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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

dilated [22], and radiculopathy may be observed during a needle EMG or during nerve conduction studies [23,24]. In a study of 101 adults with IICH, neck pain was reported in 31, paresthesia in 22, and lower back pain in 5 patients. These symptoms resolved immediately following lumbar puncture [25]. At baseline in the 165 patients in the Idiopathic Hypertension Trial, neck pain was reported in 42%, back pain in 53% and radicular leg pain in 19% [26]. In all of these reports, the authors assumed that radicular pain resulted from the filling of the nerve root sheaths near the dorsal root ganglion with cerebrospinal fluid (CSF) under high pressure [20,23,25,26]. Additionally, radicular pain was reported in children with hydrocephalus due to aqueduct stenosis [27] and in family members with IICH [28].

Facial pain

Cranial nerve deficits, such as fourth and sixth nerve palsy, and facial weakness have been reported in patients with IICH. These symptoms resolved immediately upon normalization of intracranial pressure [23].

FMP more frequently complain of temporomandibular pain, with or without numbness or burning [29]. Based on our hypothesis, the filling of the cranial nerves under high pressure would explain these symptoms.

Cognitive dysfunction

Twenty percent of patients with IICH report cognitive dysfunction resulting from pressure dysregulation in the brain [26]. When assessing cognitive function, poorer performance in several cognitive domains was observed in patients with IICH [30].

FMP also often report cognitive dysfunction termed 'fibrofog'. FMP display attention and working memory problems, particularly when they must cope with an additional source of distraction [31].

Obesity

Most patients with IICH are obese. Obesity also increases the risk of developing FM and negatively affects FM severity and physical dysfunction [32].

Several studies have shown a prevalence of obesity in FMP of approximately 40%, which is higher than the prevalence in the normal population. In addition, obese patients have an increased risk of developing FM [33].

Weight loss positively influences FM symptoms and can significantly decrease pain scores, tender point counts and tender point pain ratings [34,35].

Based on our hypothesis, this positive effect of weight loss can be explained by the decrease in intra-abdominal pressure and the subsequent decrease in CSP.

Idiopathic normal pressure hydrocephalus (INPH)

Patients with INPH are characterized by walking difficulties, urinary and fecal incontinence, and cognitive symptoms; INPH primarily occurs in elderly patients. INPH is associated with enlargement of the ventricles and a subsequent decrease in the gray matter volume.

'Normal pressure' refers to the normal opening pressure when performing a lumbar puncture. However, in patients with INPH, abnormal fluctuations in the CSP due to cardiac contractions have been observed [36]. In addition, a study that monitored the CSP using a telemetric device revealed that the adaptation of the CSP upon position changes is not well regulated in patients with INPH compared with that in normal subjects [37].

The condition appears to be extremely under diagnosed [38]. A spinal fluid tap test remains the standard of care for diagnosis [39].

Pain

Patients with INPH are typically older and therefore often suffer from musculoskeletal pain due to age-related degenerative disorders [40]. Their pain may be difficult to differentiate from peripheral neurological pain.

Gray matter volume

FMP also exhibit a 3.3-fold greater age-associated decrease in the gray matter volume than healthy controls. The longer the individuals had FM, the greater the gray matter loss [41].

Additionally, FMP revealed retinal fiber layer atrophy, indicating axonal damage in the optical nerve [42]. Based on the results of tests using mechanical stress models, the accumulation of endogenous mechanical stress in the brain, such as that noted in patients with INPH, was concluded to cause neuronal injury [43].

Urinary incontinence

Patients with INPH suffer from urinary incontinence. Urodynamic testing in patients with INPH revealed overactive detrusor as the most frequent diagnosis [44].

Similarly, urodynamic testing in FMP revealed detrusor overactivity as the most frequent diagnosis [14]. Based on our hypothesis, irritation of the fibers inside the sacral nerve roots innervating the detrusor muscle is the cause of an overactive bladder.

Gait

Patients with INPH suffer from gait disturbances, such as ataxia, which present as an abnormal tandem gait [39]. Similarly, 26% of FMP also exhibited an abnormal tandem gait and 6% exhibited ataxia [4]. Moreover, FMP walk significantly slower and display poorer balance than healthy controls [45].

Symptomatic Tarlov cysts (STC)

Tarlov cysts (TC) originate from the dilation of the nerve roots between the endoneurium and the perineurium and are predominantly present as multiple cysts. Under increased CSP, the nerve root sleeves near the dorsal root ganglion may begin to enlarge. Some of the sleeves are significantly enlarged, eroding the bony neural foramen to form large cysts of the nerve root sheath. These large cysts likely provide a temporary buffer capacity for the intraspinal pressure because they usually become symptomatic only in the fourth or fifth decade. Conversely, in other patients, the nerve root sleeves may be unable to significantly dilate. Therefore, the pressure inside the sleeves increases earlier in life and these patients may become symptomatic at an earlier age.

Because the sensory fibers in the dorsal root ganglion are the first to be affected, sensory symptoms and pain are the most prominent characteristics of patients with STC. The sacral nerves are more often affected than the higher nerve roots because the hydrostatic pressure adds to the increased intraspinal pressure [46].

