The role of exudation in chronic subdural hematomas

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Object. Chronic subdural hematomas (SDHs) are a local inflammatory process that causes the formation of a granulation tissue often referred to as the external or outer membrane. This membrane has abnormally permeable macrocapillaries. Therefore, exudation from the macrocapillaries in the outer membrane of chronic SDH may play an important role in the enlargement of chronic SDH. In this study, the authors investigated the role of exudation in chronic SDH.

Methods. The authors examined 24 patients (16 men and eight women; age range 38–86 years [mean age 61.4 years]) with 27 chronic SDHs. The clinical status of the patients was evaluated according to the classification described by Markwalder. The diagnosis was established on computed tomography (CT) scans in all cases. The authors also used the Nomura Classification for judging the lesion’s appearance on CT scans. Immediately after the diagnosis, all patients were administered 20 mCi (740 mBq) technetium-99m human serum albumin. Four hours later, blood and SDH samples were taken and radioactivity levels were measured in each. The ratio of activity of the samples taken from chronic SDH to the radioactivity of blood was determined as a percentage and defined as the exudation rate. On the follow-up CT scan obtained on postoperative Day 20, subdural collections thicker than 5 mm were determined to be reaccumulation.

Results. The correlations between the exudation rate and age of the patients, clinical grades, CT appearances, and amount of reaccumulation were investigated. In this series the average exudation rate was 13.24% (range 2.05–28.88%). The mean exudation rates according to the macrocapillaries assigned to patients were as follows: Grade 0, 8.67 ± 5.64% (three patients); Grade 1, 5.07 ± 1.43% (eight patients); Grade 2, 17.87 ± 3.73% (seven patients); and Grade 3, 19.65 ± 7.67% (six patients). Exudation rates in patients with Grades 2 and 3 were significantly higher than those in Grades 0 and 1 (p < 0.05).

The mean exudation rate according to the lesion’s appearance on CT scans were found as follows: hypodense appearance, 6.55 ± 4.52% (eight patients); isodense appearance, 11.07 ± 6.32% (five patients); hyperdense appearance, 19.47 ± 13.61% (three patients); and mixed-density appearance, 17.40 ± 5.80% (nine patients). The differences among the groups were significant (p < 0.05). The average exudation rate was statistically higher in the patients with reaccumulation (16.30 ± 8.16%) than that in the patients without reaccumulation (9.96 ± 6.84%) (p < 0.05).

Conclusions. The exudation rate in chronic SDH is correlated with a higher clinical grade (Markwalder Grade 2 or 3), mixed-density CT appearance, and reaccumulation. Therefore, exudation from macrocapillaries in the outer membrane of chronic SDH probably plays an important role in the pathophysiology and the growth of chronic SDH.

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Key Words • albumin penetration • chronic subdural hematoma • exudation • technetium-99m human serum albumin

The cause of chronic SDHs is still not clear, although they are a common form of intracranial hematomas.10,11,13–16,18,19,22 However, authors of several studies have demonstrated that the development of chronic SDH is an inflammatory process that begins as a local inflammatory reaction of the dura mater to injury or external stimuli such as blood or CSF.3,4,13–15,22 This process causes neovascularization of the outer membrane of chronic SDH and vascular hyperpermeability. Ultrastructural studies of the outer membrane of chronic SDHs have shown that these neovascular structures called macrocapillaries are abnormally permeable and have large gap junctions with an absent or incomplete basement membrane.21,23,25 Therefore, exudation through the macrocapillaries may play an important role in the enlargement of a chronic SDH.

In this study, we measured the exudation into the chronic SDH using99mTc HSA, and the correlations between the CT appearance of chronic SDH, clinical grade of the patients, and recurrence and exudation rates were analyzed. The aim of the study was to detect the role of exudation in the development of chronic SDH.

Clinical Material and Methods

Study Design

This study comprised 24 patients (16 men and eight women; mean age 61.4 years, range 38–86 years) with 27 chronic SDHs treated in our clinic. Three patients had bilateral chronic SDHs; in these patients each side of bilateral chronic SDHs was considered as a single hematoma, because some bilateral chronic SDHs exhibited imaging differences from one side to the other.14 All patients had a plasma protein level and albumin/globulin ratio within the normal ranges (3.4–4.8 and 1.06–1.2 g/dl, respectively). Patients who were alcoholics, those who used anticoagulants, and those with other diseases were excluded.

