations of the same condition.

The hypothesis presented in this article links the characteristics of fibromyalgia and unexplained widespread pain to cerebrospinal pressure dysregulation with support from scientific evidence and provides a conclusive explanation for the multitude of symptoms associated with fibromyalgia.

Introduction

Fibromyalgia (FM) is a debilitating, widespread pain disorder that is assumed to originate from inappropriate pain processing in the central nervous system. Psychological and behavioral factors are both believed to underlie the pathogenesis and complicate the treatment. This hypothesis, however, has not yet been sufficiently supported by scientific evidence. Accumulating evidence supports a peripheral neurological origin of the symptoms.

We postulate that FM and several unexplained widespread pain syndromes are caused by cerebrospinal hypertension. Thus, the symptoms originate from the filling of nerve root sleeves under high pressure with subsequent polyradiculopathy from the compression of the nerve root fibers (axons) inside the sleeves. This hypothesis provides a conclusive explanation for the multitude of symptoms associated with FM.

Evidence for a neurological origin of the symptoms in patients with FM

Neurological complaints

Several studies report sensory complaints in fibromyalgia patients (FMP) that are consistent with peripheral neuropathy.

Up to 95% of FMP complain of neuralgic pain symptoms, including

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numbness, paresthesia (prickling, needles and tingling), pain attacks (electric shocks and bursts), evoked pain (when touching the skin or when wearing tight clothes), thermal (hot and burning) pain sensations, sensitivity to temperature, severe pressure pain, and weakness in the extremities [1–6].

When patients with diabetic neuropathy and FM were compared, similar abnormal sensory complaints and pain qualities were observed at similar frequencies.

Diabetic polyneuropathy is caused by peripheral nerve damage, whereas FM is assumed to be a centralized pain syndrome. Consequently, these similar sensory symptoms were hypothesized to result from similar pain mechanisms [5,7].

Neurological symptoms

A body of evidence has shown that FMP present with detectable neurologic abnormalities.

Sensory disturbances

Scores from pin-prick tests of the lower legs reveal hypoesthesia in up to 88% of FMP [3,6].

When performing a blinded neurological examination, tingling and numbness correlated well with hypoesthesia upon pin-prick and exposure to different temperatures and vibration in any part of the body [4].

When comparing FMP with patients with depression and healthy control subjects, elevated temperature and mechanical detection thresholds were observed. FMP were less able to distinguish temperature changes. When inquiring about pain characteristics to calculate a pain score in these patients, 80% of FMP displayed neuropathic pain scores, compared with only 10% of the patients with depression and 12% of the healthy controls [8].

Muscle strength

Clinically significantly lower proximal muscle strength has been observed in FMP than in rheumatic controls, and 90% of these FMP confirmed subjective weakness [3].

Moreover, subjective weakness in the arms and legs of FMP correlated well with a blinded neurological examination, i.e., the loss of muscle mass in 13% of the FMP, compared with none of the controls [4].

Small fiber neuropathy

Studies using skin biopsies from FMP have reported reduced epidermal nerve fiber density and nerve fiber diameter [6,8,9].

This finding was later confirmed in a study assessing corneal small fiber morphology using in vivo microscopy. In this study, a decrease in the small fiber density was associated with scores on a neuropathic pain symptoms questionnaire [10].

Additionally, when using microneurography, a neurophysiological method to study small fiber function, most FMP were shown to have an abnormal C nociceptor function. Hyperexcitability and high conduction slowing was more common in FMP [11].

Small fiber neuropathy is a sensory neuropathy with superficial pain that mainly affects the toes and the feet, whereas FMP report generalized deep muscle pain and visceral pain. Therefore, the relationship between small fiber neuropathy and FM has been criticized [8,12].

Based on our hypothesis, however, damage to the small fibers would result from axonal degeneration of their central afferents (i.e., the sensory nerves) due to increased pressure inside the nerve roots, including the sacral nerve roots that innervate the bladder and the bowel.

Axonal involvement

Additional evidence has been provided by nerve conduction studies (NCS) and electromyography (EMG), which reveal signs of demyelation and axonal injury in the legs.

NCS have shown a slowing in the sensory nerves in the legs and/or increased latency of the S1 Hoffmann-reflexes in 33% of FMP, compared with none of the rheumatic patients. Conduction slowing is a sign of demyelation. Additionally, EMG results have shown denervation in the legs, which was clinically and significantly correlated with proximal muscle weakness in 15% of FMP [3].

Sensory action potential amplitudes and velocities were within normal limits in patients with depression and FMP. However, the mean action potential amplitude was lower for FMP than for depressed patients without FM [8]. A lower action potential amplitude may be an indication of axonal damage. However, this study did not report whether the differences were statistically significant.

In addition, abnormalities in pain-related evoked potentials have been revealed upon stimulation of the face, hands and feet, indicating abnormalities in the small fibers or their central afferents, i.e., the sensory nerves [8].

Finally, sural nerve biopsies revealed segmental demyelation in 36% of patients without signs of inflammation, indicating an absence of inflammatory-mediated polyneuropathy [3].

Neurogenic bladder and bowel symptoms, sphincter dysfunction and genital pain

FMPs often have symptoms of neurogenic bowel, bladder, and sphincter dysfunction. Urine retention, increased urinary frequency, urge urinary incontinence, and constipation are common in FMP [13]. Detrusor overactivity is the most common urodynamic abnormality observed in FMP [14]. Most FMP have at least one functional gastrointestinal disorder, such as abdominal pain, constipation, bloating, diarrhea, anorectal pain, and fecal incontinence [15].

The sensory innervation of the perineum and the genitals, the motor innervation of the pelvic floor and the sphincters, and the autonomic innervation of the bladder and the transverse and descending colon are supplied by the sacral nerve roots S2, S3 and S4. Based on our hypothesis, the urological, bowel and sphincter symptoms would thus originate from the compression of nerve fibers in the sacral nerve roots.

The compression inside the sacral nerve roots might also explain why FM is often associated with genital pain disorders [16].

FMP respond to drugs that are used for peripheral neuropathic pain

In a review of randomized controlled trials using duloxetine, duloxetine reduced pain in both patients with FM and those with painful diabetic neuropathy by more than 50% compared to the placebo [17].

According to data from systematic reviews, low doses of amitriptyline are effective for the treatment of neuralgic pain and FM [18].

Pregabalin has also shown efficacy. In a recent review of double-blind, randomized, controlled trials, Pregabalin was more efficacious in relieving pain than placebo [19].

Similarities between intracranial and intraspinal pressure-induced conditions and FM

Idiopathic intracranial hypertension (IICH)

IICH is a condition characterized by a significant increase in the CSP due to an unknown cause. It mainly occurs in young, obese women and presents as papilledema and visual loss.

Radicular pain

Several authors have reported on radicular pain in patients with IICH. Radicular pain is a common but under-recognized symptom in patients with IICH [20,21].

In patients with IICH, spinal nerve root sheaths can be markedly