the various remote structures that are functionally associated with M1 and involved in chronic pain and pain relief [24,30]. Two positron emission tomography (PET) studies demonstrated that motor cortex stimulation increased the regional cerebral blood flow in the various structures related to pain perception and the emotional aspects of pain, such as the thalamus, insula, limbic system, and upper brain stem [11,19]. Lefaucheur et al. reported that rTMS of M1 restored defective intracortical inhibition in patients with chronic neuropathic pain and proved the alterations within the stimulus site [27]. However, the patient characteristics in these previous reports were heterogeneous. These subjects were patients with CPSP, but some also had neuropathic pain due to spinal or peripheral nerve lesions.

In this study, we concentrated the rTMS effects within M1 in patients with CPSP. A single- or paired-pulse transcranial magnetic stimulation (TMS) allowed us to evaluate the cortical excitability of M1, measuring motor evoked potentials (MEP) [23,47]. The objective of this study was to assess the alterations of cortical excitability in patients with intractable CPSP before and after rTMS of M1.

2. Methods

2.1. Subjects

Subjects were 21 consecutive patients with CPSP (12 men and 9 women), with a mean ± standard deviation age of 59.6 ± 9.0 years and with an average pain duration of 48.1 ± 55.0 months before the experiment. All patients were diagnosed with CPSP according to the following criteria [20]: (1) development of pain after stroke, (2) sensory disturbance corresponding to the cerebral lesion, (3) pain located within the region of sensory disturbance, and (4) exclusion of other causes of pain. All patients had an intractable continuous pain in their hand lasting more than 6 months despite appropriate medical treatments. We excluded patients with severe motor weakness corresponding to less than grade 2 in the manual muscle test because of the insufficient MEP evoked by TMS in the affected hand. The lesions from stroke were located in the thalamus ($n = 8$), putamen ($n = 7$), brain stem ($n = 4$), and subcortex ($n = 2$). All the patients had a sensory deficit in their painful zone and described their pain as burning, aching, squeezing, pricking, or numb; pain occurred in the unilateral body including the hand. Allodynia was observed in 13 patients (62%) and hyperpathia in 4 patients (19%). Patient characteristics and clinical data are summarized in Table 1.

Eight healthy volunteers were also enrolled onto this study (8 men; mean age, 52.5 ± 10.0 years). All subjects were right-handed. They had no neurological diseases, and no lesions were evident on magnetic resonance imaging.

2.2. Overview of experiments

A session of 5 Hz rTMS of M1 corresponding to the painful hand was applied to all the patients [14,41]. Cortical excitability within M1 was evaluated by the single- or paired-pulse TMS before and after an rTMS session. Cortical excitability was measured in the same side as rTMS performance. Pain intensity was examined in each patient before and after rTMS using a visual analog scale (VAS). The healthy controls underwent the same single- or paired-pulse TMS measurements in M1 of both hemispheres. We assessed alterations in cortical excitability and the relationship between pain relief and cortical excitability changes.

The ethics committee of Osaka University Hospital approved this study (approval 07099), and written informed consent was obtained from all subjects participating in this study.

2.3. Motor cortical excitability testing

Motor cortical excitability testing was applied by the single- or paired-pulse TMS using a reversed-current, figure-8 double 70-mm coil (Magstim Company, Carmarthenshire, UK) and the Magstim 200 magnetic stimulator (Magstim Company). A Magstim 200 magnetic stimulator provides single monophasic pulses. Two Magstim 200 magnetic stimulators were connected to a Bistim module (Magstim Company) delivering paired pulses. Subjects lay down on the bed to keep their hands relaxed, and their heads were fixed to avoid displacement of the stimulus site during cortical excitability testing and rTMS. The center of the TMS coil was placed on M1 corresponding to the hand using the optical TMS navigation system (Brainsight, Rogue Research Inc, Montreal, Quebec, Canada) and fixed by means of an articulated coil holder. The handle of the reversed-current coil was directed anteromedially so that the intracerebral current was induced to the same direction as the standard double coil handle placed in the posterolateral direction. Finally, the optimal stimulus site was determined on the basis of the highest amplitude MEP in the abductor pollicis brevis (APB) muscles. The MEPs were recorded from surface electrodes placed on the belly and tendon of the contralateral APB muscles through a 20 to 3000 Hz band-pass filter using Neuropack electromyography (MEB-2208, Nihon Kohden, Tokyo, Japan).

Five indices, including (1) resting motor threshold (RMT), (2) MEP amplitude at 120% of RMT (MEP120), (3) cortical silent period (CSP), (4) short interval intracortical inhibition (SICI), and (5) intracortical facilitation (ICF), were measured as parameters of motor cortical excitability. The RMT was defined as the minimum stimulus intensity evoking MEPs of $\geqslant 50\ \mu V$ at least 5 of 10 times under complete muscle relaxation [39]. RMT was measured by reducing the stimulus intensity in steps of 1% from the suprathreshold intensity. Complete muscle relaxation was monitored by the electromyograms (EMG) from the APB muscles. Subsequently, 15 MEPs were recorded at 120% of RMT, and the average peak-to-peak amplitude of MEPs was determined as MEP120. CSP was measured by single TMS pulses at 130% of RMT, while subjects executed a continuous maximum voluntary contraction of their APB muscles. To ensure adequate contractions of the target muscle, EMG feedback was provided for the subjects. Eight trials were rectified and superimposed. CSP was defined as the minimum duration from stimulus delivery to the return of voluntary activity [21]. Paired-pulse stimulation was performed in accordance with Kujirai et al. [23]. A conditioning stimulus was set at 80% of RMT, and a test stimulus was set at 120% of RMT. Interstimulus intervals were set at 2 and 4 ms for SICI, and 10 and 15 ms for ICF. Ten trials of each interstimulus interval were randomly intermixed with nonconditioned trials (test stimulus only). Finally, a total of 50 trials were delivered, and the average peak-to-peak MEP amplitude ($MEP_{conditioned}$) was calculated for each condition. SICI and ICF were defined follows: $SICI = 100\% - (MEP_{conditioned}/MEP_{nonconditioned})$ and $ICF = MEP_{conditioned}/MEP_{nonconditioned}$. Each stimulation was separated by at least 5 s in order to avoid carryover effects.

2.4. rTMS procedure

The rTMS was applied through a figure-8 coil (MC B-70, Medtronic Functional Diagnostics A/S, Skovlunde, Denmark) and connected to a MagPro magnetic stimulator (Medtronic Functional Diagnostics A/S), which provides repetitive biphasic pulses. The TMS coil was placed with the optical TMS navigation system (Brainsight) and fixed by the coil holder in the same way used for motor cortical excitability testing. The RMT was determined by stimulation of the region of M1 corresponding to the hand representation. A potential equivalent to 90% intensity of RMT was used for repetitive stimulation. Ten trains of 5 Hz rTMS were delivered

Table 1
Patients' clinical characteristics.