Abbreviations used in this paper: CSF = cerebrospinal fluid; CT = computed tomography; HSA = human serum albumin; IL = interleukin; SDH = subdural hematoma; 99mTc = technetium-99m.
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The diagnosis of a chronic SDH was established on CT scans in all cases. The imaging appearance of these lesions was assessed according to the classification described by Nomura et al.\textsuperscript{18} We also used the neurological classification described by Markwalder et al.\textsuperscript{13,14} for the evaluation of the clinical status of the patients. Patients who were assigned a neurological grade of 4 were excluded from the study because they had undergone emergency surgery. Immediately after the diagnosis, all patients were administered 20 mCi (740 MBq) \textsuperscript{99m}Tc HSA. Four hours after the administration of \textsuperscript{99m}Tc HSA the patients underwent surgery following induction of general anesthesia, and the hematomas were evacuated through bur holes. A 1-ml sample was removed from the hematoma, and care was taken to avoid contamination by blood. At the same time a 1-ml peripheric blood sample was also obtained. The radioactivity of these samples was assessed using Packard Auto-Gamma, Cobra Gamma Counting System (Packard Instrument Co.), and the rate of exudation was calculated using the following formula: hematoma sample radioactivity/blood sample radioactivity \times 100.

After the evacuation of hematoma, a subdural drain was inserted and drainage was continued for 3 to 4 days according to the daily drainage volume. No negative pressure was applied to the drain. On postoperative Day 20 a follow-up CT scan was obtained in all patients, and a subdural collection thicker than 5 mm was determined to be a reaccumulation.

\textbf{Statistical Analysis}

Values are expressed as the means ± standard deviations. The differences between two parameters were tested using the Mann–Whitney U-test. Differences among multiple groups were tested by one-way analysis of variance followed by the Tukey test for multiple comparisons.

\textbf{Results}

The sex, age, clinical grade, appearance of hematomas on CT, exudation rate, and reaccumulation of the patients are shown in Table 1. Seventeen patients had a history of head injury, whereas others described no traumatic event; three patients had bilateral hematomas. In this series the overall mean exudation rate was 13.24\% (range 2.05–28.88\%). The mean exudation rate was 9.92\% in the patients younger than 60 years of age and 15.53\% ± 8.24\% in the older patients. These results were statistically insignificant (p > 0.05). In men, the average exudation rate was 11.84 ± 8.04\%, whereas it was 16.06 ± 7.86\% in women. Again, these results were not statistically significant (p > 0.05).

The correlation between the neurological grades and average exudation rates is shown in Fig. 1. The average exudation rates and the number of patients with neurological Grades 0, 1, 2, and 3 were 8.67 ± 5.64\% (three patients), 5.07 ± 1.43\% (eight patients), 17.87 ± 3.73\% (seven patients), and 19.65 ± 7.67\% (six patients), respectively. The differences among the groups were significant. The mean exudation rates were significantly higher in patients with Grade 2 or 3 than that in patients with Grade 0 or 1 (p < 0.05).

According to the appearance of the SDHs on CT scans the average exudation rates were as follows: in the hypodense group (eight patients) the rate was 6.55 ± 4.52\%, in the isodense group (five patients) the rate was 11.07 ± 6.32\%, in the hyperdense group (three patients) the rate was 19.47 ± 13.61\%, and in the mixed-density group (nine patients) the rate was 17.40 ± 5.80\% (Fig. 2).

Only one patient’s lesion had a layered appearance on CT scans; because of the rarity and similarity of this type, the patient in this case was included in the mixed-density group. In two of three patients with bilateral chronic SDHs, both lesions appeared the same on CT scans, whereas in the other the lesions were different from each other. However, the exudation rates were similar in each of these cases (7.98 and 8.85\% [Case 4], 23.87 and 22.68\% [Case 5], and 18.35 and 19.81\% [Case 17]). Regarding the appearance of the chronic SDHs on CT scans, the differences among patients with different grades were statistically significant. The exudation rate in mixed-density hematomas was significantly higher than that in the hypodense hematomas (p < 0.05). As shown in Fig. 3, mixed-density hematomas were more likely to occur in patients with neurological Grade 2 (three patients) and Grade 3 (five patients), whereas hypodensity hematomas were more frequently seen in patients with Grade 0 (two patients) and Grade 1 (five patients).

