Measurement of Inflammatory Cytokines and Thrombomodulin in Chronic Subdural Hematoma

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Abstract

Inflammation and the coagulation system may influence the genesis of chronic subdural hematoma (CSDH). The appearance of CSDH on computed tomography (CT) varies with the stage of the hematoma. This study investigated the pathogenesis and the recurrence of CSDH by comparing cytokine levels with the CT features of CSDH in 26 patients with 34 CSDHs who underwent single burr-hole surgery at our hospital between October 2004 and November 2006. The hematoma components removed during the procedure were examined, and the hematoma serum levels of cytokines measured such as thrombomodulin (TM), interleukin-6 (IL-6), tumor necrosis factor- α (TNF α), and interleukin-10 (IL-10). Using CT, mixed density hematomas were distinguished from other homogeneous hematomas, and found that the TM level was significantly higher in mixed density hematomas than in homogeneous hematomas ($p = 0.043$). Mixed density hematomas were classified into three subtypes (laminar, separated, and trabecular hematomas). The TM level was significantly higher in laminar and separated hematomas than in other hematomas ($p = 0.01$). The levels of IL-6, TNF α , and IL-10 were extremely high, but showed no significant differences in relation to the CT features. Mixed density hematomas had high recurrence rate, as reported previously, and TM level was high in mixed density hematomas such as laminar and separated mixed density hematomas. The present findings suggest that the types of CSDH associated with high TM levels tend to have higher recurrence rate.

Key words: chronic subdural hematoma, computed tomography, cytokines, thrombomodulin, interleukin

Introduction

Chronic subdural hematoma (CSDH) commonly requires neurosurgical treatment, and often recurs after surgery. Previous studies have suggested that local anticoagulation and inflammatory changes may influence the pathogenesis of CSDH, although the process has not been clearly elucidated.^{16,28,32,35,38} The transformation of traumatic subdural hygromas into CSDH has been discussed in several studies.^{7,23}

Computed tomography (CT) of CSDH often shows changes in the components of hematomas, and there may be an association between CT appearance and altered cytokine levels in CSDH.^{15,19,20} In particular, thrombomodulin (TM) has an anticoagulatory function and is expressed after endothelial cell injury.^{5,10}

TM has been measured in hematomas and has been implicated in the expansion of CSDH.¹⁸ However, no studies have evaluated the relationship between TM in CSDH and the CT characteristics. Many studies have found that the recurrence rate of CSDH is correlated with the CT findings.

The present study measured the TM levels in CSDH with various CT findings, and investigated the relationship between TM level in CSDH and recurrence of CSDH. The inflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor- α (TNF α), as well as the anti-inflammatory cytokine interleukin-10 (IL-10) were also measured. The CT appearance of the lesions were also evaluated.

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Materials and Methods

This study included 26 patients, 22 men and 4 women aged 32–98 years (mean 73.8 years), with 34 CSDHs treated in our hospital from October 2004 to November 2006. Six patients had bilateral hematomas and two patients had recurrence of hematoma. The mean Glasgow Coma Scale score of patients on admission was 13.5 (range 3–15). No patient had coagulopathy or systemic inflammatory changes detected by blood testing or in their past medical history. The diagnosis of CSDH was established using CT in all cases. The CT appearance of hematomas was evaluated according to density and internal architecture. Hematomas were classified into low density (6 hematomas), iso density (10 hematomas), and mixed density (18 hematomas). No patient had a high density hematoma. Additionally, low, iso, and high density hematomas were characterized as the homogeneous type, and mixed density hematomas were classified as laminar (5 hematomas), separated (9 hematomas), or trabecular types (4 hematomas). Mixed density hematomas were subdivided because of the changes in appearance by the point of development.^{19,20} Laminar type hematomas had a thin high density layer along the inner membrane, separated type hematomas contained two components of

different densities with a clear boundary, and trabecular type hematomas had a high density septum running between the inner and outer membranes on a mixed density background. Figure 1 demonstrates examples of these CT subtypes. The CT classification of hematomas was based on discussion in our institution by three or more qualified neurosurgeons, certified by the Japan Neurosurgical Society. After diagnosis, single burr-hole drainage of the hematoma was performed. The hematoma serum removed during this procedure was separated by centrifugation at 3000g for 10 minutes and stored at -70°C until analysis.

