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Laboratory Investigation

# Correlation of the Beta-Trace Protein and Inflammatory Cytokines with Magnetic Resonance Imaging in Chronic Subdural Hematomas : A Prospective Study

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**Objective :** Magnetic resonance imaging (MRI) of chronic subdural hematoma (CSDH) detects various patterns, which can be attributed to many factors. The purpose of this study was to measure the level of interleukin-6 (IL-6), interleukin-8 (IL-8), and highly specific protein [beta-trace protein (βTP)] for cerebrospinal fluid (CSF) in CSDHs, and correlate the levels of these markers with the MRI findings.
**Methods :** Thirty one patients, treated surgically for CSDH, were divided on the basis of MRI findings into hyperintense and non-hyperintense groups. The concentrations of IL-6, IL-8, and βTP in the subdural fluid and serum were measured. The βTP was considered to indicate an admixture of CSF to the subdural fluid if βTP in the subdural fluid ($\beta TP_{SF}$)/βTP in the serum ($\beta TP_{SER}$) >2.
**Results :** The mean concentrations of IL-6 and IL-8 of the hyperintense group (n=17) of T1-WI MRI were 3975.1±1040.8 pg/mL and 6873.2±6365.4 pg/mL, whereas them of the non-hyperintense group (n=14) were 2173.5±1042.1 pg/mL and 2851.2±6267.5 pg/mL ($p$<0.001 and $p$=0.004). The mean concentrations of $\beta TP_{SF}$ and the ratio of $\beta TP_{SF}/\beta TP_{SER}$ of the hyperintense group (n=13) of T2-WI MRI were 7.3±2.9 mg/L and 12.6±5.4, whereas them of the non-hyperintense group (n=18) were 4.3±2.3 mg/L and 7.5±3.9 ($p$=0.011 and $p$=0.011).
**Conclusion :** The hyperintense group on T1-WI MRI of CSDHs exhibited higher concentrations of IL-6 and IL-8 than non-hyperintense group. And, the hyperintese group on T2-WI MRI exhibited higher concentrations of $\beta TP_{SF}$ and the ratio of $\beta TP_{SF}/\beta TP_{SER}$ than non-hyperintense group. These findings appear to be associated with rebleeding and CSF admixture in the CSDHs.

**Key Words :** Chronic subdural hematoma · Interleukin · Beta-trace protein · Magnetic resonance imaging.

## INTRODUCTION

The complex mechanism of pathogenesis for chronic subdural hematoma (CSDH) involves repetitive microhemorrhages from the neomembranes, inflammatory processes in the neomembranes, local hyperfibrinolysis, and cerebrospinal fluid (CSF) leakage into the subdural space[6,9,15,17,22,27,30,33]. As a result, many coagulofibrinolytic factors, inflammatory cytokines, angiogenic growth factors, and highly specific proteins for CSF [beta-trace protein (βTP)] have been associated with CSDHs[5,10,12,17,25,34], and some studies have suggested that various types of CSDHs, as observed on CT, are associated with coagulofibrinolytic factors, inflammatory cytokines, and angiogenic growth factors[5,12,19,23-26].

MRI of CSDHs provides more precise information about the localization, extent, and mass effect of a hematoma on adjacent structures. And, MRI findings of CSDHs are attributed to many factors including the age of the hematoma, the presences of rehemorrhage, and the hematocrit status in CSDHs[11]. However, there have been no reports to date on correlations between MRI findings and biomolecules in the CSDH.

The purpose of this study was to measure the levels of interleukin-6 (IL-6) and interleukin-8 (IL-8), as typical inflammatory cytokines in patients with a CSDH and correlate these markers with MRI signal intensity. In addition, we measured the concentration of βTP in the subdural hematoma and investigated whether CSF admixture to the CSDHs influenced MRI findings.

## MATERIALS AND METHODS

### Patient selection

Between January and December 2013, 48 consecutive patients had been admitted to our institute for surgical manage-

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ment of CSDH. Of these, 17 patients with the following risk factors were excluded from this study : long-term use of thrombolytics, anticoagulants, or anti-inflammatroy therapy or hemodialysis (n=12); concomitant infection, inflammatory, hematological or neoplastic disorders, liver dysfunction, dementia, coagulopathy, or diabetes mellitus (n=2); presence of a ventriculoperitoneal shunt for hydrocephalus (n=3). The remaining 31 patients were enrolled in this prospective study and provided written informed consent to participate in the study.

