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Original Article

Impact of low coagulation factor XIII activity in patients with chronic subdural hematoma associated with cerebrospinal fluid hypovolemia: A retrospective study

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In memory of Dr. Iwao Takeshita.

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Abstract

Background: Cerebrospinal fluid hypovolemia (CSFH) is sometimes associated with chronic subdural hematomas (CSHs). Affected patients often develop enlargement and recurrence of the CSH, even if appropriate treatments such as epidural blood patch (EBP) and/or burr-hole surgery for the CSH are performed. This situation may lead to subclinical coagulopathy, including low coagulation factor XIII (CFXIII) activity. We retrospectively analyzed whether CFXIII activity was involved in the development of CSHs and post-treatment exacerbation of CSHs in patients with CSFH.

Methods: We diagnosed CSFH by radioisotope (RI), magnetic resonance imaging (MRI) and computed tomography (CT) findings, and CSH by CT and/or MRI findings. The plasma CFXIII activity was assessed on admission. All patients with CSFH initially received conservative treatments. When these treatments were ineffective, the patients underwent EBP and/or CSH surgery according to previously reported therapeutic strategies.

Results: Among 206 patients with CSFH, 19 developed CSHs. Fourteen patients with a thin hematoma underwent EBP and three with a thick hematoma underwent CSH surgery immediately after EBP on the same day. We were unable to diagnose two patients with CSFH at the time of admission, and one of these two patients underwent repeated CSH surgery before obtaining the correct diagnosis. Seven patients (36.8%) developed CSH exacerbation after the treatment. The CFXIII activity was significantly lower in patients with than without a CSH (42.1% vs. 12.8%, respectively; $P = 0.003$). The CFXIII activity was significantly lower in patients with

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than without post-treatment CSH exacerbation ($P = 0.046$). All five patients with low CFXIII activity who developed CSH exacerbation received intravenous injection of CFXIII and had no recurrence of CSH after the additional treatment.

Conclusion: In patients with CSFH, low CFXIII activity is one of the risk factors for both the development of a CSH and the post-treatment exacerbation CSH.

Key Words: Cerebrospinal fluid hypovolemia, chronic subdural hematoma, coagulation factor, coagulation factor XIII, intractable chronic subdural hematoma

INTRODUCTION

It is well known that chronic subdural hematomas (CSHs) are associated with cerebrospinal fluid hypovolemia (CSFH).[4,6,17,19,21] The most widely accepted pathophysiological explanation of the association between CSH and CSFH involves leakage of spinal cerebrospinal fluid (CSF) with secondary sagging of the brain;[18] this may tear congested bridging veins and cause them to bleed between the inner layer of the dura mater and the arachnoid or between the outer and inner layers of the dura, resulting in the development of a CSH.[4] Moreover, further enlargement of a CSH is believed to be caused by microbleeding from the fragile walls of sprouting vessels and accumulation of fluid in this newly created space following the osmotic gradient created by blood degradation products.[4]

With respect to the therapeutic strategy for a CSFH-associated CSH, Takahashi *et al.*[21] suggested that if the hematoma is thin (<14 mm), epidural blood patch (EBP) should be performed prior to burr-hole surgery for CSH (CSH surgery) and that if the hematoma is thick (>15 mm), CSH surgery should be performed immediately after EBP. However, patients often develop enlargement or recurrence of the CSH, and their clinical condition may worsen and lead to a morbid outcome even after appropriate treatment.[15,21]

Subclinical coagulopathy should be suspected in patients with an intractable CSH.[2] Among the various coagulation factors (CFs), low activity of CFXIII is thought to be one of the important factors in the development of intractable CSH.[5] Low activity of CFXIII should be examined in patients with abnormal bleeding who had normal activated partial thromboplastin time (APTT), prothrombin time (PT), fibrinogen level, platelet count, and bleeding time.[10] Albanse *et al.*[2] reported three cases of intractable CSHs in young adults with CFXIII deficiency. CFXIII is a pro-enzyme (pro-transglutaminase) that stabilizes fibrin clots in the final stages of blood coagulation, becoming activated by the concerted action of thrombin and calcium [Figure 1].[1,11] Activated CFXIII (CFXIIIa) then stabilizes the endothelium of vessels by cross-linking single endothelial cells.[16]

Although, various CFs including CFVII, CFX, and CFXI could lead to intractable CSH,[3,9,20] in the present study, we focused on the clinical value of CFXIII activity since the intravenous administration of CFXIII accelerates healing of CSF leak sites from the perspective of CSFH treatment.[14] We retrospectively analyzed whether low CFXIII activity was involved in the development of CSH and in the exacerbation of CSH after treatment in patient with CSFH-associated CSH. In this study, we aimed to elucidate the impact of low CFXIII activity on CSFH-associated CSH.