Enzyme immuno assay was used to measure TM (normal range 2.1–4.1 FU/ml in male, 1.8–3.9 FU/ml in female), chemiluminescent enzyme immunoassay to measure IL-6 (normal range ≤ 4.0 pg/ml), and enzyme-linked immunosorbent assay to measure IL-10 (normal range ≤ 5 pg/ml) and $\text{TNF}\alpha$ (normal range 0.6–2.8 pg/ml). The values of IL-6 and IL-10 were expressed as the median, interquartile range, and range. The values of TM and $\text{TNF}\alpha$ were expressed as the mean $\pm$ standard deviation (SD), and the Mann-Whitney test was used to compare the various stages of hematoma. Statistical analysis was performed using commercially available statistical software (SPSS 16.0.2; IBM, Armonk, New York, USA).

This study was conducted in accordance with the ethical standards of the Nippon Medical School Hospital ethics committee. All participants provided written informed consent.

Results

Table 1 provides an overview of patient characteristics (age, sex, clinical symptoms on admission, midline shift on CT, and postoperative recurrence). Neither age nor sex affected the values of any cytokines. The levels of TM, IL-6, IL-10, and $\text{TNF}\alpha$ in hematomas were higher than normal values; in

Fig. 1 Computed tomography scans demonstrating examples of three types of mixed density chronic subdural hematoma: laminar (A), separated (B), and trabecular (C) types.

Table 1 Overview of patient characteristics

	Low density hematoma (n = 6)	Iso density hematoma (n = 10)	Mixed density hematoma (n = 18)
Mean age (range), yrs	73.83 (56–92)	70.8 (32–92)	75.44 (33–98)
Sex (male/female)	5/1	9/1	15/3
Mean GCS score (range)	12.17 (3–15)	14.3 (12–15)	13.44 (8–15)
Paresis	3	4	14
Aphasia or dysarthria	1	3	3
Midline shift	4	5	9
Recurrence	1	0	1

GCS: Glasgow Coma Scale.

particular, the levels of IL-6, IL-10, and TNF α were markedly higher (Tables 2 and 3). The values of IL-6, IL-10, and TNF α showed no significant differences with CT density and appearance. The level of TM was significantly higher in mixed density hematomas than in homogeneous hematomas ($p < 0.05$) (Fig. 2). The average TM level was 4.9 ± 2.0 FU/ml (mean $\pm$ SD) in mixed density hematomas ($n = 18$) and 4.3 ± 3.3 FU/ml in homogeneous hematomas ($n = 16$) ($p = 0.043$).

The value of TM was 6.2 ± 2.0 FU/ml in laminar hematomas ($n = 5$), and 3.5 ± 0.8 FU/ml in trabecular hematomas ($n = 4$) ($p = 0.026$). No differences were found between other subtypes of mixed density hematomas (laminar, separated, and trabecular types). Laminar and separated hematomas may have similarly high recurrence rates,¹⁹⁾ and we found significantly higher TM values in laminar and separated hematomas compared with other types ($p < 0.05$) (Fig. 3). The TM value was 5.3 ± 2.0 FU/ml in laminar and separated hematomas ($n = 14$) and 4.2 ± 2.9 FU/ml in homogeneous and trabecular hematomas ($n = 20$) ($p = 0.01$).

Discussion

CSDH shows changes in CT density with time. The initial stage appears as low density on CT, the mature stage as iso or high density, the progressive stage as mixed density, and the resolving stage as

Table 2 Values of thrombomodulin (TM) and tumor necrosis factor- α (TNF α) in chronic subdural hematomas

Hematoma	TM (FU/ml)	TNF α (pg/ml)
Low density ($n = 6$)	4.7 ± 4.4	8910.0 ± 7708.1
Iso density ($n = 10$)	4.1 ± 2.7	8763.0 ± 4810.0
Mixed density ($n = 18$)	4.9 ± 2.0	8136.1 ± 4113.0

Values are means $\pm$ standard deviation. Normal range of TM (enzyme immuno assay): 2.1–4.1 FU/ml in male, 1.8–3.9 FU/ml in female. Normal range of TNF α (enzyme-linked immunosorbent assay): 0.6–2.8 pg/ml.

