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Spinal fluid evacuation may provide temporary relief for patients with unexplained widespread pain and fibromyalgia

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A B S T R A C T

Fibromyalgia (FM) exhibits characteristics of a neurological disorder, and similarities have been identified between FM and idiopathic intracranial hypertension (IICH). When intracranial pressure rises, the drainage of excess cerebrospinal fluid (CSF) through the subarachnoid space of the cranial and spinal nerves increases. Higher CSF pressure irritates nerve fibers inside nerve root sheaths and may consequently cause radicular pain, as was reported in patients with IICH. Moreover, the cut-off of 20–25 cm H_20 used to define IICH may be too high, as has been suggested in patients with chronic fatigue syndrome. We hypothesize that the neurological symptoms of FM are caused by the dysregulation of cerebrospinal pressure (CSP) and that spinal fluid drainage can relieve this pain.

Exploring the processes underlying increased CSP may provide an alternative explanation for the generation of unexplained widespread pain (WSP) and FM as opposed to central sensitization.

Additionally, when performing a lumbar puncture for diagnostic reasons, it is useful to measure opening pressure in patients with chronic WSP.

Introduction

Chronic pain is highly prevalent in the general population and is associated with a high rate of disability and poor quality of life. Although unexplained chronic widespread pain (WSP) and fibromyalgia (FM) are considered centralized pain disorders, the exact pathophysiology of these conditions remains unknown. Because of the neurological signs and symptoms and several similarities with other pressure dysregulation disorders, these conditions have been hypothesized to be caused by impaired cerebrospinal pressure (CSP) regulation [1–3].

Similarities exist among FM, WSP and CSP dysregulation syndromes, such as idiopathic intracranial hypertension (IICH), idiopathic normal pressure hydrocephalus (INPH) and symptomatic Tarlov cysts (TCs) [4].

Cerebrospinal fluid (CSF) is produced in the ventricular choroid plexus. It circulates inside the ventricles and enters the intracranial subarachnoid space via the cisterna magna before entering the cranial and spinal subarachnoid spaces. CSF is absorbed through cranial arachnoid granulations directly into the veins or through the lymphatic system of the cranial and the spinal nerves [5].

When intracranial pressure increases, drainage of excess CSF through the cranial and the spinal nerves increases [6]. Increased CSP inside the nerves irritates the nerve fibers and consequently causes widespread radicular pain [7,8]. Higgins et al. [9] previously suggested that using 20 or 25 cm H_20 is probably too high a cut-off to define abnormal intracranial pressure.

We hypothesize that the neurological symptoms of FM and chronic unexplained WSP may be caused by CSP dysregulation [4]. Consequently, withdrawal of spinal fluid might relieve pain in patients suffering from FM and unexplained WSP.

Cerebrospinal pressure (CSP) measurements obtained during a diagnostic lumbar puncture and results of CSF drainage in 30 FM patients were retrospectively reviewed, and pilot data supporting the above hypothesis are presented.

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CSP regulation

IICH, INPH and symptomatic TCs are CSP dysregulation disorders, all of which are largely underdiagnosed [10–13].

When the human body moves from a supine to an upright position, the cerebrospinal fluid pressure in the lower part of the body rises, and pressure in the upper part drops. From an evolutionary point of view, CSP regulation mechanisms were initially designed for quadrupeds. Thus, due to the upright position of bipeds and especially combined with the predominance of sitting activities of our society, the CSP regulation mechanisms are more under stress [14].

Therefore, in some individuals, CSP regulation mechanisms may fail to properly regulate pressure in the upright position.

CSP versus blood pressure

No clear reference values exist for CSP, and controversies exist regarding the OP cut-off value to diagnose IICH (> 20 cm H_2O in non-obese and 25 cm H_2O in obese patients). This threshold is likely too high [9,15]. The effect of chronic or intermittent moderately increased CSP on the brain and the peripheral nerves is unknown. The effects of CSP on the brain and the peripheral nerves can be compared to the effects of blood pressure on the heart and blood vessels. The American Heart Association has long considered a systolic blood pressure < 140 mmHg and a diastolic blood pressure < 90 mmHg as normal values. However, in 2003, updated recommendations were issued. Based on epidemiological studies, it was estimated that the risk of cardiovascular disease begins at a blood pressure of 115/75 mmHg and doubles with each increment of 20/11 mmHg [16].