Patient	Age, y	Sex	Stroke	Pain duration, month	Current medication	Motor weakness	Sensory deficit	Allodynia	Hyperpathia	Baseline VAS score	VAS reduction after rTMS,%
1	61	M	Lt brain stem infarction	29	TCA, SSRI, BZD	Mild	Severe	+	–	95	21.1
2	65	F	Rt subcortical infarction	37	TCA, BZD, NSAID	Moderate	Mild	+	+	83	33.3
3	56	M	Rt subcortical hemorrhage	7	CZP	Mild	Mild	+	–	97	0
4	64	F	Rt putaminal hemorrhage	37	TCA, GBP	Moderate	Mild	+	+	100	0
5	48	M	Rt thalamic hemorrhage	7	GBP, PB, BZD, NSAID	Mild	Mild	–	–	59	41.5
6	48	M	Rt putaminal hemorrhage	6	TCA, GBP, MEX	–	Severe	+	–	80	100
7	64	M	Lt putaminal hemorrhage	16	CZP, ZNS, BZD, NSAID	Mild	Mild	+	+	86	21.4
8	57	F	Lt putaminal hemorrhage	30	CZP	Mild	Severe	+	+	100	65
9	59	F	Rt putaminal hemorrhage	180	CZP	–	Mild	+	–	77	22.2
10	76	M	Lt thalamic hemorrhage	216	TCA, GBP, MEX	Moderate	Severe	–	–	56	57.1
11	64	M	Lt thalamic hemorrhage	37	TCA, GBP	Moderate	Severe	–	–	81	62.5
12	63	M	Rt thalamic hemorrhage	88	SSRI, GBP, BZD	Moderate	Mild	–	–	89	50
13	52	F	Rt thalamic hemorrhage	8	TCA, GBP	–	Mild	+	+	98	0
14	51	F	Rt putaminal hemorrhage	46	PHT	Mild	Severe	+	–	52	16.7
15	35	M	Rt thalamic hemorrhage	14	GBP	–	Mild	+	+	45	14.3
16	66	F	Lt thalamic hemorrhage	18	GBP	Mild	Mild	+	–	76	7.1
17	58	F	Rt brain stem hemorrhage	86	SSRI, CZP, CBZ, BZD	Mild	Mild	–	–	99	75
18	73	M	Rt thalamic infarction	40	NSAID	Mild	Severe	–	–	89	0
19	65	M	Lt brain stem hemorrhage	39	TCA, GBP	–	Mild	–	–	53	0
20	65	F	Rt brain stem infarction	20	SSRI	Mild	Severe	+	+	75	11.8
21	62	M	Lt putaminal hemorrhage	20	TCA, GBP	Mild	Mild	–	–	50	19

Rt, right; Lt, left; TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor; BZD, benzodiazepine; NSAID, nonsteroidal anti-inflammatory drug; CZP, clonazepam; GBP, gabapentin; PB, phenobarbital; MEX, mexiletine; ZNS, zonisamide; PHT, phenytoin; CBZ, carbamazepine; VAS, visual analog scale; rTMS, repetitive transcranial magnetic stimulation.

to M1, corresponding to the painful hand, for 10 s with 50 s of intertrain interval. Thus, a total of 500 pulses were applied in an rTMS session. The details of this rTMS protocol have been reported previously [14,41]. This protocol was carried out in accordance with the guidelines for safe use of rTMS [38].

2.5. Statistical analysis

Patients were assigned to 1 of 2 groups: responders (⩾30% pain reduction after rTMS) and nonresponders (<30% pain reduction) [8]. Differences of cortical excitability indices between each group at baseline were evaluated by Mann-Whitney *U* test. Alterations of these indices after rTMS were evaluated by Wilcoxon's signed-rank test. Nonparametric tests were adopted because the analyzed groups were not estimated to have a normal distribution. In all comparisons, findings with $P < .05$ were considered statistically significant.

3. Results

All patients completed the study without adverse effects. Eight of 21 patients experienced ⩾30% pain reduction in their VAS after rTMS, and these patients were categorized as responders. Between responders and nonresponders, there were no significant differences in any patient characteristics (age, sex, duration of pain, stroke type, pain laterality, severity of motor and sensory disturbances, and VAS at baseline) and the stimulus intensities of rTMS.

The RMT of all patients was higher than those of controls (65.5 ± 3.0% vs 56.7 ± 2.3%, $P = .035$). There were no significant differences in the other parameters between the patients and controls (Table 2). The ICF of the responders significantly increased after the rTMS session (110.3 ± 12.5% vs 170.0 ± 28.3%, $P = .039$). There were no significant changes in the other parameters (Table 3). The ICF of the responders was significantly lower than those of the controls and the nonresponders at baseline (110.3 ± 12.5% vs 168.0 ± 18.8%, $P = .035$, and vs 188.3 ± 21.7%, $P = .019$) (Fig. 1).

4. Discussion

To our knowledge, this study is the first to document alteration of cortical excitability within M1 in CPSP patients. We studied the cortical excitability changes in CPSP patients and healthy controls by means of single- or paired-pulse TMS methods. Our findings revealed that RMT in patients with CPSP was elevated and the im-

Table 2
Cortical excitability measurements at baseline.

Characteristic	Patients, mean (SEM)	Controls, mean (SEM)	P
RMT, %	65.5 (3.0)	56.7 (2.3)	.035*
MEP amplitude, µV	655 (80)	707 (105)	.818
CSP, ms	167.9 (10.4)	148.4 (8.7)	.238
SICI, %	32.0 (8.7)	47.3 (7.0)	.350
ICF, %	158.6 (16.5)	168.0 (18.8)	.530

SEM, standard error of mean; RMT, resting motor threshold; MEP, motor evoked potential; CSP, cortical silent period; SICI, short interval intracortical inhibition; ICF, intracortical facilitation.
* $P < .05$ for differences in mean values between patients and controls by Mann-Whitney *U* test.

Table 3
Changes in cortical excitability measurements after rTMS.

Characteristic	Good response		Poor response	
	Mean (SEM)	P	Mean (SEM)	P
RMT, %		.171		.833
Baseline	62.9 (5.8)		67.1 (3.1)	
Post-rTMS	64.6 (6.1)		66.8 (2.6)	
MEP amplitude, µV		.945		.455
Baseline	589 (97)		695 (114)	
Post-rTMS	602 (138)		810 (132)	
CSP, ms		.461		.067
Baseline	186.8 (19.8)		156.2 (10.2)	
Post-rTMS	171.3 (20.6)		162.2 (11.1)	
SICI, %		.313		.735
Baseline	40.8 (10.7)		26.7 (12.3)	
Post-rTMS	30.6 (12.1)		16.7 (19.1)	
ICF, %		.039*		1.000
Baseline	110.3 (12.5)		188.3 (21.7)	
Post-rTMS	170.0 (28.3)		183.6 (28.0)	

rTMS, repetitive transcranial magnetic stimulation; SEM, standard error of mean; RMT, resting motor threshold; MEP, motor evoked potential; CSP, cortical silent period; SICI, short interval intracortical inhibition; ICF, intracortical facilitation.
* $P < .05$ for differences in mean values between patients and controls by Mann-Whitney *U* test.

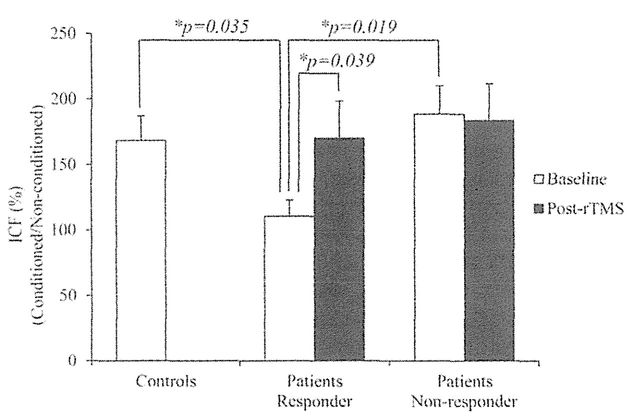

Fig. 1. ICF in responders was lower than ICF in controls and nonresponders at baseline (110.3 ± 12.5% vs 168.0 ± 18.8%, $P = .035$, and vs 188.3 ± 21.7%, $P = .019$). ICF of responders significantly increased after the rTMS session (110.3 ± 12.5% vs 170.0 ± 28.3%, $P = .039$). ICF, intracortical facilitation; rTMS, repetitive transcranial magnetic stimulation.

paired ICF in the responders was restored after high-frequency rTMS of M1. Restoration of a normal ICF value was accompanied by successful pain relief.

In patients after stroke, it is well known that damage of motor tracts resulted in elevation of the motor threshold in the affected hemisphere [5]. Fifteen of 21 patients studied in this study had mild or moderate motor weakness. The elevated RMT in this study seemed to reflect the condition with motor weakness after stroke.

SICI and ICF are considered to reflect the functions of interneurons within M1. SICI is likely to reflect GABAergic inhibitory interneurons, especially $GABA_A$ function [23,37], while ICF is thought to mainly reflect glutamatergic excitatory interneurons within M1 [37,47]. Several studies have investigated ICF and SICI alterations in patients with various chronic pain conditions: various neuropathic pain [27,45], complex regional pain syndrome type I [9], or fibromyalgia [44]. These studies have demonstrated that a chronic pain state is reflected by a decrease in SICI and a tendency for ICF to decrease as a whole. Our results are consistent with previous reports in that ICF and SICI tended to decrease.