### Radiological imaging

Imaging was performed on high spiral CT systems and on 1.5 Tesla MR scanners before burr hole drainage. On the basis of CT scanning, the CSDHs were classified into 2 groups, a homogenous group and a heterogenous group, according to the classification system suggested by Park et al.[25] (Fig. 1). MRI of the CSDHs was classified into 4 groups, according to signal intensity suggested by Senturk et al.[29] : low, iso, high signal, and mixed intensity. Then we subdivided the four groups into two different groups : a hyperintense group and a non-hyperintense group (Fig. 2).

### Measurement of IL-6 and IL-8 by ELISA

Samples of the subdural hematoma and venous blood were obtained at burr hole drainage. The subdural hematoma sample was obtained through the dura mater with a disposable plastic syringe via a burr hole before the dural incision. Peripheral venous blood samples were also taken from the patients. All samples were collected into siliconized vaccum tubes containing protamine sulfate and ethylenediamine tetraacetic acid and were immediately centrifuged at 2500 to 3000 rpm for 10 minutes. The supernatants were stored in sealed polypropylene tubes at -70°C until analysis. Concentrations of IL-6 and IL-8 in the subdural fluid and venous blood were measured with an ELISA kit (R&D System Co, Minneapolis, MN, USA; dilution 1 : 100) using monoclonal antibodies.

### Measurement of βTP

The βTP is a marker highly specific for CSF, and more than 99% of the βTP is produced by the choroid plexus in the central nervous system, and is obtained in the CSF. The βTP concentration in CSF is 32 to 35 times higher than the βTP concentration in the serum ($\beta TP_{SER}$)[1,28]. Samples of subdural fluid with a βTP concentration in the subdural fluid ($\beta TP_{SF}$) at least twice as high as the $\beta TP_{SER}$ ($\beta TP_{SF}/\beta TP_{SER}>2$, corresponding to a rate of at least 5% CSF in the subdural fluid) were considered indicative of the presence of CSF in the subdural fluid. If the ratio of $\beta TP_{SF}/\beta TP_{SER}$ in the subdural fluid was <2, a CSF admixture to the subdural fluid was not considered to be present[13]. In addition, the concentration of βTP reflected the amount of CSF present in the CSDH[17].

Levels of βTP in the subdural fluid and serum were measured with an ELISA kit [Cayman Chemical, Ann Arbor, MI, USA, dilution 1 : 100 (subdural flu-

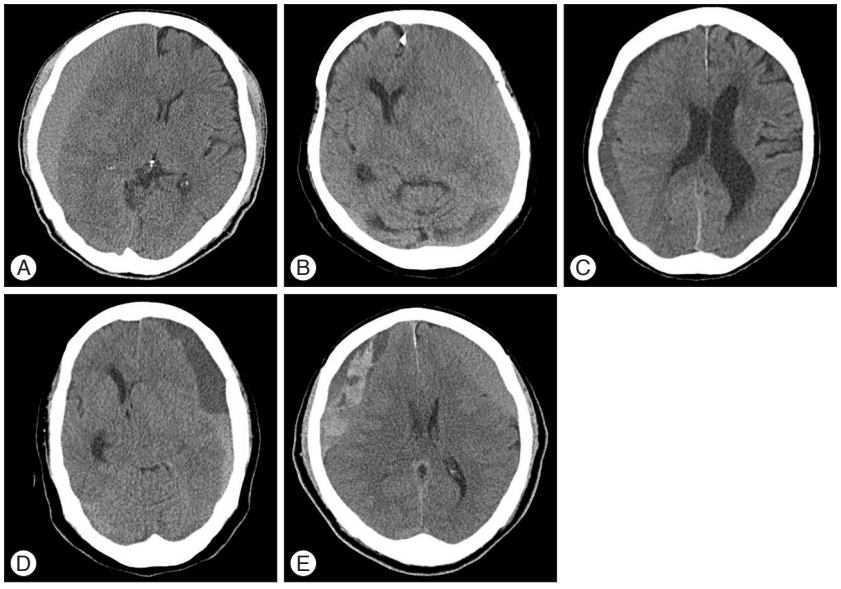


**Fig. 1.** Axial computed tomography scans revealing a homogenous group, with high density (A), isodensity (B), and low density types (C) and a heterogenous group, with the layering (D) and mixed density types (E).