Table 3 Values of interleukin-6 (IL-6) and interleukin-10 (IL-10) in chronic subdural hematomas

Hematoma	IL-6 (pg/ml)	IL-10 (pg/ml)
Low density	17900/6060–22525/3210–96900	22/3.75–38.75/2–271
Iso density	10100/5535–19600/2080–78200	13/5.5–60/2–120
Mixed density	12450/7835–28650/1310–104000	28.5/8.75–81.75/2–217

Values are median/interquartile range/range. Normal range of IL-6 (chemiluminescent enzyme immunoassay): ≤ 4.0 pg/ml. Normal range of IL-10 (enzyme-linked immunosorbent assay): ≤ 5.0 pg/ml.

Fig. 2 Thrombomodulin (TM) level (mean $\pm$ standard deviation) in mixed density hematomas and homogeneous hematomas. * $p < 0.05$. CT: computed tomography.

Fig. 3 Thrombomodulin (TM) level (mean $\pm$ standard deviation) in laminar and separated hematomas versus homogeneous and trabecular hematomas. * $p < 0.05$. CT: computed tomography.

relatively low density or low density without mass sign.^{15,30)} Some studies have grouped low, iso, and high density hematomas as a homogeneous stage, whereas the laminar stage may be a subtype of the homogeneous stage.¹⁹⁾ However, this study classified laminar hematomas as a subtype of mixed density hematomas, as classification of CSDH on CT has varied between studies.^{20,30)}

CSDH was originally described as an inflammatory disease, using the term “pachymeningitis hemorrhagica interna,”³⁶⁾ but the causative factor of CSDH is now known to be trauma, not inflammation.³³⁾ Recently, some studies have highlighted the relationship between local inflammation in CSDH and the mechanism of initiation and propagation of CSDH.^{2,4)} Subdural fluid from patients with CSDH contained a significantly higher level of TNF α and IL-6 than that found in blood, so that the cytokines in the subdural fluid may not permeate from the blood but are synthesized and released in situ from cells facing the subdural space or from inflammatory cells infiltrating into the space, where local and specific inflammation occurred.²⁹⁾ IL-6 is a pleiotropic cytokine that influences immune and inflammatory responses and is one of the major physiological mediators of the acute phase reaction.^{14,24)} IL-6 can cause enlargement of the gap junction between endothelial cells and can increase vascular permeability.^{29,39)} We found high levels of IL-6 and TNF α , which are inflammatory cytokines, in hematomas. However, we did not find any significant differences between the various IL-6 values in hematomas classified by CT appearance, nor between the TNF α values.

The present study found that the level of IL-10, another anti-inflammatory cytokine, was higher than normal but did not vary significantly according to the CT density or appearance of hematomas. The levels of IL-6 and IL-10 were measured in the subdural fluid obtained from patients with CSDH, and found that patients in the low IL-10 group tended to have separated hematomas on CT, suggesting that IL-10 acts as a deactivator of inflammation in the pathogenesis of CSDH.³⁷⁾ The values of IL-6, TNF α , and IL-10 found in our data were far higher than those obtained by several previous studies. In our study, the value of IL-6 was 2549.0 ± 395.9 pg/ml or 1321.0 ± 258.8 pg/dl; the value of TNF α was 41.1 ± 8.8 pg/ml; and the value of IL-10 was 56.4 ± 96.4 pg/dl.^{8,11,29,37)} Our study design did not allow us to determine the role of inflammatory change in hematomas, but the markedly elevated levels of inflammatory and anti-inflammatory cytokines in hematomas were particularly interesting findings. Our patients did not have inflammatory basic diseases or im-

munological disorders, so the reasons for the markedly elevated levels of cytokines were unclear.