Neurogenic bladder and bowel symptoms and genitourinary pain

Compression of the lumbosacral plexus produces a chronic cauda equine syndrome, i.e., perineal and genitourinary pain and numbness, neurogenic bowel, bladder, and sphincter disturbances. Using NCS/EMG, axonal damage in patients with STC has been shown to be the source of the debilitating symptoms [47].

Again, similar to patients with FM and INPH, overactivity of the detrusor muscle is the most prominent characteristic of patients with STC upon urodynamic testing [48].

Based on our hypothesis, excessive pressure inside the sacral nerve roots might explain why most FMP and patients with STC display neurogenic bladder, bowel, and sphincter symptoms and genital pain.

Onset

For both FM and STC, onset is often preceded by physical trauma, including motor vehicle accidents, falls, childbirth, or physical exertion

[47,49]. Based on our hypothesis, onset would occur due to a sudden significant increase in the CSP.

Chronic pain

STC are largely under-recognized, particularly when they are small. Therefore, patients with STC may have been diagnosed with FM or may have unexplained back, perineal, pelvic, and/or leg pain.

Role of the blood-nerve barrier (BNB)

The blood-nerve barrier (BNB) in peripheral nerves forms an interface similar to that of the blood-brain barrier in the central nervous system. The BNB regulates the permeability of the perineurium and the capillaries in the endoneurium to maintain homeostasis within the axonal and neuronal environment [50].

The use of MRI to measure dorsal root ganglion perfusion revealed increased permeability of the dorsal root ganglion BNB compared with that of spinal nerves. The purpose of this more permeable structure of the BNB is to provide nutrients and oxygen to meet the high metabolic demands of the sensory cell bodies within the dorsal root ganglion. However, this particularly leaky structure makes sensory neurons more vulnerable to harmful stimuli, such as mechanical pressure or toxic agents. These noxious stimuli might cause changes in neuronal activity or excitability and can thus generate chronic neuropathic pain. The MRI study also revealed that women exhibited significantly increased vascular permeability within the dorsal root ganglion compared with men. This finding might explain why women are more susceptible to chronic neuropathic pain [51].

Additionally, the permeable BNB in the dorsal root ganglion might explain why increased CSF pressure inside the nerve roots may cause CSF leakage between the endoneurium and the perineurium predominantly in the dorsal root ganglion, such as that noted in the generation of Tarlov cysts.

Idiopathic CSP dysregulation as a cause of FM and unexplained widespread pain: testing the hypothesis

CSP measurements involve methodological problems. CSP assessed during a lumbar puncture may be normal, such as in patients with INPH. Values between 200 and 250 mm water are considered borderline and values over 250 mm water are definitely elevated, such as in patients with IICH [52]. Surgical insertion of a telemetric device for long-term CSP monitoring would be more accurate; however, it is a more invasive procedure [37]. Therefore, similar to INPH, interventional placebo-controlled spinal fluid tap testing is the gold standard [39]. Additionally, prospective blinded controlled studies comparing patients with STC, FMP, and healthy controls should be performed. The data to be assessed include: a comprehensive history, symptom severity scores [53], sensory testing using a pin-prick test, strength testing, knee and Achilles tendon reflexes, a tandem gait test, a revision of the MRI to detect possible nerve root dilations and TCs, NCS/EMG, and measurement of the retinal nerve layer thickness using an optical microscope.

Conclusions

To date, the pathophysiology of FM has not been clearly determined. We aimed to examine the condition from another perspective. We propose that chronic idiopathic CSP dysregulation underlies both FM and the clinical entity of STC, which both present as peripheral neurological disorders. IICH and INPH are likely other manifestations of the same condition. As the BNB is more permeable at the dorsal root ganglion, excess internal pressure may cause leakage of CSF into the endoneurial compartment, leading to perturbation of the endoneurial homeostasis. Thus, axons and sensory cell bodies may be harmed, inducing chronic pain and paresthesia.

Because psychological problems are believed to underlie chronic pain conditions and patients exhibit exercise intolerance, the patients are often stigmatized and held responsible for their pain. Based on this hypothesis, the psychological symptoms of FMP, such as depression and catastrophizing, would be a consequence of the underestimated refractory debilitating neuropathic pain instead of the cause. In addition, the patients' fear of moving may be realistic because an upright position and particularly exertion may increase CSP and thus produce more neurogenic pain, leading to exercise intolerance. Conversely, lying down decreases CSP and may relieve the pain, which explains the typically more sedentary lifestyle of FMP.

If the hypothesis is confirmed, FM and several other unexplained widespread pain syndromes would be considered chronic neurological disorders. Psychologically, this definition would represent a significant difference in the way the patients and their relatives, peers and physicians view the disease.

Confirmation of our hypothesis will also open perspectives for treatment. Future research should focus on lowering the CSP. Treatments that are commonly used for patients with IICH, such as acetazolamide, might be an option for the treatment of exacerbations of FM symptoms and lumboperitoneal or ventriculoperitoneal shunting might be an option for severely debilitating or progressive cases.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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