High-frequency (eg, 5 Hz) rTMS is referred to as excitatory rTMS and is thought to increase cortical excitability. Several studies applying high-frequency rTMS to M1 have reported an immediate increase of excitability in healthy volunteers (increased MEP amplitude, decreased SICI, and increased ICF), although the other studies have reported no change [10]. We first demonstrated an increase in ICF in the responders of CPSP patients after 5 Hz rTMS of M1. In this study, SICI did not significantly change after rTMS; however, there was a tendency for SICI to decrease. These findings were consistent with the previous reports, revealing high-frequency rTMS, increased ICF, and decreased SICI. Lefaucheur et al. reported that defective SICI was restored in parallel with pain relief after 10 Hz rTMS of M1 in 22 patients with various types of neuropathic pain (10 strokes, 4 peripheral nerve lesions, 4 brachial plexus lesions, and 4 spinal cord lesions) [27]. These results can fit to the deafferentation theory with cortical and subcortical hyperactivities, and the potential therapeutic action of motor cortex stimulation on pain processing areas [13,22,35], although SICI increase due to the high-frequency rTMS was the opposite to results in healthy subjects. Our results seem to be contrary to the results from the study reported by Lefaucheur et al. However, according to the theory of cortical hyperactivity, motor cortex hyperactivity may result in a compensatory decrease in ICF. Furthermore, rTMS might reduce pain-related hyperactivity, resulting in restoration of the compensatory decrease in ICF along with pain relief. A study demonstrated that rTMS effects on cortical excitability depended more on baseline individual values than on stimulation frequency [6]. The difference between our results and those reported by Lefaucheur et al. may be rooted in the different sources of neuropathic pain and the difference of the baseline individual values in cortical excitability.

rTMS stimulates the neuronal tissue electrically in a manner similar to EMCS, evoking eddy current within the cortex [25], and similar descending volleys were evoked by TMS and EMCS [7]. The frequency and duration of pulses are different between rTMS and EMCS; nevertheless, the analgesic effects produced by rTMS and EMCS have many common points. For instance, pain relief often delayed and prolonged after the stimulation period of rTMS in a similar time course as EMCS [26,33,42], and the efficacy of rTMS on pain relief has been reported to correlate with EMCS efficacy [15,29]. Therefore, the mechanism behind pain relief through high-frequency rTMS may be similar to that of EMCS. According to PET activation studies, EMCS seems to activate several brain areas related to pain perception, affective–emotional components, and the descending pain inhibitory system, such as the posterior thalamus, insula, anterior cingulate cortex, orbitofrontal cortex, and upper brain stem [11,19]. rTMS also activated remote and widespread areas in a PET study [40]. A recent study suggested that inhibition of thalamic sensory neurons and disinhibition of the neurons in the periaqueductal gray played a role in pain relief induced by the motor cortex stimulation in naive rats [35]. The process of pain relief resulting from rTMS or EMCS suggests that the stimuli act locally in M1, then modulate the interconnected remote deep brain structures through the subcortical fibers. Our diffusion tensor fiber tracking study demonstrated that the rTMS efficacy in pain relief related to good preservation of the thalamocortical tract and corticospinal tract [12]. In addition, we reported that rTMS and EMCS provided better pain relief in patients without cerebral lesions [15,41]. These results suggest that subcortical fibers and various remote deep brain structures play an important role in pain reduction by rTMS. High-frequency rTMS may reinforce propagation from M1 to such remote regions resulting in pain relief and strengthening the function of intracortical excitatory interneurons within M1.

Our findings demonstrated that ICF in responders was significantly lower compared with that in nonresponders and controls at baseline. The basis for these differences is difficult to explain with certainty. The physiology of ICF is not clear compared to that of SICI, and only a small number of studies have reported ICF alterations in patients with neurological disease. One study investigating intracortical excitatory mechanisms in patients with stroke found reduced SICI but normal ICF in the affected hemisphere [31]. Furthermore, there were no significant differences in patient characteristics or medications between the responders and nonresponders in the present study. Therefore, our findings demonstrating ICF decrease were not simply caused by a poststroke condition, by patient characteristics, or by medication. The state of low ICF at baseline may be associated with the clinical efficacy of rTMS in patients with CPSP, and the patient with low ICF may be a good candidate for the rTMS intervention.

In conclusion, we found alterations of cortical excitability in M1 in CPSP patients with high-frequency rTMS in M1. Our findings suggest that restoration of abnormal cortical excitability might be one of the mechanisms underlying pain relief as a result of rTMS in CPSP.

Conflict of interest statement

The authors report no conflict of interest.

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綜説

脳脊髄液減少症研究の現況と展望

The present state and view of the cerebrospinal fluid hypovolemia research

篠永正道

Abstract

Spontaneous intracranial hypotension is a rare disease characterized by orthostatic headache, low cerebrospinal fluid pressure and diffuse dural enhancement in brain MRI. German neurologist Schaltenbrand reported that orthostatic headache by low cerebrospinal fluid pressure in 1938. This disease came to be known after development of radiological diagnosis in 1990'. The author reported that cerebrospinal fluid leak is induced in the whiplash sequelae after traffic accident in 2003. Cerebrospinal fluid hypovolemia got into the news social. A lot of doctors deny the cerebrospinal fluid leak after mild traffic accident. The Cerebrospinal Fluid Hypovolemia Society is started up in 2003 and 11 research meeting held until today. The research group of Ministry of Health, Labour and Welfare was made in 2007. The image diagnostic criteria of cerebrospinal fluid leakage syndrome model were made in 2012. Neither the mechanism of the cerebrospinal fluid leak nor the mechanism of symptoms are understood well. The pathophysiology of cerebrospinal fluid hypovolemia is expected by researching the cerebrospinal fluid circulation.

Key words: intracranial hypotension, cerebrospinal fluid hypovolemia, mild traumatic brain injury, whiplash associated disorder, epidural blood patch

はじめに

本稿では脳脊髄液減少症をめぐる多くの問題点や課題を取り上げ，豊富な自験例の分析を含めて脳脊髄液減少症の本質に迫る議論を展開したい．

脳脊髄液減少症ほど医学の世界で批判にさらされ，かつマスコミで頻繁に取り上げられる疾患はないと思われる．その主な理由は交通事故という極めて社会性の強い事柄に関連し，利害が複雑に絡んでいるからにほかならない．比較的軽微な外傷により硬膜が裂けて脳脊髄液が漏れることはありえないという医学の常識に照らすと，軽微な外傷で脳脊髄液が漏出し，脳脊髄液が減少する考えは受け入れ難いのであろう．病名に関しては，脳脊髄液減少症，低髄液圧症候群，脳脊髄液漏出症，低髄液圧性頭痛と様々な病名が用いられているが，疾患概念の根本は脳脊髄液減少であるから，脳脊髄液減少症が最も本質に近い病名ではないかと考えている．

1．脳脊髄液減少症の歩み

低髄液圧により起立性頭痛が生じることは70年ほど前から知られていた．1938年にドイ

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ツの神経内科医であるSchaltenbrandは脳脊髄液が減少することにより起立性頭痛が出現することを初めて論文に書いた[1]. 脳脊髄液が減少することをaliquorrheaと称し, 脳脊髄液の産生減少が原因と推測したが, 脳脊髄液の漏出については述べていない. その後, 低髄液圧または脳脊髄液減少による病態についての論文は極めて限られていたが, 1990年頃から, 診断におけるMRIやRI脳槽シンチグラフィーの有用性が明らかになってから, 多くの症例報告や論文がみられるようになった[2].

研究を牽引したのは, 米国Mayo Clinic神経内科のMokriである. Mokriは症状をもたらすのは低髄液圧ではなく脳脊髄液の減少であると述べている[3]. これまでの報告は, 特に明らかな外傷がなく原因が同定できない特発性低髄液圧症候群がほとんどであった. 腰椎穿刺後に起立性頭痛が生じることは外科医, 麻酔科医にとっては日常茶飯に経験することである. 特に外傷などの原因がはっきりせず, 起立性頭痛が生じる特発性低髄液圧症候群は, 頭痛の極めてまれな鑑別診断として神経内科領域では知られていた.