MATERIALS AND METHODS

Diagnosis of cerebrospinal fluid hypovolemia

Patients with orthostatic headache admitted to our department from 1994 to 2015, clinically suspected of having CSFH underwent radioisotope (RI) cisternography, brain magnetic resonance imaging (MRI), and/or computed tomography (CT). RI cisternography was performed to check for direct and indirect findings of CSF leakage. Direct findings were defined as focal areas of increased activity in unilateral or bilateral regions of the paraspinal area, and indirect findings were defined as early visualization of bladder activity (radioactivity in the urinary bladder 1–3 h after injection), no visualization of activity over the brain convexities (no remarkable accumulation around the brain convexities 24 h after injection), rapid disappearance of spinal activity (1–5 h after injection), and abnormal visualization of the root sleeves (asymmetric activity outlining the spinal nerve roots at any time after injection).[12]

MRI and/or CT were performed on all patients to exclude the presence of intracranial lesions such as tumors or hemorrhage. MRI with gadolinium enhancement was performed to check for diffuse meningeal enhancement. Analysis of brain descent was based on the incisural line and foramen magnum line on mid-sagittal MRI.

We diagnosed CSFH by RI, MRI, and CT findings. Evaluation of the radiological images was based on visual inspection by experienced neurosurgeons (I.T. and T.S.) and two radiologists. No differences in their interpretations were noted on independent assessments.

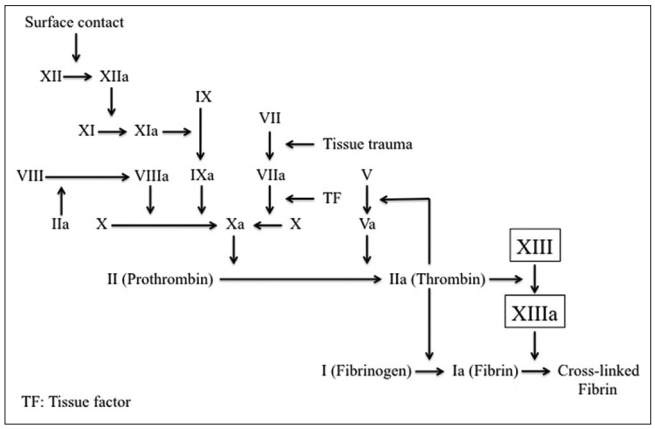

Figure 1: Coagulation cascade. The extrinsic and intrinsic pathways serve to activate coagulation factor (CF) X to Xa, a component of the prothrombinase complex that converts prothrombin (CFII) to thrombin (CFIIa). Thrombin activates CFXIII to XIIIa, which stabilizes the fibrin clot by covalently cross-linked fibrin. Abbreviations within figure: TF, tissue factor

Diagnosis of chronic subdural hematoma

We diagnosed CSH by CT and/or MRI findings. The hematoma was defined as thin when its maximum thickness was <14 mm and as thick when its thickness was >15 mm. Patients with subdural hygromas were excluded from this study. Evaluation of CT and MRI findings was also based on visual inspection by experienced neurosurgeons (I.T. and T.S.) and radiologists. No differences in their interpretations were noted on independent assessments.

Clinical assessment for coagulation factor XIII activity and other factors

We assessed the CFXIII activity (normal range, 70–140%) in plasma obtained on admission in 206 patients. From 1994 to 2006 (Cases 5, 7, 12, 15, 17 and 19), we recorded whether the CFXIII activity was <70% or ≥70%; from 2007 onward, we recorded the detailed CFXIII activity. CFXIII activity of ≥70% was defined as normal.