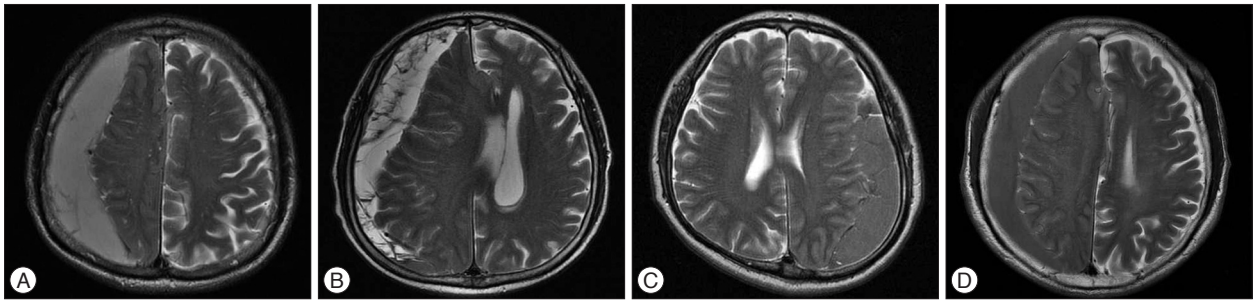


**Fig. 2.** Axial T2-weighted magnetic resonance imaging showing a hyperintense group, with homogenous (A) and mixed types (B) and a non-hyperintense group, with isointense (C) and hypointense types (D).

id), 1 : 10 (serum)] using monoclonal antibodies.

### Statistical analysis

The levels of IL-6, IL-8, and βTP in the CSDHs were compared between two groups on CT and MRI, respectively. Statistical analysis was performed using the chi-square test and Mann-Whitney test. Data are presented as the mean±standard deviation. All analyses were performed using SPSS 14.0 for Windows (SPSS Inc., Chicago, IL, USA). A $p$-value<0.05 was accepted as the threshold for statistical significance.

## RESULTS

### Clinical and radiological data

Thirty one patients were enrolled in the study and their main characteristics are summarized in Table 1. There were 23 men and 8 women, with ages ranging from 38 to 86 (average, 67.6 years). Head trauma during the week preceding admission was reported by 24 (77%) patients. The time interval between head injury and operation date ranged from 19 to 64 days (average, 40.3 days). All of the CSDH cases underwent burr hole drainage. The removal of the subdural hematomas resulted in a good recovery in all cases. Three (9.7%) patients underwent re-operation on the same side due to the recurrence of the CSDH. There were no statistically significant differences between a hyperintense group and a non-hyperintense group in terms of demographic characteristics, history of head injury, the time interval between trauma and operation, and recurrence.

The distribution of hematomas according to their CT and MRI characteristics is shown in Table 1 and 2. CT and MRI showed bilaterality of CSDH in 3 patients (9.6%), and mean CSDH thickness ranged from 8 mm to 36 mm (average, 20.9

**Table 1.** Patients' characteristics and radiologic findings

| Case No. | Age/sex | History of trauma | Days from trauma | Recurrence | Thickness (mm) | Bilateral CSDH | MRI intensity | | CT density |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | T1-WI | T2-WI | |
| 1 | 75/M | Yes | 38 | No | 36 | No | High | Low | Homogenous |
| 2 | 58/M | Yes | 64 | No | 29 | No | High | Low | Heterogenous |
| 3 | 80/F | No | None | No | 35 | No | High | Low | Heterogenous |
| 4 | 40/M | Yes | 45 | No | 13 | No | High | High | Homogenous |
| 5 | 66/M | Yes | 40 | No | 18 | No | Low | Low | Homogenous |
| 6 | 58/F | No | None | Yes | 20 | No | Low | High | Heterogenous |
| 7 | 62/F | Yes | 58 | No | 22 | No | Low | High | Heterogenous |
| 8 | 59/M | Yes | 30 | No | 20 | No | High | Low | Heterogenous |
| 9 | 68/M | No | None | No | 21 | No | High | High | Heterogenous |
| 10 | 74/M | Yes | 30 | No | 22 | No | Low | Low | Homogenous |
| 11 | 73/M | Yes | 25 | No | 16 | No | High | High | Heterogenous |
| 12 | 74/M | Yes | 37 | No | 15 | No | High | High | Heterogenous |
| 13 | 50/M | Yes | 62 | No | 23 | No | High | Low | Heterogenous |
| 14 | 80/F | No | None | No | 33 | No | High | Low | Heterogenous |
| 15 | 77/M | Yes | 32 | No | 20 | No | High | Low | Homogenous |
| 16 | 80/M | Yes | 19 | No | 18 | Yes | High | Low | Heterogenous |
| 17 | 82/F | Yes | 21 | No | 31 | No | Iso | Low | Homogenous |
| 18 | 86/M | Yes | 30 | No | 10 | No | High | High | Heterogenous |
| 19 | 71/M | No | None | No | 19 | No | Low | High | Homogenous |
| 20 | 38/M | Yes | 60 | No | 17 | No | Iso | High | Homogenous |
| 21 | 76/M | No | None | No | 24 | No | High | Low | Heterogenous |
| 22 | 72/M | Yes | 32 | No | 20 | No | High | High | Homogenous |
| 23 | 74/F | Yes | 30 | No | 21 | No | High | Low | Heterogenous |
| 24 | 72/M | Yes | 42 | No | 20 | No | Low | Low | Heterogenous |
| 25 | 72/F | No | None | No | 19 | No | Iso | Low | Heterogenous |
| 26 | 80/F | Yes | 45 | No | 8 | No | Low | High | Homogenous |
| 27 | 57/M | Yes | 64 | No | 9 | Yes | Iso | Low | Homogenous |
| 28 | 57/M | Yes | 44 | No | 27 | No | Iso | High | Homogenous |
| 29 | 64/M | Yes | 57 | No | 26 | No | High | Iso | Heterogenous |
| 30 | 71/M | Yes | 30 | Yes | 22 | No | Low | Low | Homogenous |
| 31 | 73/M | Yes | 31 | Yes | 13 | Yes | Low | High | Heterogenous |