TM is a thrombin receptor on capillary endothelial cells that inhibits blood clotting by forming a complex with thrombin and activated protein C.^{5,6,21)} Vascular endothelial injury increases the plasma-soluble TM level.^{10,31)} The plasma-soluble TM level was higher in hematomas than in peripheral blood ($p < 0.0001$), suggesting that the sinusoidal vessels in the outer membrane of CSDH were continuously damaged and TM was expressed, which triggered hemorrhaging from the outer membrane.¹⁸⁾ TM inhibits hemostatic thrombus formation in the hematoma, so the CSDH continued to expand without coagulation. TM levels in hematomas were compared with the levels in peripheral blood, but the relationship between TM values and CT findings in hematomas was not evaluated.¹⁸⁾ In this study, we compared TM values in hematomas with CT density and appearance of the hematomas.

Recurrence after surgical treatment is common and several studies have reported average rates of recurrence of 5–30%.^{1,3,26)} In an attempt to reduce the recurrence rate, various surgical methods have been used with different number of burr holes, duration of drainage, irrigation technique, and several other factors.⁴⁰⁾

In the present study, we performed single burr hole surgery, and removed and irrigated the hematoma, but because only two patients had recurrence (1 low density hematoma, 1 laminar type hematoma) during this investigation period, we could not analyze recurrence rates. The low density hematoma recurred as trabecular type hematoma, and the laminar type hematoma recurred as iso density hematoma. We classified hematomas into three density subtypes and measured the TM values. The recurrence rate of hematoma types have been reported as homogeneous 15%, laminar 19%, separated 36%, and trabecular 0%.¹⁹⁾ In homogeneous hematomas, differences in CT density did not affect the recurrence rate.³⁴⁾ Mixed density hematomas had a high recurrence rate, and the recurrence rate of the separated type was highest and that of the trabecular type was lowest.^{9,12,19,20,25,29)} Hyperfibrinolysis might be involved, as the fibrinogen and d-dimer levels in heterogeneous hematomas were higher than those in homogeneous hematomas.²²⁾

The present study found that TM values in separated and laminar hematomas were significantly higher than in homogeneous and trabecular hematomas, and the recurrence rate of separated and laminar hematomas is known to be significantly higher than that of other hematomas.¹⁹⁾ Therefore, we suggest that hematomas with high TM values tend to

present as mixed density hematomas (particularly laminar and separated) on CT, and may have a higher recurrence rate.

Review of other patient characteristics than CT findings showed a significant effect of sex on TM levels; concentrations were higher in males compared to females.²⁷⁾ However, our study found neither age nor sex affected the values of any cytokines. Similar to previous findings, 29 (85.3%) of our hematomas were males and 5 (14.7%) were females.¹³⁾ Mean age (73.8 years) of our patients was also similar to other studies.^{13,17)}

In conclusion, we found high levels of TM, IL-6, IL-10, and TNF α in the hematoma contents of CSDH. Evaluation of these cytokine levels according to CT appearance found only the TM values showed significant differences. However, the SD of the TM values was high, indicating wide dispersion of TM, so we will continue our investigation with more cases. Therefore, at this time, it may be more correct to say that we have trends in the high level of TM values with CT appearance rather than significant differences in TM values. Local inflammatory changes must have some effect on the pathogenesis of CSDH, but we were unable to clearly delineate the involvement of inflammatory and anti-inflammatory cytokines in this study. As reported previously, mixed density hematomas had a high recurrence rate, and TM level was high in mixed density hematomas in our study. Considering this relationship, we suggest that the types of CSDH associated with high TM values (mixed density, laminar, and separated hematomas) tend to have higher recurrence rates. The TM level can be measured objectively, in contrast to the subjective CT appearance, so may be a good index for anticipating the recurrence of CSDH. We consider that the pathogenesis is likely to involve endothelial cell injury at the outer membrane of CSDH resulting in increased TM level, with resulting higher anticoagulant function increasing the hematoma size and causing the recurrence of CSDH. Therefore, medication which inhibits TM may potentially decrease the recurrence rate of CSDH. Clinicians treating mixed density, laminar, and separated type hematomas, which may have high TM values, should be aware of the increased risk of recurrence.

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