Furthermore, factors possibly related to post-treatment CSH exacerbation were statistically analyzed. Patient variables included sex, age, CSH site, hematoma thickness at first treatment, direct findings, indirect findings, and MRI findings (diffuse meningeal enhancement and descent of brain).

Therapeutic strategy

All patients with CSFH initially received conservative treatments such as bed rest, analgesics, generous oral fluid intake, and fluid drip infusion. When these treatments were ineffective as evidenced by clinical and/or neuroradiological findings, the patients underwent EBP and/or CSH surgery according to the similar strategies reported by Takahashi *et al.*[21]

The performance of EBP involved injection of autologous blood into the epidural space at the level of the cervical, thoracic, or lumbar vertebra according to the RI cisternography results. For CSH surgery, patients underwent a standard neurosurgical procedure with full evacuation of all hematoma compartments including several washing steps with saline solution through a single burr-hole. A temporary soft silicone subdural drain was placed in the subdural space and connected to a closed drainage system for 12 to 24 h. Patients with bilateral CSHs received the same treatment on both sides. EBP and CSH surgery were performed with the same techniques by experienced neurosurgeons.

Diagnosis of chronic subdural hematoma exacerbation and additional therapeutic strategy

We diagnosed patients with CSH enlargement or recurrence (CSH exacerbation group) by evaluating repeated CT scans after the treatment. We performed repeated CT scans on postoperative day 1, day 7, and day 14 routinely. CSH enlargement was diagnosed when the maximum post-treatment hematoma thickness was larger than the pretreatment thickness. We performed reoperation when the hematoma became large in thickness.

In the CSH exacerbation group, a purified pasteurized CFXIII concentrate (Fibrogammin P; CSL Behring, Tokyo, Japan) was intravenously administered at 24 mL/day for 5 days if the CFXIII activity was <70%.

All patients were followed up to check whether there were serious complications and recurrence of CSH or not after the last treatment (follow-up period; mean: 8.0 years, range: 2–21 years).

Statistical analysis

JMP 11.0 software (SAS Institute, Cary, NC, USA) was used to perform the statistical analyses. Univariate analyses were conducted to determine the relationship between the development of CSFH-associated CSH and low CFXIII activity, and the risk factors for CSFH-associated CSH exacerbation after EBP and/or CSH surgery. We compared CSH exacerbation and non-exacerbation using t-statistics for continuous variables and χ^2 statistics for categorical variables. The risk factors for CSFH-associated CSH exacerbation after EBP and CSH surgery were analyzed with only univariate analysis because of the small sample size. A P value of <0.050 was considered statistically significant.

The clinical data, treatments, and outcomes were obtained from the medical records. All patients provided written informed consent.

RESULTS

In total, 206 patients were conclusively diagnosed with CSFH based on RI, MRI, and CT findings. The patients comprised 95 males and 111 females aged 12 to 72 years (mean, 36.2 years).

Table 1: Clinical characters of 19 patients in chronic subdural hematoma with cerebrospinal fluid hypovolemia

Case No.	Age/ Sex	CSH site	Hematoma thickness at first treatment	Direct findings	CSF leak point	Indirect findings	Descent of brain	Diffuse meningeal enhancement	XIII activity (%)	Treatment	CFXIII injection	CSH exacerbation
1	63/M	Bil	Thin	+	Lu	+	+	+	85	E→S	-	+
2	43/M	Uni	Thin	+	Lu	+	-	-	77.6	E→S	-	+
3	51/M	Bil	Thin	-		+	+	+	53.1	E→E/S	+	+
4	46/M	Bil	Thin	+	Th	+	-	+	67.2	E→S	+	+
5	49/F	Bil	Thin	+	Th/Lu	+	+	+	<70	E→E→E→E/S→E/S	+	+
6	49/M	Bil	Thin	-		+	-	+	67.5	E→E→S→E→E→S→E	+	+
7	43/M	Bil	Thick	-		+	+	+	<70	S→S→S→E/S	+	+
8	67/F	Bil	Thin	-		+	-	+	86.6	E	-	-
9	42/F	Bil	Thin	+	Th/Lu	+	-	-	102.7	E	-	-
10	29/F	Uni	Thin	+	Th/Lu	+	+	+	60.8	E	-	-
11	44/F	Uni	Thin	-		+	+	+	55.5	E	-	-
12	40/F	Uni	Thin	-		+	-	+	70<	E	-	-
13	31/F	Bil	Thin	+	Lu/Sa	+	-	+	80.7	E	-	-
14	46/M	Uni	Thin	-		+	-	+	72.4	E	-	-
15	46/M	Uni	Thin	-		+	-	+	70<	E	-	-
16	30/M	Uni	Thick	-		+	-	+	67.7	E/S	-	-
17	60/M	Bil	Thick	-		+	-	+	70<	E/S	-	-
18	55/M	Bil	Thick	+	Lu	+	-	+	76.1	E/S	-	-
19	59/F	Bil	Thick	-		+	-	+	70<	S (→E)	-	-