M : male, F : female, CSDH : chronic subdural hematoma, MRI : magnetic resonance imaging, WI : weighted image, CT : computed tomography

**Table 2.** Distributions of hematomas according to characteristics of CT density and MRI intensity

| CT | T1-WI MRI | | T2-WI MRI | |
|---|---|---|---|---|
| | Hyperintense | Non-hyperintense | Hyperintense | Non-hyperintense |
| Homogenous (13) | 4 | 9 | 6 | 7 |
| Heterogenous (18) | 13 | 5 | 7 | 11 |

CT : computed tomography, WI : weighted image, MRI : magnetic resonance imaging

mm). Thirteen hematomas (42%) were homogenous and 18 (58%) were heterogenous on CT scans. According to the MRI, 17 (55%) of hematomas were hyperintense on T1-weighted image and 14 hematomas (45%) were hyperintense on T2-WI. There was no statistically significant difference between a hyperintense group and a non-hyperintense group in terms of bilaterality and thickness of CSDH, and no correlation between MRI and CT.

### Laboratory findings

All concentrations of IL-6, IL-8, and βTP from the CSDHs were higher than in the peripheral venous blood. The ratio of $\beta TP_{SF}/\beta TP_{SER}$ was >2 in 100% of the patients with a CSDH. We compared the concentrations and ratio between the groups for CT and MRI, respectively (Table 3).

In the T1-WI MRI, the mean concentrations of IL-6 and IL-8 for the hyperintense group (n=18) were 3975.1±1040.8 pg/mL and 6873.2±6365.4 pg/mL, respectively, whereas those for the non-hyperintense group (n=13) were 2173.5±1042.1 pg/mL and 2851.2±6267.5 pg/mL. For T1-WI MRI, the mean concentrations of IL-6 and IL-8 for the hyperintense group were significantly higher than the non-hyperintense group, respectively ($p$<0.001 and $p$=0.004).

For T2-WI MRI, the mean concentrations of $\beta TP_{SF}$ and the ratio of $\beta TP_{SF}/\beta TP_{SER}$ for the hyperintense group (n=13) were 7.3±2.9 mg/L and 12.6±5.4, whereas those for the non-hyperintense group (n=18) were 4.3±2.3 mg/L and 7.5±3.9. In T2-WI MRI, the mean concentration of $\beta TP_{SF}$ and the ratio of $\beta TP_{SF}/\beta TP_{SER}$ for the hyperintense group were significantly higher than the non-hyperintense group, respectively ($p$=0.011 and $p$=0.011).

In the CT scan, the concentration of IL-6 in the heterogenous group (3680.6±1238.6 pg/mL) was significantly higher than the homogenous group (2697.2±1355.9 pg/mL) ($p$=0.035). However, there were no significant differences between mean concentrations of IL-8, $\beta TP_{SF}$ and the ratio of $\beta TP_{SF}/\beta TP_{SER}$ from CSDHs observed between the two groups ($p$=0.135 and $p$=0.679).