問題が生じたのは鞭打ち症後遺症の原因の一つとして脳脊髄液の漏出が提唱されたことにある[4]. 鞭打ち症後遺症は, 主として追突事故の後に頭痛, 頸部痛, 手足のしびれ, めまい, 耳鳴り, 視力低下など様々な症状が持続する疾患である. 我が国では1970年前後には交通事故が多発し交通戦争とも呼ばれていた. 整形外科が中心となり様々な研究が行われたが疾患の本態, 治療法は解明されないままであった. 一方海外では米国神経外科医のOmmayaらが微細な軸索損傷が疾患の本態であると提唱し軽度外傷性脳損傷という概念が打ち立てられたが, 診断法や治療法は未解決であった[5]. 2000年に著者は鞭打ち症後遺症の原因の一つとして脳脊髄液漏出説を考えたが, 学会で初めて演題採用されたのは2003年の脊髄外科学会であった. 脳脊髄液が減少することにより多彩な症状が出現する疾患については, 10年前から有志が集まって研究会を立ち上げ, 現在までに11回の研究集会を続け, 多くの知見が集積された. また, 紆余曲折を経て, 厚生労働省研究班(脳脊髄液減少症の診断と治療の確立に関する研究)が発足し, 脳脊髄液漏出症画像診断基準が作成され, ブラッドパッチ治療が先進医療として認められるようになった.

2. 脳脊髄液減少症の概説

ここで脳脊髄液減少症について簡単に解説したい. この疾患とほとんど同義語として使われている低髄液圧症候群は, 起立性頭痛, 低髄液圧, 造影脳MRIでのびまん性硬膜肥厚を3徴とする症候群で, 原因が不明なものは特発性低髄液圧症候群(spontaneous intracranial hypotension: SIH)といわれ, これまでに多くの症例報告がなされている. 頻度は人口10万人あたり4-5人といわれている. ほとんどは脳脊髄液の漏出が原因であるが, 漏出の機序は不明である. Mokriは些細な外傷が原因になる可能性を述べており, 正常髄液圧の例もあり, 起立性頭痛を呈さない例もあることをも述べている. また, 症状を引き起こすのは髄液圧低下ではなく髄液量の減少であるから脳脊髄液減少症(cerebrospinal fluid(CSF) hypovolemia, のちにCSF volume depletionと改称)という病名を提唱した. 著者はこのMokriの提唱した脳脊髄液減少症がこの疾患の本態を最も的確に表した病名と考えている. 厚生労働省研究班では脳脊髄液量を測定することはできないので, この病名はふさわしくないとの考えから脳脊髄液漏出症という病名を採用した.

症状は頭痛, 殊に起立時に増悪する頭痛が主であるが, 起立性頭痛を伴わない例の報告もある. 頭痛以外の症状は頸部痛, 背部痛, 腰痛, めまい, 耳鳴り, 難聴, 音過敏, 光過敏, 複視, 視力低下, 性欲低下, 睡眠障害, 記憶力・集中力低下, 易疲労など多彩である. 画像診断ができることがこの疾患の診断の強みでもあり, 脳MRIでの脳沈下, 血液量増加など脳脊髄液減少の所見をみることと, CTミエログラフィー, RI脳槽シンチグラフィー, MRミエログラフィーなどで脳脊髄液の漏出をみることで診断で

きる.

治療は，脳脊髄液の漏出があれば漏出を止め，脳脊髄液の量を増加させることである．急性期であれば2週間程度の臥床安静で漏出はほとんど止まるが，慢性期に移行すると臥床安静のみで漏出が止まる比率は低下し，ブラッドパッチのように積極的に漏出を止める治療手段が必要になる．ブラッドパッチは脳脊髄液漏出の治療法として確立しており，適切な手技で行えば安全で効果的な治療法である．しかしブラッドパッチは危険な治療法であることが殊更強調された論文もみられる．著者はこれまでに3,000件を超えるブラッドパッチ治療を行ってきたが，重篤な合併症は皆無であり，おおむね8割を超える患者が症状の改善を示した．脳脊髄液減少症研究会メンバーが行ったブラッドパッチは1万件を超えると推定されるが，多くの例で症状の改善が得られており，安全で効果のある治療法である．

3．脳脊髄液減少症の併発病態

1）慢性硬膜下血腫

60歳未満の比較的若年者の慢性硬膜下血腫の原因の多くは脳脊髄液減少症である．外傷性の慢性硬膜下血腫の発生メカニズムについても不明な点が多いが，脳脊髄液減少症に併発する慢性硬膜下血腫の発生機序も解明されていない．慢性的に髄液が減少ないし髄液圧が低下すると脳の沈下に伴い硬膜下腔に髄液が貯留し，架橋静脈が牽引されることにより出血すると考えられている．時に重症化し意識障害を伴い死亡する例も報告されている．ブラッドパッチを優先させるか，穿頭ドレナージを優先させるかは学会でもしばしば議論されている．

2）静脈洞血栓症

脳脊髄液減少症に静脈洞血栓症が併発することが報告されている．脳脊髄液の減少により代償的に血液量が増加し，静脈の拡張と静脈循環遅延が生じ，静脈内血栓が生じると考えられている．著者はこれまでに1,200人以上の脳脊髄液減少症患者を診てきたが，静脈洞血栓症は経験したことがない．

3）胸郭出口症候群

外傷後脳脊髄液減少症にはしばしば胸郭出口症候群が併発する．外傷により前斜角筋が過度に伸展し，その後，斜角筋の肥大，腱様化を生じて腕神経叢を圧迫する例と脳脊髄液減少により異常な筋緊張亢進状態が続いて神経を圧迫する例がある．保存的治療で症状が改善しない場合は，著者は前斜角筋離断・神経剥離術を行っており，これまでに治療した150例のほぼ全例で症状が改善している．

4）慢性疲労症候群

慢性化した脳脊髄液減少症患者はしばしば強い倦怠感・易疲労感を訴え，慢性疲労症候群と診断されることがまれではない．慢性疲労症候群の病態はまだ十分に解明されておらず，脳脊髄液の関与も考えられる．

5）線維筋痛症

線維筋痛症は四肢・体幹の強い自発痛と半数以上の圧痛点の存在から診断される．しばしば脳脊髄液減少症の患者が線維筋痛症と診断される．脳脊髄液減少症はしばしば四肢・体幹の痛みを伴うので脳脊髄液減少症の症状の一つであるのか，線維筋痛症を合併しているのか判断は難しい．外傷後の線維筋痛症は脳脊髄液減少症を念頭に置いて診療する必要があると思われる．

4．海外での研究

軽度の外傷による脳脊髄液の漏出に関しては海外での論文は少なく，報告の大部分は特発性である．イタリアのFranziniらは2010年のJ Neurosurgで特異な疾患概念を提唱している[7]．彼らの仮説では，脳脊髄液減少は髄液の漏出ではなく下大静脈の圧低下により腰椎硬膜外の圧低下が生じ，脳脊髄液が硬膜外静脈に過剰に吸収され髄液量が低下することにより引き起こされ起立性頭痛などの症状が低下する，L1-2のブラッドパッチ治療を行うことにより症状が改善するという．これについてはイタリアのFerranteらが反論していが，Ferranteらもブラッドパッチは症状改善に著効することを述べている[8]．2004年に発刊された国際頭痛分類の低髄液圧性頭痛の診断基準[9]については多くの批

判がなされており，イタリアのMeaらは国際頭痛分類に合致したのは3%にすぎないと述べている[10]．2011年にカリフォルニアのSchievinkらが診断基準の改訂版を発表した[11]．この1-2年のうちに正式に国際頭痛分類改訂版が出る予定であり，低髄液圧性頭痛の診断基準も改訂されることになる．