M: Male, F: Female, CSH: Chronic subdural hematoma, Bil: Bilateral, Uni: Unilateral, CFXIII: Coagulation factor XIII, E: Epidural blood patch, S: Surgery, E/S: Evacuation of hematoma immediately after EBP on the same day

Characteristics of patients with CSFH-associated CSH

Nineteen of 206 patients (9.2%) had a CSFH-associated CSH (CSH occurrence group) [Table 1]. These patients comprised 11 males and 8 females aged 29 to 67 years (mean, 47.0 years). Twelve patients (63.2%) had bilateral CSHs, and seven patients (36.8%) had a unilateral CSH. Fourteen patients (73.7%) had thin CSHs and five patients (26.3%) had thick CSHs. Direct findings of CSF leakage were present on RI cisternography in eight patients (42.1%); the CSF leakage point was present at the level of the thoracic vertebra in one patient, at the level of the thoracolumbar vertebra in three, at the level of the lumbar vertebra in three, and at the level of the lumbosacral vertebra in one. Indirect findings of CSF leakage on RI cisternography were seen in all patients (100%). Six patients (31.6%) exhibited descent of the brain on mid-sagittal MRI. Seventeen patients (89.5%) showed diffuse meningeal enhancement on MRI with gadolinium administration. Eight patients (42.1%) had normal CFXIII activity and 11 (57.9%) had activity of <70%. No patients underwent anticoagulation drug administration or had a history of abnormal bleeding and any liver disease. All patients had normal APTT, PT, fibrinogen level, and platelet count. Fourteen patients with thin CSHs underwent EBP, and three patients with thick CSHs underwent CSH surgery immediately after EBP on the same day. We were unable to diagnose two patients with CSFH on admission, and these patients underwent CSH surgery first (Cases 7 and 19) [Table 1].

Characteristics of patients with chronic subdural hematoma exacerbation after the first treatment

Seven patients (36.8%) developed CSH exacerbation after the first treatment (CSH exacerbation group). Six patients underwent EBP first followed by an additional EBP and/or CSH surgery 1 or 2 days later. One patient (Case 7) underwent repeated CSH surgery before the correct diagnosis was obtained and an additional CSH surgery immediately after EBP on the same day after the diagnosis was obtained. Twelve patients did not develop CSH exacerbation after the first treatment (non-CSH exacerbation group) [Table 1].

Relationship between development of CSFH-associated CSH and low CFXIII activity

In a comparison of the CSH occurrence group and non-CSH occurrence group, a univariate analysis was performed to evaluate the relationship between the development of CSFH-associated CSH and low CFXIII activity. Low CFXIII activity was significantly associated with CSH occurrence (42.1% vs. 12.8%, $P = 0.003$) [Table 2].

Relationship between post-treatment CSH exacerbation and low CFXIII activity

In the CSH exacerbation group, five patients (71.4%) (Cases 3, 4, 5, 6, and 7) had low CFXIII activity and

two (28.6%) had normal CFXIII activity. In the non-CSH exacerbation group; however, nine patients (75.0%) had normal CFXIII activity and three (25.0%) had low CFXIII activity. Even among patients with low CFXIII activity, three patients (Cases 10, 11, and 16) had no recurrence of CSH after the first treatment. In particular, Case 16 had a thick hematoma and low CFXIII activity, but did not develop exacerbation of the hematoma following CSH surgery immediately after EBP on the same day. However, the univariate analyses revealed that low CFXIII activity was significantly associated with CSH exacerbation. Other factors were not statistically significant [Table 3].