## DISCUSSION

The pathogeneses of CSDHs remain unclear. However, the inflammatory and angiogenic process of the neomembrane, along with the cycle of rebleeding, coagulation, and fibrinolysis are hypothesized to be at the center of the development and progression of CSDHs[6,9,15,17,22,27,30,33]. As a result, many molecular markers for CSDHs have been demonstrated, and they can be classified as follows : 1) tissue plasminogen activator, plasminplasmin inhibitor complex, thrombomodulin, fibrinogen and D-dimer in relation with coagulation and fibrinolytic activity[12,19,23,25,26]; 2) IL-6, IL-8, IL-10 and tumor necrosis factor-α in relation with inflammatory process in the neomambrane[5,10,12]; and 3) vascular endothelial growth factor, basic fibroblast growth factor and platelet-derived growth factor in relation with angiogenic activity of the neomembrane[10,33,34]. And, Kristof et al.[17] recently reported the presence of the βTP in the subdural hematoma, and suggested that CSF leakage into the subdural space is present in the vast majority of patients (94%) with CSDH, and CSF leakage could be involved in the pathogenesis of CSDH.

Some studies have suggested that there were significant differences between molecular markers according to the various types of CSDHs, as identified on CT scans. Frati et al.[5] reported that in the trabecular and layering types of CSDHs, the concentrations of IL-6 and IL-8 were increased. Nomura et al.[23] and Park et al.[25] described higher fibrinogen and higher D-dimer levels in the layering and mixed density types. However, the relationship between biomolecules in CSDHs and MRI has not yet been reported, despite the more precise information this would give. In our study, we found higher levels of IL-6 and IL-8 in the T1-WI MRI hyperintense group of CSDHs and higher levels of βTP in the T2-WI MRI hyperintense group of CSDHs, and described the association between levels of these markers and findings on MRI.

CSDHs seem to present the typical features of chronic inflammatory processes. The outer membrane of a CSDH is a source of some cytokines, and IL-6 and IL-8 were demonstrated in the subdural hematoma. IL-6 increases vascular permeability through the enlargement of gaps between endothelial cells, and IL-8 contributes to the growth of immature capillaries with fibrinolytic activity[14,21]. Frati et al.[5] reported that the concentrations of IL-6 and IL-8 were increased in the heterogenous groups of CSDHs on CT scans, and suggested that these findings on CT may be associated with rebleeding of CSDHs.

On MRI, the hematocrit, mehemoglobin and free $Fe^{3+}$ levels are major factors causing prominent shortening in relaxation times, thus showing hyperintensity on T1-WI[3]. Hyperintensity on T1-WI generally represents methemoglobin, a typical component of a subacute hematoma[7,8]. CSDHs may be slightly hypointense to isointense relative to grey matter on T1-WI. Fobben et al.[4] postulated that these signal intensity changes result from a decrease in free methemoglobin concentration, either by dilution, absorption and/or degradation. However, the persistence of hyperintensity beyond its expected time interval, typical

**Table 3.** The levels of IL-6, IL-8, βTP, and the ratio of $\beta TP_{SF}/\beta TP_{SER}$ in chronic subdural hematoma and peripheral venous blood by classification of CT and MRI pattern

| | T1-WI MRI | | | T2-WI MRI | | | CT | | |
|---|---|---|---|---|---|---|---|---|---|
| | High (n=17) | Non-high (n=14) | *p* value | High (n=13) | Non-high (n=18) | *p* value | Homogenous (n=13) | Heterogenous (n=18) | *p* value |
| IL-6 | | | | | | | | | |
| Subdural fluid (pg/mL) | 3975.1±1040.8 | 2173.5±1042.1 | <0.001* | 3285.1±1300.3 | 3231.0±1445.3 | 0.902 | 2697.2±1355.9 | 3680.6±1238.6 | 0.035* |
| Serum | 4.4±4.4 | 5.7±8.9 | 0.658 | 6.1±8.1 | 3.7±2.9 | 0.927 | 2.9±2.6 | 5.9±6.9 | 0.305 |
| IL-8 | | | | | | | | | |
| Subdural fluid (pg/mL) | 6873.2±6365.4 | 2851.2±6267.5 | 0.004* | 7528.6±8380.2 | 3495.1±4316.5 | 0.242 | 3694.2±6328.8 | 6264.4±5673.4 | 0.135 |
| Serum | 4.5±4.0 | 3.1±2.1 | 0.134 | 3.0±1.6 | 4.6±4.2 | 0.325 | 3.1±2.0 | 4.5±4.1 | 0.195 |
| β-trace protein | | | | | | | | | |
| Subdural fluid (mg/L) | 5.0±3.1 | 6.2±2.7 | 0.211 | 7.3±2.9 | 4.3±2.3 | 0.011* | 5.2±2.8 | 5.8±3.1 | 0.679 |
| Serum | 0.6±0.2 | 0.6±0.2 | 0.594 | 0.6±0.1 | 0.6±0.2 | 0.798 | 0.6±0.1 | 0.6±0.2 | 0.650 |
| $\beta TP_{SF}/\beta TP_{SER}$ ratio | 8.6±5.6 | 10.9±4.6 | 0.125 | 12.6±5.4 | 7.5±3.9 | 0.011* | 9.0±4.3 | 10.0±5.9 | 0.890 |