5. 日本での研究

1）脳脊髄液減少症研究会

2003年に有志が集まって第1回の低髄液圧減少症研究会が行われた．この研究会は2005年に脳脊髄液減少症研究会と名称を改め，2013年までおよそ年1回の学術研究会を続けており，第11回研究会が3月末に東京で開催された．症状，診断法，治療法および基礎的研究に関して熱心な討論が行われており，脳脊髄液の循環，画像診断，疾患概念についても自由に意見を述べ合い脳脊髄液減少症の研究に寄与している．2004年に公表された国際頭痛学会が作成した国際頭痛分類，低髄液圧性頭痛の診断基準は実情に即しておらず，多くの患者を脳脊髄液減少症の診断から遠ざけることから，1年かけて11人のガイドライン作成委員が議論し，2007年には脳脊髄液減少症ガイドライン2007を作成した[12]．この診断基準は，実践的であり，多くの病院で用いられた．

2013年3月末に行われた第11回研究会では，合併した慢性硬膜下血腫の治療法，針孔からの髄液漏出についての研究発表，髄液排液・硬膜外酸素生食注入療法，フィブリン糊による硬膜外パッチ療法，小児の脳脊髄液減少症，画像診断の工夫，新たな診断・治療ガイドラインの提案などについて，活発な議論が展開された．MRIの画像診断については山梨大学堀越らにより毎回新しい知見が報告されている[13]．

2）厚生労働省研究班(嘉山班)

2007年の日本脳神経外科学会で脳脊髄液減少症のシンポジウムが行われ，この疾患の有無についても賛否両論が述べられたが，当時の学術委員長であった山形大学 嘉山教授が主任となって関連各学会(日本神経学会，日本整形外科学会，日本頭痛学会，日本脳神経外傷学会など)からの参加もあり，実際に多くの患者を診療している脳脊髄液減少症研究会のメンバーも参加して臨床研究が始められた．2011年に100例の起立性頭痛患者が登録され，分析した結果，23例で脳脊髄液の漏出が確認された．この中で外傷に起因した例は5例で2例が交通事故であった．この分析から，確実に漏れている例に関しての画像診断基準が作成された．研究した症例の中にはCTミエログラフィーを行った例は少なかったが，文献などからCTミエログラフィーの有用性が強調され，一方，RI脳槽シンチグラフィーについては針孔からの漏れの可能性を考え，腰椎部の左右対称性の'漏出像'については参考にとどめるとされた．この診断基準は公に認められた診断基準であるから，労災や裁判ではかなりの重みをもって評価されている．また障害年金について，従来は脳脊髄液減少症では認められなかったのが，診断基準ができたため比較的通りやすくなった．現在は第2期の研究を行っており，確実に漏れている例のみならず，周辺病態も含めて，かつブラッドパッチの治療効果の検討も行っており，2014年3月には一定の方向性が出されるものと期待されている．特に脳脊髄液漏出の診断には腰椎穿刺前の脊髄MRI T2強調脂肪抑制画像が有用であることが検討され，新たな診断基準では重要な位置を占めるのではないかと思われる．

3）日本脳神経外傷学会の研究

日本脳神経外傷学会では2006年から外傷に伴う低髄液圧症候群作業部会を発足し，23回に及ぶ作業部会を開いてきた．著者も参考人として作業部会に呼ばれたことがある．2008年9月から1年間，症例の登録を各施設に依頼したが結局集まったのは25例で，そのうち23例について国際頭痛分類基準を参考に検討を加えた．その結果外傷により髄液が漏れることはあっても極めてまれであることが示された．この研究結果をもとに外傷に伴う低髄液圧症候群の診断基準が定められたが，国際頭痛分類の診断基準を追随する内容である[14]．

6. 課　　題

1) 軽微な外傷での漏出機序

そもそも追突事故のように比較的軽微な外傷で，実際に脳脊髄液が漏れるかどうか疑問視する意見も多い．脊髄を包んでいる硬膜は名前のごとく硬い膜で，軽微な外傷で裂けることは絶対ありえないとの意見である．RI脳槽シンチグラフィーやCTミエログラフィーをみると脳脊髄液は神経根から漏れているようにみえる．この部分では解剖学的にくも膜が行き止まっており，神経根で折り返す構造をしており，subarachnoid angleと称されている．この部分から脳脊髄液が末梢神経に還流しているのではないかとの見解もある[15]．著者は衝撃が加わったり，髄液圧が一気に上昇するとこの部分でくも膜が神経根部から剥がれるのではないかと考えており，くも膜下腔外に漏れた脳脊髄液は硬膜から末梢神経のepineuriumに移行する比較的粗な部分から脳脊髄液が硬膜外に流出すると考えている．

2) 症状発生機序

脳脊髄液が減少するとなぜ多彩な症状が出現するのであろうか．Mokriは2つの説を述べている[6]．一つは脳脊髄液が減少すると座位・立位で浮力が減少しそのため脳が沈下して架橋静脈，脳神経が牽引され頭痛や脳神経症状が生じるという説，もう一つはMonro-Kellieの法則に従って脳脊髄液が減少すると代償性に血液量が増加し，うっ血によって脳機能が抑制されるという説である．はたしてこれが正しいのであろうか．まだ仮説の段階であるから実験的に実証する必要がある．著者は高次脳機能障害を呈した脳脊髄液減少症患者にRI脳血流シンチグラフィーを施行し，前頭葉の脳血流低下を認め，ブラッドパッチ治療で血流改善が得られた例を経験した．今後このような知見を集めることでうっ血説を実証できるのではないかと考えている．そのほか脳脊髄液が神経伝達物質の代謝産物の運搬を担っているとの考えもあり，症状発現には幾つかの未知の機序もあるのではないかと考えている．今後脳脊髄液の循環を研究することで症状の発生機序も解明されると思われる．

3) 画像診断

脳脊髄液減少の画像診断としては，びまん性硬膜肥厚が強調されているが，実際のところ漏出症例で明らかなびまん性硬膜肥厚を呈するのはさほど多くはない．Schievinkが報告しているように硬膜下腔拡大，硬膜造影，静脈拡張，下垂体腫大，脳沈下を複数呈するのを脳脊髄液減少所見とした方がよいと考えるが[16]，問題は正常と異常の境をどのように判定するかであろう．脳脊髄液の漏出については，現時点ではRI脳槽シンチグラフィー，CTミエログラフィー，MRミエログラフィー/脊髄MRI T2強調脂肪抑制画像を組み合わせて総合的に診断するのが最も信頼性が高いと思われる．それぞれの検査に一長一短があり，1つの検査で判定するのは難しいのではないか．RI検査の腰椎クリスマスツリー様の対称性漏出像は厚生労働省研究班の漏出画像診断基準では参考所見とされており，漏出とはみなされていないが，穿刺前にT2強調脂肪抑制画像で硬膜外に液体が証明されればクリスマスツリーを漏れと判断できるのではないかと考えている．25Gペンシルポイント針を用いれば針孔からの漏出量は極めて少量にとどまると考えている．

7. 小児の脳脊髄液減少症

小児の脳脊髄液減少症/低髄液圧症候群の文献はほとんどみられなかったが，最近になり高橋らが詳しい報告をしている[17]．小児でも脳脊髄液が漏出することはありえるのだろうか．小児は幾つかの理由から，むしろ成人より脳脊髄液減少症の発生頻度は高いのではないかと考えている．理由の1つは硬膜，くも膜が成長途上のため脆弱であること，次に小児は動きが激しく転倒，衝突，けんか，スポーツなどで強い衝撃が脊柱に加わりやすいこと，3つ目には小児期は相対的に髄液量が少なくわずかな髄液減少で症状が出現することが挙げられる．実際に転倒，スポーツなどのあと頭痛，めまい，吐き気，倦怠などの症状が続き登校が困難になる例がしばしばみられる．小児科領域ではまだ脳脊髄液