In the CSH exacerbation group, all five patients with low CFXIII activity (Cases 3, 4, 5, 6, and 7) received intravenous injection of CFXIII. Three patients experienced no recurrence of CSH just after the second treatment (Cases 3, 4, and 7), and two patients finally had no recurrence of CSH after repeated XIII injections and additional treatments (Cases 5 and 6).

Representative case (Case 3)

Case 3 is a representative case, and his clinical course is shown in Figure 2a. This 51-year-old man developed orthostatic headache and dizziness. Axial MRI with fluid attenuated inversion recovery and CT demonstrated thin CSHs bilaterally [Figure 2b and c]. T1-weighted MRI with gadolinium showed diffuse meningeal enhancement [Figure 2d]. No displacement of the brain stem was seen on mid-sagittal T2-weighted MRI [Figure 2e]. RI cisternography revealed no direct sign of CSFH; however, we observed an indirect sign of CSFH: No visualization of RI activity over the cerebral convexities even after 24 h of the intrathecal injection [Figure 2f]. CFXIII activity was low at 53.1%, because the CSHs were thin, the patient underwent EBP only. His symptoms disappeared just after the EBP; however, he experienced a continuous headache on the 5th day after EBP, and CT demonstrated that the CSHs had slightly increased in size [Figure 2g]. On the 12th day after the first EBP, the CSHs had further increased in size [Figure 2h], and mid-sagittal T2-weighted MRI showed backward displacement of the brain stem [Figure 2i]. After intravenous administration of CFXIII concentrate, the patient underwent a second EBP. As CSHs were thick, CSH surgery was also performed immediately after EBP on the same day. The post-CSH surgery course was uneventful. CT on the 18th day after the second treatment revealed complete disappearance of the CSHs [Figure 2j], and mid-sagittal T2-weighted MRI on the 48th day the second treatment revealed disappearance of the brain stem displacement [Figure 2k].

Table 2: Relationship between development of CSH associated with CSFH and CFXIII activity

	Development of CSH		*P*
	(+) *n*=19	(-) *n*=187	
CFXIII activity (%)			0.003*
≥70%	11 (57.9%)	163 (87.2%)	
<70%	8 (42.1%)	24 (12.8%)	

CSH: Chronic subdural hematoma, CFXIII: coagulation factor XIII, *Statically significant *P*<0.05

DISCUSSION

The present study revealed that low CFXIII activity was significantly associated with CSH occurrence vs. non-occurrence (42.1% vs. 12.8%, respectively; $P = 0.003$). Bosche B *et al.*[5] reported that patients with spontaneous CSHs showed significantly lower CFXIII activity than those with non-spontaneous CSHs and concluded that CFXIII deficiency might play a pathophysiological role

Table 3: Univariate analysis of risk factors for CSH exacerbation after EBP and/or CSH surgery

Patient variables	CSH exacerbation group (*n*=7)	CSH non-exacerbation group (*n*=12)	*P*
Male (%)	6 (85.7%)	5 (41.7%)	0.051
Age (years)	49.1±6.33	45.8±11.9	0.325
CSH Site			
Unilateral	1 (14.3%)	6 (50%)	0.105
Bilateral	6 (85.7%)	6 (50%)	0.105
Hematoma thickness at first treatment			
Thin	6 (85.7%)	8 (66.7%)	0.348
Thick	1 (14.3%)	4 (33.3%)	0.348
Direct findings+	4 (57.1%)	4 (33.3%)	0.311
Indirect findings+	7 (100%)	12 (100%)	-
Diffuse meningeal enhancement+	6 (85.7%)	11 (91.7%)	0.688
Descent of brain+	4 (57.1%)	2 (16.7%)	0.068
CFXIII activity (%)			
≥70%	2 (28.6%)	9 (75%)	0.046*
<70%	5 (71.4%)	3 (25%)	

EBP: Epidural blood patch, CSH: Chronic subdural hematoma, CFXIII: Coagulation factor XIII, * Statically significant *P*<0.05