Value represents mean±standard deviation. *Significant difference ($p$<0.05) between groups by Mann-Whitney U test. IL : interleukin, βTP : β-trace protein, CT : computed tomography, WI : weighted image, MRI : magnetic resonance imaging, SF : subdural fluid, SER : serum

of the subacute intracranial hematoma, is a common observation, which is probably due to repeated hemorrhage[29]. Our data showed significantly high IL-6 and IL-8 levels in CSDHs, with hyperintensity on T1-WI MRI. And, this finding is similar with the high IL-6 level in the heterogenous group on CT scans. Therefore, high IL-6 and IL-8 levels in CSDHs may be a marker for the hyperintense group on T1-WI MRI, corresponding to a likely probability of recent rebleeding.

The βTP (prostaglandin-D2-synthase) is an ideal marker to identify a CSF admixture into the subdural fluid. More than 99% of βTP is contained within the CSF, and it is synthesized mainly by the choroid plexus of the CNS, whereas a very small amount of βTP is synthesized outside the CNS, mainly in the heart and blood. The βTP concentration is 32–34 times higher in the CSF (8–40 mg/L) compared to the serum (0.3–0.76 mg/L)[1,28].

Kristof et al.[17] suggested that $\beta TP_{SF}/\beta TP_{SER}>2$ corresponded to a rate of at least 5% CSF in the subdural fluid, and that this was considered indicative of the presence of CSF in the subdural fluid. And, they reported that CSF was present in the subdural fluid in the vast majority (62 of 67 patients; 93%) of patients with CSDH, and that the concentration of βTP reflected the amount of CSF present. Although the mechanism of CSF leakage (and its component βTP) into the subdural space in CSDHs remains unknown, two hypotheses were suggested in the literature : 1) CSF (and its component βTP) enters the subdural space of CSDH through the arachnoid tear that acts as a valve[2,18,31,32] and 2) CSF (and its component βTP) crosses the inner membrane of the CSDH into the subdural space by diffusion/exudation[6,20].

In the majority of cases, a CSDH appears hyperintense on T2-WI because blood degradation products, especially methemoglobin, appear hyperintense on such images[16]. However, our study demonstrated that the mean concentration of $\beta TP_{SF}$ and the ratio of $\beta TP_{SF}/\beta TP_{SER}$ in the T2-WI MRI hyperintense group were significantly higher than in the non-hyperintense group, and indicated more CSF admixture to the CSDHs in the T2-WI MRI hyperintense group. Therefore, the higher subdural concentrations of βTP and the higher ratio of $\beta TP_{SF}/\beta TP_{SER}$ may provide good markers for CSDHs for the hyperintense group on T2-WI MRI, and CSF admixture to the CSDHs may provide another possibility for the T2-WI MRI hyperintensity for CSDHs.

In the present study, we did not conduct a comparative study between patients with and without a recurrence, because the recurrent cases (9.7%) were fairly low. In future, a prospective study is needed to evaluate the relationship between prognostic markers and the recurrence rate based on the MRI findings.

## CONCLUSION

In this paper, the subdural concentrations of IL-6 and IL-8 in CSDHs were relatively higher in the T1-WI MRI hyperintense group compared to the non-hyperintense group, and we suggested that the subdural concentrations of IL-6 and IL-8 in CS-

DHs may be a marker for the hyperintense group on T1-WI MRI, corresponding to a likely probability of recent rebleeding. Additionally, the subdural concentration of $\beta TP_{SF}$ and the ratio of $\beta TP_{SF}/\beta TP_{SER}$ in CSDHs were relatively higher in the T2-WI MRI hyperintense group compared to the non-hyperintense group, and reflected more CSF admixture to the CSDH. Therefore, CSF admixture to the CSDHs may provide another possibility for the T2-WI MRI hyperintensity for CSDHs.

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