減少症という疾患の認知度が低く，片頭痛，起立性障害，心因性登校困難症と診断されることが多いようである．小児の脳脊髄液減少症の特徴としては，起立性頭痛が多いこと，脳MRI検査では異常がみられない場合が多いこと，早期の臥床安静でほとんど症状が改善すること，ブラッドパッチの効果が著しく高いことが挙げられる．比較的軽度の外傷後に起立性頭痛，吐き気，めまいなどを訴えるときは，脳脊髄液の漏出を疑って，トイレ以外の起立は禁じる厳密な臥床安静を1-2週間保つことである．多くの例で症状は改善している．臥床安静で症状改善しないとき，臥床安静の時期を逸してしまったときは漏出の検査を行って，必要であればブラッドパッチを行うことで症状の改善が期待できる．重要なことは症状を慢性化させないことである．事故後数年間寝たきりになって貴重な成長期を無為に過ごすことがないように，医療者は肝に銘ずることが大切である．

8. ブラッドパッチ以外の新しい治療について

1) フィブリン糊パッチ

Schievinkは頸部からの脳脊髄液漏出例にCTガイド下で椎間孔に穿刺し，フィブリン糊を注入して漏出を止める方法を述べている[16]．著者は複数回のブラッドパッチでの漏出が止まらない例に対して，生理食塩液で3-4倍希釈したフィブリン糊を通常のブラッドパッチと同様に透視下で硬膜外穿刺して注入するフィブリン糊パッチを試みており，満足すべき結果を得ている．更に血液注入により強い炎症反応を併発した例に用いて症状の悪化を防ぐことができている．今後はこのような治療法も選択肢の一つに加わるであろう．

2) 人工髄液による髄液補充療法

ブラッドパッチを行って脳脊髄液の漏出は止まったものの，なかなか脳脊髄液が増加しない例がある．長期間減少した髄液量で産生・吸収のバランスがくずれてしまったからではないかと考えている．このような例に対し，硬膜外に生理食塩液を注入し，腰椎くも膜下腔の脳脊髄液を頭蓋内に押し上げ，症状改善をもたらす生理食塩液硬膜外注入治療(生食パッチと称している)を行い，ある程度の効果は得られてきたが，効果が一過性にとどまる例が多かった．このような例に人工髄液(正式には脳脊髄液洗浄・還流液，製品名アートセレブ)を腰椎くも膜下腔に注入する治療を試みている．2011年3月～2013年3月まで約400例に治療を行ってきた．この治療は新たな治療法であるため病院内倫理委員会で検討し，認可が下りた後に治療を始めた．約7割の例で何らかの症状の改善が得られている．特に副作用はみられなかった．今後の更なる研究により一般化することを期待している．

9. 研究の展望

1) 脳脊髄液産生吸収の新しい理論

脳脊髄液の産生・吸収・循環に関しては未知の部分が多い．従来，脳脊髄液は大部分が脳室内の脈絡叢で産生され，上矢状洞近傍のくも膜顆粒で吸収されるといわれてきたが，クロアチアのKlaricaらは猫を使った動物実験で，脳脊髄液の多くは脳表面の微小血管から産生され，同部で吸収される説を唱えている[18]．一部は神経根部でリンパ管から吸収されるが，その割合は低いとのことである．髄液は混じり合いながらbulk flowで循環していると述べられている．大分大学解剖学の三浦は猿を使った研究で，頸椎では硬膜外および神経根に活発なリンパ組織があり，この部分から脳脊髄液が吸収されることを実証した[19]．これらの研究は脳脊髄液の産生・吸収の理論を大幅に書き換えることになると思われる．

2) 脳脊髄液減少の意義 —新たな疾患群としての位置づけ

特発性低髄液圧症候群については，その疾患の存在，診断，治療について特に異論はないと思われる．問題となるのはどこから脳脊髄液が漏れるのか，どのような機序で漏れるのかがよくわかっていないことと，この疾患が十分に認知されておらず，しばしば適切な診断と治療が行われていない点である．国際頭痛分類の‘低

髄液圧性頭痛'診断基準が改訂されれば，より適切な診断が行われるようになるのではないかと期待している．一方，軽度の外傷による脳脊髄液漏出については，まだかなりの異論があり，外傷性脳脊髄液漏出症の存在を認めない医師も少なくない．しかし，現実に交通事故により多彩な症状が長期間続き，深刻な身体的，精神的，経済的，社会的問題を抱えていた患者がブラッドパッチ治療で改善する例を多く見ていると，外傷によって脳脊髄液が漏れることは十分にありえると考えざるをえない．

脳脊髄液が減少する病態については，内科，神経内科，脳神経外科などの教科書には全く記載がない．これはなぜなのだろうか．多くの患者を診た経験では，脳脊髄液が減少することにより多彩な症状が出現し，脳脊髄液を増やすことにより症状が軽減している．個々の患者で脳脊髄液の量を計測することは現状では実際的ではない．年齢により，また個人によっても脳脊髄液の量はかなり幅がある．小児では脳脊髄液の量は少なく，高齢者ではかなり多い．神経系の機能を維持するための髄液量は個人によって異なり，ある一線を下回ると症状が出現するのではないかと思われる．では，なぜある一線を下回ると症状が出現するのか．現在のところよくわかっていない．いずれにせよ脳脊髄液が減少する病態について今後，多方面から研究する必要があるのではないだろうか．脳脊髄液が神経系の機能の保持に重要な役割を果たしていることに異論をはさむ医師・研究者はいないと思われる．

3）脳脊髄液の循環に関する新しい知見

東海大学脳神経外科の山田はtime-SLIP法によりMRIで髄液の循環を観察し，従来の考えとは大きく異なる脳脊髄液循環について発表している[20]．これはまさにイノベーション的な重要な研究である．第3脳室内ではダイナミックな脳脊髄液の動きがあり，くも膜下腔でも心拍動に一致しない拍動による髄液の流れがあり，脳脊髄液の吸収もくも膜顆粒から上矢洞に流出するのはむしろ少ないことを述べている．クロアチアのKlaricaの仮説とも一部重なる部分があるのは興味深い．脳脊髄液減少症は物理的に脳脊髄液が減少するのではなく，機能的に脳脊髄液が減少することにより脳脊髄液循環が遅滞して，神経伝達物質や代謝産物の運搬に支障をきたすため多様な症状が出現するという考えも浮かび上がってくる．これまでは診断に関しても，脳脊髄液の減少(Monro-Kellieの法則が当てはまることを前提にして)ないし脳脊髄液の漏出の画像所見を追ってきたが，脳脊髄液循環に注目する必要があると思われる．脳脊髄液減少症患者のtime-SLIP法によるMRI脳脊髄液循環動態検査を行えば，新たな世界がみえてくるのかもしれない．なぜブラッドパッチが症状を改善させるのかに対する答えも見いだせるのかもしれない．水頭症に対するシャント手術の効果と脳脊髄液減少症に対するブラッドパッチの効果は，脳脊髄液循環改善という意味では共通しているのかもしれない．

おわりに

最後に脳脊髄液減少症をめぐる社会的問題について触れたい．

ブラッドパッチの保険適用

脳脊髄液減少症は極めて社会性の高い疾患である．約10年前まではブラッドパッチ治療は硬膜外ブロックとして健康保険で治療を行っていた．ところがこれは健康保険の範囲を逸脱した医療行為であるとして，健康保険で行うことはできなくなった．そのため自費治療で検査，ブラッドパッチを行わなくてはならなくなり，患者には1回の入院で数十万円の多大な出費が必要となり，適切な検査・治療が行えない患者が多く出現した．患者団体の熱心な働きかけで2008年には脳脊髄液減少症の検査は健康保険でできるようになった．厚生労働省研究班の脳脊髄液漏出症画像診断基準が公表されたことを受けて，2012年6月から先進医療の申請が認められた病院では，入院費は健康保険でブラッドパッチにかかる費用は自費で行うことができるようになった．この成果によっては2014年の中央社会保険医療協議会(中医協)でブラッドパッチの診療報酬収載が認められる可能性が出て

きた．健康保険でブラッドパッチができるようになれば，多くの病院でブラッドパッチ治療が可能になり，脳脊髄液減少症の診療は格段に行いやすくなるに違いない．その波及効果は交通事故における損害保険会社の対応にも変化をもたらし，現在全国で多く行われている訴訟にも多大な影響を与えることは明らかである．

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Lumbar puncture-related cerebrospinal fluid leakage on magnetic resonance myelography: is it a clinically significant finding?