Unfortunately, unlike arterial pressure, assessing CSP poses methodological problems. First, CSP measurement requires an invasive technique as opposed to the non-invasive technique used to measure blood pressure. Second, measuring CSP or blood pressure represents only one moment in time. When assessing blood pressure, several measurements or monitoring are required for an appropriate diagnosis of arterial hypertension. Similarly, assessing static cerebrospinal OP during a lumbar puncture may reveal a normal value, as has been observed in patients with INPH [11]. However, when using invasive CSP monitoring in patients with INPH, abnormal fluctuations of the CSP [17] and/or inadequate adaptation of the CSP upon position changes have been recorded [18].

Consequently, epidemiological studies on the link between moderately or intermittently increased CSP levels and disease are difficult to perform. To date, the most prominent signs of CSP dysregulation are papilledema in IICH patients presenting with vision loss; enlarged ventricles in patients with INPH presenting with dementia, gait problems, and incontinence; or large TCs in patients presenting with radicular pain. These obvious symptoms and signs may be the end stages of pressure dysregulation that have progressed over previous years or decades.

Opening pressure

An OP > 20 cm H_2O has been found in 19% of patients with chronic unresponsive migraine. Moreover, a higher prevalence of WSP has been reported in both IICH and chronic unresponsive migraine patients [8,15]. IICH without papilledema mimicking chronic migraine is probably much more prevalent than believed, is often misdiagnosed as chronic migraine and is refractory to preventive treatments [19]. In patients with IICH and headache without papilledema, lower mean OPs have been reported than in those with IICH with papilledema [20].

A mean OP of 19.0 cm H_2O was measured in patients with CFS suffering from severe headaches, indicating that increased cranial pressure may be responsible for fatigue, headaches and cognitive dysfunction in CFS patients [9].

The authors suggest that a cut-off of 20–25 cm H_20 may be too high to define Idiopathic Intracranial Hypertension (IICH).

Remarkably, the mean OP of 19.7 cm H_2O measured in our chronic pain patients (mean age 42.0 ± 11.2 years – range 21–61 years) is very similar. Furthermore, 6 of our chronic pain patients were also diagnosed with chronic fatigue syndrome (CFS).

The characteristics of the patients and the results of spinal fluid drainage are presented in Table 1

Table 1
Patient characteristics and lumbar puncture data.

	Sex	Age	BMI kg/m^3	FM	EDS	TCs	CFS	EMG L3-S4 myotomes	OP	Symptom improvement after lumbar puncture
1	m	57		x				0	23	Yes
2	f	37	> 25			x		DA + AA reflex	15	Yes
3	f	38	> 25	x	x	x		DA + AA reflex	16	Yes
4	f	34		x				0		Yes
5	f	44				x		DA + AA reflex	11	Yes
6	m	41	> 30	x			x	0	17	Yes
7	f	57				x		DA	18	No
8	m	30				x		0	32	No
9	f	51		x			x	0	18	Yes
10	f	45				x		DA + AA reflex	21	Yes
11	f	45		x	x	x	x	DA + AA reflex	15	Yes
12	f	23		x	x			DA + AA reflex	15,5	Yes
13	f	42		x		x	x	0	23	Yes
14	f	56						0	18	Yes
15	f	32	> 30	x				0	28	Yes
16	m	31		x				0	22	No
17	m	29		x				0	20	Yes
18	f	38		x		x		0	15	Yes
19	f	51				x		0	24	Yes
20	m	40				x		DA + AA reflex	13	No
21	f	29	> 30	x				DA	23	Yes
22	m	52		x				0	19,5	No
23	f	48		x		x	x	0	24	Yes
24	f	63		x		x	x	normal	14	No
25	m	29		x				0	21	No
26	m	55						0	23	No
27	m	21						normal	23	Yes
28	m	45	> 25	x		x		0	24	Yes
29	m	36						DA	23	No
30	f	61				x		0	12	Yes

FM = Fibromyalgia, EDS = Ehlers-Danlos Syndrome, TC = Tarlov cysts, CFS = Chronic Fatigue Syndrome, EMG = Electromyography, OP = Opening Pressure.
DA = denervation activity, AA reflex = delayed ano-anal reflex.

Spinal fluid taps

Diagnostic spinal fluid tap tests have been used in patients with INPH. Cognitive impairment, gait problems and urine incontinence improved despite an OP < 20 cm H_2O in most patients [11].