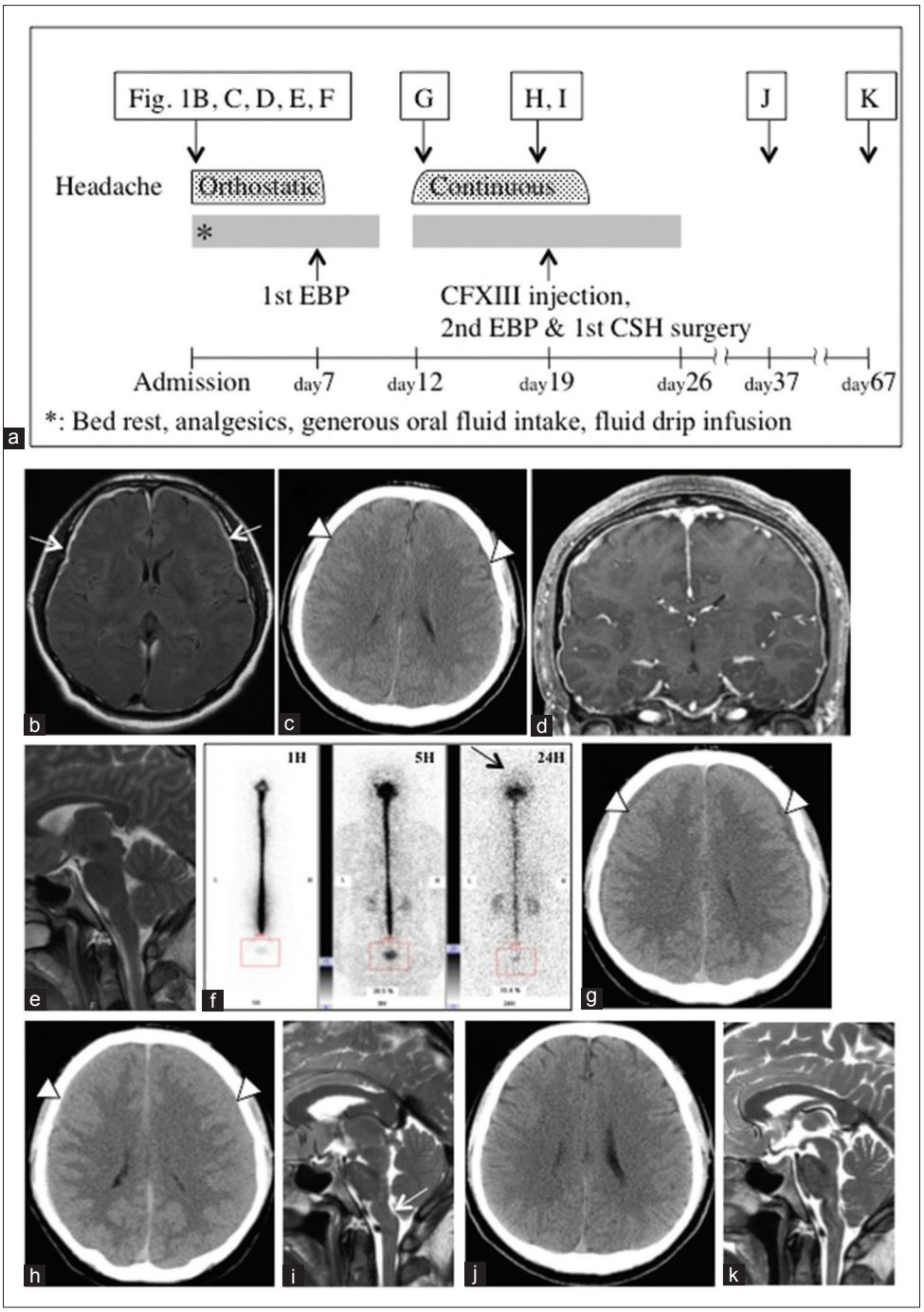

Figure 2: (a) Clinical course. (b) MRI with FLAIR on admission showed thin chronic subdural hematomas (CSHs) on both sides (white arrows). (c) Axial CT depicted bilateral thin CSHs. (d) Coronal T1-weighted MRI with gadolinium showed diffuse meningeal enhancement. (e) No displacement of the brain stem was seen on the mid-sagittal T2-weighted MRI. (f) Although RI cisternography 1, 5, and 24 h after intrathecal injection of RI revealed no apparent cerebrospinal fluid leakage, no visualization of RI activity over the cerebral convexities was seen even after 24 h. (g) Axial CT scan on the 5th day after EBP demonstrated that the CSHs were slightly increased in size. (h) Axial CT scan on the 12th day after the first EBP depicted that the thin CSHs had apparently increased. (i) Mid-sagittal T2-weighted MRI on the 12th day after the first EBP showed backward displacement of the brain stem. (j) Axial CT scan on the 18th day after the second treatment revealed complete disappearance of the CSHs. (k) Disappearance of the brain stem displacement was seen on mid-sagittal T2-weighted MRI on the 48th day after the second treatment. Abbreviations within figure: EBP, epidural blood patch; CFXIII, coagulation factor XIII; CSH, chronic subdural hematoma

in the development of spontaneous CSHs. CFXIII is involved in protection against fibrinolytic enzymes[13] and potentially in angiogenesis.[7] Thus, lower CFXIII activity destabilizes the vessel endothelium, and in patients with CSFH, disturbs the repair of CSF leak sites[14] and may cause intractable CSHs. However, because not all

patients with low CFXIII activity developed CSHs in our study, we concluded that low CFXIII activity may not be the sole factor, but instead one of the risk factors for the development of CSFH-associated CSH.

To the best of our knowledge, a systematic study of the risk factors for CSFH-associated CSH exacerbation after treatment has not been performed. Previous authors[15,21] have speculated that CSH exacerbation occurs because the intracranial pressure changes dramatically after EBP and/or CSH surgery. Our univariate analyses indicated that among the potential risk factors, low CFXIII activity is a risk factor for CSH exacerbation after treatment. In patients with a CSH, considering the pre-existing fragile neovascularization of the membranes covering a potential spontaneous hematoma,[23] a decrease in CFXIII activity may result in further vascular leakage, breakdown of vessel integrity, and subsequent CSH recurrence.