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Abstract

Background: Post-dural puncture headache (PDPH) due to excessive cerebrospinal fluid (CSF) leakage is a well-known complication of lumbar puncture. Although various factors, especially the type of spinal needle, have been demonstrated to be associated with PDPH, the clinical implications of CSF leakage detected on magnetic resonance myelography (MRM) images remain unclear. The objective of this case–control study was to evaluate the association between radiologically visualized CSF leakage and PDPH.

Methods: Clinical data including patients' age and gender, types of spinal needle, duration of bed rest, interval between lumbar puncture procedures and MRM studies, and incidence of PDPH were compared between patients who were radiologically-positive and -negative for CSF leakage.

Results: Of the 22 patients with definite CSF leakage on MRM images, most were asymptomatic (86%, 19/22). The remaining three patients, who were suffering from PDPH, only complained of headaches and were treated conservatively. In a review of patients' clinical data, there were no significant differences in any parameter including the incidence of PDPH between the 22 patients who were radiologically-positive for CSF leakage and the 31 radiologically-negative patients.

Conclusion: The significance of radiologically visualized CSF leakage should not be overestimated, as most such incidents are not associated with PDPH and do not require any treatment.

Keywords: Lumbar puncture, Cerebrospinal fluid leakage, Post-dural puncture headache, Magnetic resonance myelography, Magnetic resonance imaging

Background

Lumbar puncture is generally performed in daily medical practice to measure the pressure in the subarachnoid space, to obtain cerebrospinal fluid (CSF) samples for analysis, to inject contrast medium for myelography, or to induce spinal anesthesia. However, puncturing the dura has the potential to lead to excessive CSF leakage, and CSF hypovolemia subsequent to excessive CSF leakage can lead to post-dural puncture headache (PDPH), which has been regarded as a complication of lumbar puncture for over a century [1]. Its clinical characteristics including its incidence and associated factors have been evaluated in previous studies [2,3].

Recently, neuroimaging techniques including radioisotope cisternography (RICG) and magnetic resonance imaging (MRI) have enabled the visualization of postpuncture CSF leakage in the epidural space [4,5]. Considering its pathophysiology, it is indisputable that postpuncture CSF leakage contributes to the development of PDPH [2,3]. However, the incidence and clinical implications of radiologically visualized postpuncture CSF leakage have rarely been evaluated [6,7]. These studies evaluated only a small number of selected subjects, so a larger number of unselected subjects in daily medical practice appear necessary for the evaluation of the clinical implication of radiologically visualized postpuncture CSF leakages.

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Furthermore, such iatrogenic CSF leakage can make it difficult to differentiate between PDPH and spontaneous intracranial hypotension (SIH) [4,5]. Taking these problems into consideration, we aimed to investigate the clinical implication of radiologically visualized postpuncture CSF leakage in daily medical practice.

Methods

Subjects

This was a retrospective study evaluating the incidence and clinical characteristics of postpuncture CSF leakage using data obtained at a single medical center, and was approved by the Ethics Committee for Clinical Research of Nagoya City University Graduate School of Medical Sciences, which waived the requirement for informed consent. The privacy of the patients was completely protected. Between January 2009 and March 2012, 329 lumbar punctures were performed to obtain samples for CSF analysis in 251 patients with various neurological disorders (e.g., multiple sclerosis, infectious meningitis, etc.) at the Department of Neurology. Of these 329 examinations, 270 were excluded because no subsequent magnetic resonance myelography (MRM) study was performed within 14 days of the lumbar puncture. There were two reasons why MRI examinations were not performed in these patients. The one was that their primary illness did not require lumbar MRI examinations (e.g. viral meningitis), and the other was that the examination and admission schedules did not allow to perform MRI examinations after lumbar punctures. As a result, 59 examinations involving 53 patients who underwent subsequent thoracolumbar or lumbar MRM studies were included in this study. The lumbar puncture procedures were mainly performed using 21-gauge (G) Quincke spinal needles at the L3/4 or L4/5 intervertebral level. PDPH was diagnosed according to the previously published diagnostic criteria [3].

MRM protocol and image analysis

The thoracolumbar or lumbar MRM studies were performed on a 1.5-T imager (Gyroscan Intera; Philips Medical Systems, Best, The Netherlands) using a synergy spine phased-array coil. The 2D MRM sequence was performed using the following parameters: turbo spin echo (TSE) sequence; repetition time/echo time, 8000 ms/1000 ms; field of view, 350–500 mm; matrix, 512 × 142; slice thickness, 40–50 mm; section orientation, coronal; and TSE factor, 256. Basically, this sequence was utilized as a localizer scan in our institution. Postpuncture CSF leakage was diagnosed according to the previously reported imaging findings by the consensus of two experienced physicians (K.S. and M.N.), who were blinded to the patients' clinical information [5,8]. Additionally, to differentiate CSF leakages from mistakable findings such as water component at the intervertebral joints, root sleeves and perineural cysts, postpuncture MRM findings were compared with findings of other sequences such as axial and sagittal T2-weighted images in each patient.

Statistical analysis

Statistical analyses were carried out using the SPSS 11.0 statistical software program (Dr. SPSS II for Windows, standard version 11.0; SPSS Inc., Chicago, IL, USA). The unpaired t test was used for comparisons of age distributions. Fisher's exact test was used for comparisons of the gender distribution and PDPH incidence between the two patient populations. Pearson's chi-squared test was used for comparisons of the spinal needle gauge and puncture level. The Mann–Whitney U test was used to compare the duration of bed rest and the interval between the lumbar puncture and MRM study. Differences were considered significant when $p < 0.05$.

Results

The characteristics of the patients are summarized in Table 1. Twenty-two MRM studies involving 22 patients exhibited postpuncture CSF leakage (37%, 22/59). All except four of these radiologically visualized leakages were bilateral and were mainly located in the paraspinal areas at the lumbosacral level (Figure 1). Of the 22 patients, only three suffered from PDPH (14%, 3/22), which occurred within 48 hours of the lumbar puncture and persisted for one to six days. No other symptoms associated with PDPH, such as nausea, vomiting, or hearing loss, were observed. These patients were treated in a conservative manner including bed rest, appropriate hydration, and non-steroidal anti-inflammatory drugs. The other asymptomatic patients did not require any kind of treatment for their CSF leakage.

In 37 CSF leakage-negative MRM studies, five patients suffered from PDPH (14%, 5/37). In a review of the patients' clinical data including the incidence of PDPH, their basic characteristics and the details of puncture procedures, no significant differences were detected in any parameter between the radiologically CSF leakage-positive and -negative patients (Table 1).

Discussion

Considering the advantage of high contrast resolution, ability to depict the entire spinal subarachnoid space including fluid collections and leakages, and non-invasive nature (i.e., no LP and no radiation exposures), MRM may be regarded as the first-line examination in the diagnosis of CSF leakages. Its high contrast resolution contributes to detect indirect findings such as epidural-paraspinal fluid collections, especially small amounts of leakages along bone structures [9-11]. Furthermore, MRM with intrathecal gadolinium injection can provide both physiologic and morphologic information, which enables the detection of

Table 1 Patient characteristics

	CSF leakage-positive exams (n = 22)		CSF leakage-negative exams (n = 37)		p value
Age (years)	50 ± 18 (17–86)		56 ± 19 (17–86)		0.27
Gender (male: female)	12: 10		19: 12*		0.66
Underlying disorders					
Neuropathy/neuritis	8		6		
Demyelination	4		9		
Infection	3		2		
Hydrocephalus	1		3		
Degenerative disease	1		3		
Others	5		8		
Gauge of spinal needle	21 G	−19	21 G	− 18	0.18
	19 G	− 1	19 G	− 2	
	23 G	− 1	23 G	− 6	
	Unknown	− 1	Unknown	− 11	
Puncture level	L3/4	− 4	L3/4	− 6	0.69
	L4/5	− 12	L4/5	− 16	
	L5/S	− 0	L5/S	− 1	
	Unknown	− 6	Unknown	− 14	
Duration of bed rest (hour)	1 h	− 1	1 h	− 0	0.06
	1.5 h	− 1	1.5 h	− 0	
	2 h	− 20	2 h	− 37	
Duration between LP and MRM (days)	1.8 ± 2.6		4.0 ± 4.3		0.13
Post-dural puncture headache	3 (14%)		5 (14%)		0.66