Diagnostic spinal fluid taps have also recently been used in patients with CFS and chronic migraine. In CFS, withdrawal of spinal fluid temporarily improved fatigue symptoms in all 5 patients with an OP > 20 cm H_2O and in 12 of 15 patients with an OP between 12 and 20 cm H_2O (in total 85%) [21]. Similarly, in patients with chronic unresponsive migraine, withdrawal of CSF relieved headaches in 3 of 6 (50%) patients with a CSP > 20 cm H_2O [9,22].

In our cases, 50% of the chronic pain patients had a CSP < 20 cm H_2O. Nevertheless, 70% of the patients felt relief of their symptoms following spinal fluid withdrawal during a few hours to 8 weeks,

regardless of whether their CSP was > 20 cm H_2O.

Improvements mentioned by the patients included the following; relief of lower back pain, leg pain and/or coccygodynia; disappearance of headache; improved concentration, mood, and sleep; reduced mental fogginess; ability to sit longer without pain; enhanced walking ability; decreased urinary frequency; greater ease in emptying the bowels and/or bladder; and reduced jaw pain.

Radiculopathy

In patients with IICH, radicular symptoms are common but under recognized. Evacuation of CSF in these IICH patients also relieves radicular pain symptoms [8,23–28].

Favorable spinal fluid withdrawal results in 70% of our patients may also indicate that the pain in FM and chronic WSP is likely radicular pain, similar to the radicular pain in IICH. Nonetheless, a placebo effect might be involved.

Moreover, FM exhibits characteristics of a neurological disorder, such as sensory symptoms and signs similar to peripheral neuropathy [1–3] as well as small fiber neuropathy [1,29,30] and hyperexcitable C-nociceptors [31].

Additionally, electromyographic abnormalities have been detected in patients with IICH [32], FM [33], and STCs [7,23,34]. Sacral nerve roots are more at risk for irritation of the inner nerve fibers because in the sacrum, the hydrostatic pressure in the spinal canal adds to the increased CSP. We reviewed the electrophysiological test prepuncture data that were available for 12 of our patients. Moderate to severe denervation activity was observed in the lowest sacral myotomes of all 12 patients: in the S2 (intrinsic foot muscles) or the S3-S4 (external anal sphincter) myotomes. The ano-anal reflex is supplied by nerve roots S3 and S4. A delayed ano-anal reflex indicates dysfunction of the efferent (motor) and/or afferent (sensory) nerve fibers of the reflex arc.

Ehlers Danlos syndrome

An association between Ehlers-Danlos syndrome and IICH has been suggested [35]. At least 89% of patients with Ehlers Danlos syndrome complain of moderate to severe pain, and radiculopathy is diagnosed in 68% of patients [36]. Although the etiology of the radicular pain is yet not clear, based on our hypothesis, it might be associated with increased cerebrospinal pressure.

Symptomatic TCs

A TC is a dilated nerve root sheath near the dorsal root ganglion caused by increased hydrostatic pressure in the spinal canal. The generation of TCs can be compared to the generation of aneurysms of the arterial blood vessels in patients with arterial hypertension [37]. Hydrostatic pressure is added to the increased CSP in the sacrum due to the upright position. In some patients, the nerve roots leaving the dural sac gradually enlarge over years, ultimately forming small or large TCs. TCs may thus be considered a sign of CSP dysregulation [34]. In our patients, MRI findings of the lumbosacral spine revealed TCs on the sacral nerve roots in 15 (50%) patients.

The glymphatic pathway

Recent evidence has revealed the existence of a brain-wide pathway for waste clearance. This system consists of a network of paravascular channels and has been called the “glymphatic” pathway [38].

Within the glymphatic system, a large proportion of subarachnoid CSF recirculates through the brain parenchyma to facilitate the clearance of interstitial solutes, including amyloid-β. In a recent correspondence, Wostyn et al speculated that fibromyalgia may be at least in part caused by a ‘glymphatic overload syndrome’ that ultimately creates stagnation in the flow through the perivascular spaces and interstitium of the brain and peripheral nerves, with the consequential accumulation of substances toxic to sensory neurons. Thus, a glymphatic malfunction may be an alternate explanation for the symptomatic improvements observed after CSF drainage [39].

Future research

Additional studies using CSP monitoring in chronic pain patients and double blind randomized placebo-controlled studies using spinal fluid tap tests and standardized symptom questionnaires are required.

Conclusion

Exploring issues related to moderately to severely elevated CSP may provide possible methods for the diagnosis and treatment of several debilitating conditions, such as unexplained chronic WSP and FM.

It is advised to measure OP when performing a lumbar puncture for diagnostic reasons in patients with chronic pain.

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Conflict of interest statement

We have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.mehy.2018.06.017.

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