[5] Moreover, the CSH arising from the membranes and the subsequent coagulation could lead to auxiliary consumption of CFXIII due to blood loss.[8,22] These mechanisms may lead to formation of an intractable CSH even after appropriate treatment in patients with low CFXIII activity. Bosche *et al.*[5] reported that 6 of 18 patients with spontaneous CSH had significantly lower CFXIII activity and developed rebleeding events after hematoma evacuation. The authors concluded that CFXIII activity might predict rebleeding events after treatment.

Five of our patients with low CFXIII activity developed CSH exacerbation after treatment. All patients received CFXIII injection and had no recurrence of CSH. From the perspective of CSFH treatment, intravenous administration of CFXIII accelerates healing of CSF leak sites.[14] Despite the potential side effects of CFXIII injection, such as thrombosis, allergic reaction, and viral transmission, no adverse effects were seen in our patients. Since we did not have control study, it is reasonably safe to conclude that, for patients with lower CFXIII activity, CFXIII injection may help to prevent CSH exacerbation.

There are several limitations of the present study. First, the sample size was relatively small. Second, a variety of pathophysiologies associated with CSFH might affect the exacerbation of the hematoma. Despite low CFXIII activity, three patients (Cases 10, 11, and 16) had no recurrence of CSH after the first treatment. In particular, Case 16 (thick hematoma and low CFXIII activity) did not develop exacerbation of the hematoma following CSH surgery immediately after EBP on the same day. Third, we only focused on CFXIII and other standard coagulant parameters were not considered. Fourth, whether CSFH patients without CSH underwent anticoagulant agents and had platelet dysfunction and liver disease or not were not examined. Therefore, further studies with larger cohorts should be conducted.

CONCLUSIONS

This preliminary study indicates that low CFXIII activity is one of the risk factors for the development of CSHs and exacerbation of CSHs after treatment in patients with CSFH. Intravenous injection of CFXIII may help to prevent CSH exacerbation. Thus, measurement of CFXIII activity could be considered in the management of intractable CSHs associated with CSFH.

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Conflicts of interest
There are no conflicts of interest.

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