Data are shown as absolute numbers or the mean ± standard deviation.
*Six of the CSF leakage-negative patients underwent two CSF analyses.
Note: CSF = cerebrospinal fluid; exams = examinations; n = number of exams; G = gauge; L = lumbar; S = sacral; h = hours; LP = lumbar puncture; MRM = magnetic resonance myelography.

direct CSF leakages with higher sensitivity than any other technique including computed tomography myelography [9]. In the present study, similar to the previous study evaluating ICSFL on MRM [5], CSF leakage was distributed around nerve roots and paraspinal area at the lumbosacral level. Predominant lumbosacral distribution was not surprising because the thecal punctures were performed at this location. It is expected that these characteristic paraspinal fluid collections are the result of CSF escaping from the epidural space into the paraspinal loose connective tissues, similar to the retrospinal C1–2 fluid collection reported in patients with PDPH and SIH [12,13]. In addition to these anatomical factors, the low resolution of the 2D MRM sequence depicts CSF leakages in the paraspinal area more definitely than those around nerve roots in this study.

Although the association between PDPH and CSF abnormalities (i.e., between CSF loss and a reduction in intracranial pressure) is not disputed, the exact pathophysiology of PDPH remains unclear. PDPH is considered to be caused by the hole left in the dura after the lumbar puncture needle has been withdrawn, which can allow CSF leakage from the subarachnoid space [14]. Among the various risk factors for PDPH including puncture procedure variables, patient characteristics, and a past history of chronic headaches, the size and design of the needle used for the lumbar puncture are the most significant determinants of PDPH [2,3,15]. As a result, its incidence can vary widely, depending on the population involved and the needles and techniques used [3,16,17]. The incidence of PDPH in this study (14%) was comparable to that described in a previous report in which 20G cutting spinal needles were used [18].

It is worth noting that the incidence of PDPH did not differ significantly between the radiologically CSF leakage-positive and -negative patients in our study. On the surface, these findings do not seem to support the hypothesis that CSF leakage through dural holes causes PDPH. However, several previous studies have indicated that the volume of CSF lost via leakage and CSF hypotension are not associated with PDPH and have also questioned the dural hole hypothesis [16,19]. In addition, neuroimaging studies performed with MRI or RICG after lumbar puncture have revealed that some patients with postpuncture

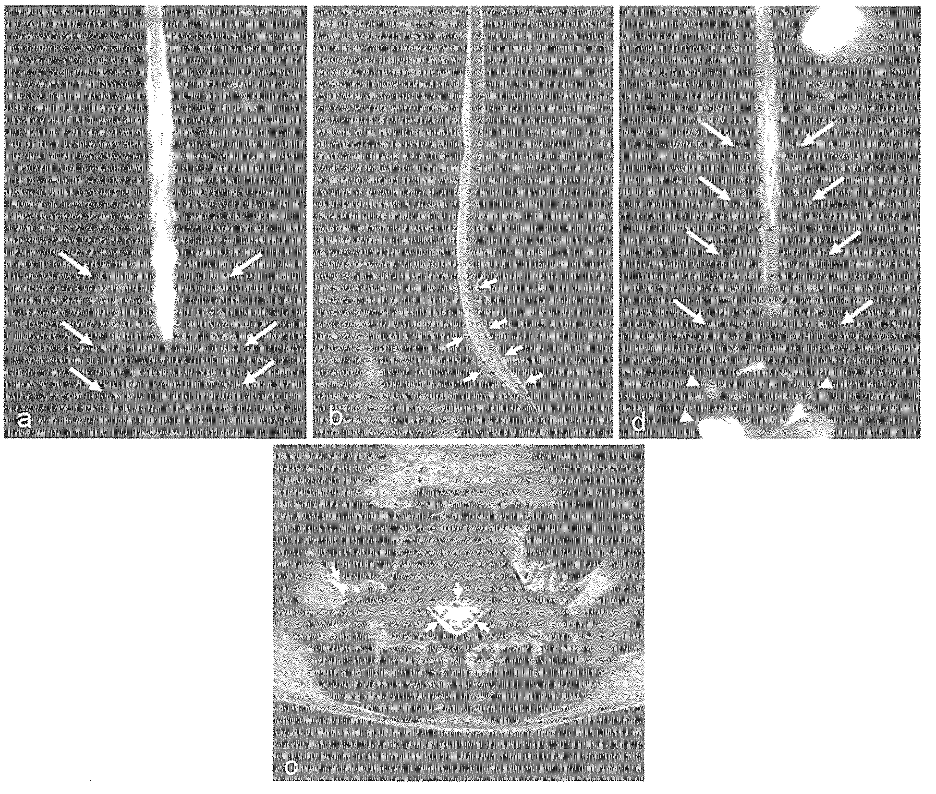

Figure 1 Representative magnetic resonance myelography (MRM) images of postpuncture cerebrospinal fluid (CSF) leakage. 2D MRM images were performed about 28 and 6 hours after the lumbar punctures in a 44-year-old male with chronic inflammatory demyelinating polyneuropathy (patient A) and a 42-year-old female with multiple sclerosis (patient B), respectively. Bilateral fluid collection around the nerve roots and paraspinal area **(a, d)** were depicted on 2D MRM images (arrows). Additionally, sagittal fat-suppressed T2-weighted **(b)** and axial T2-weighted **(c)** images of patient A revealed abnormal epidural and paraspinal fluid collections (arrowheads). In spite of such leakage, patient A was asymptomatic. However, patient B complained of an orthostatic headache that had persisted for six days. Arrowheads indicate fluid accumulation that was unrelated to CSF leakage (e.g., the bladder and ovarian cysts).

CSF leakage are asymptomatic [4-6]. However, such leakages can still cause clinical problems, especially with the diagnosis of disorders such as SIH [5]. Together, these findings indicate that the existence and volume of CSF leakage are not necessarily associated with PDPH and suggest that the underlying mechanisms of PDPH are more complex.

A simple older explanatory model for PDPH is that the reduction in intracranial pressure induced by persistent CSF leakage causes traction between pain-sensitive structures such as meningeal membranes, blood vessels, and nerves [3,20]. On the other hand, hypersensitivity to substance P and the Monro-Kellie doctrine, which suggests that compensatory intracranial vasodilatation is induced by CSF leakage, have recently been recognized as viable hypotheses regarding the cause of PDPH [1,21]. Considering these new hypotheses, it is not surprising that some of the patients in this study without definite CSF leakage on MRM images complained of PDPH.

A number of limitations of the present study need to be addressed. The main limitation is the relatively small study population. The lack of available clinical data due to the study's retrospective nature is also problematic point. These made it difficult to evaluate various factors that affect the incidence of PDPH, such as the number of lumbar punctures, body mass index, and the patients' medical histories. Furthermore, the incidence of CSF leakages on MRM might also be affected by the number of lumbar punctures. Another limitation is our use of the 2D MRM sequence; i.e., the lower resolution made this study qualitative rather than quantitative evaluation. To perform the precise measurement of CSF leakage, it is necessary to use the 3D MRM sequence, which achieves higher spatial resolution. Additionally, the interval between lumbar punctures and MRM may be too long in some cases. Therefore, there is a chance of resorption of CSF leak in radiologically-negative patients. In spite of these limitations, the fact remains that most of the patients with definite CSF leakage after lumbar puncture with the relatively large 21G Quincke spinal needle were asymptomatic.

Conclusion

In this study, most radiologically visualized CSF leakages are not associated with PDPH and do not require any treatment. It is important that we gain a better understanding of this asymptomatic and incidental phenomenon in order to avoid misdiagnosis and overtreatment.

Competing interests

The Authors declare that there is no conflict of interests.

Authors' contributions

KS drafted the manuscript. KS and MN performed the neuroimaging analysis. NM, KO and TY participated in the design of the study and evaluated the clinical information. MS and YO performed the statistical analysis. SK helped to check the imaging protocol. YS participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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