In this series, only one patient who exhibited a true reaccumulation underwent reoperation. On follow-up CT scans, reaccumulation was detected in 11 patients with 14 chronic SDHs (three bilateral cases). All patients’ conditions

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|}
\hline
\textbf{No.} & \textbf{Age (yrs), Sex} & \textbf{Markwalder Grade} & \textbf{CT Density} & \textbf{Reaccumulation} & \textbf{Exudation Rate} \%
\hline
1 & 66, M & 3 & mixed & no & 21.11 \\
2 & 67, M & 2 & mixed & no & 15.34 \\
3 & 72, M & 0 & iso & no & 2.05 \\
4† & 55, M & 0 & hypo & yes & 7.98 \\
5† & 66, M & 3 & mixed & yes & 8.85 \\
6 & 57, M & 2 & hyper & yes & 22.68 \\
7† & 73, M & 3 & layered & yes & 26.58 \\
8 & 58, M & 1 & hypo & no & 5.38 \\
9 & 72, M & 2 & mixed & no & 14.18 \\
10 & 52, M & 1 & hypo & yes & 5.44 \\
11 & 54, M & 1 & hypo & no & 4.09 \\
12 & 46, M & 1 & hypo & no & 7.06 \\
13 & 53, M & 1 & iso & yes & 7.21 \\
14 & 62, M & 3 & mixed & no & 2.46 \\
15 & 58, M & 1 & hyper & yes & 3.86 \\
16 & 38, M & 0 & mixed & no & 15.82 \\
17† & 86, F & 3 & mixed & yes & 19.81 \\
18 & 65, F & 2 & iso & no & 18.45 \\
19 & 38, F & 2 & mixed & yes & 17.79 \\
20 & 64, F & 1 & hypo & no & 3.67 \\
21 & 62, F & 2 & iso & no & 16.94 \\
22 & 64, F & 3 & hyper & yes & 28.88 \\
23 & 61, F & 2 & hypo & yes & 16.73 \\
24 & 62, F & 1 & iso & no & 3.92 \\
\hline
\end{tabular}
\caption{Characteristics in 24 patients with a total of 27 chronic SDHs\*}
\end{table}

\* hyper = hyperdense; hypo = hypodense; iso = isodense.
† Patients with bilateral lesions.
‡ This patient underwent a reoperation.

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were neurologically stable, and they were treated with steroid medication and observation. The average exudation rate was 16.30 ± 8.16% in cases of reaccumulation, whereas it was 9.96 ± 6.84% in cases with no reaccumulation (Fig. 4). The difference between the two groups was statistically significant (p < 0.05).

According to CT classification, hyperdense and mixed-density chronic SDHs tend to reaccumulate (Table 2). In addition, reaccumulation was seen more commonly in patients with neurological Grade 3 (Table 3).

Discussion

Virchow was the first to describe chronic SDH as a dural inflammatory disease called “pachymeningitis hemorrhagica interna.” Authors of several studies have also revealed that chronic SDH initiates as a local inflammatory process of the dura mater to the external stimuli such as blood, CSF, or blood products.4,13–15,24 According to Friede and Schachenmayr4 and Haines and colleagues,7,8 traumatic detachment of the inner dural layer creates a space filled with CSF, blood, or both. This space is virtual and is referred to as the subdural space. Then mesenchymal cells of the inner dural layer proliferate and form an inflammatory capsule or membrane. This is the outer membrane of the hematoma and is a kind of granulation tissue containing inflammatory cells, immature vessels, and connective fibers.

However, the inner membrane of the hematoma consists of collagen bundles and it has no vascular structures. On electron microscopic examination, it was shown that vascular structures of the outer membrane—called macrocapillaries—had gap junctions of 0.6 to 8 μm in diameter and an incomplete or absent basement membrane, which caused exudation of intravascular content.23–25 Findings from immunohistochemical studies also demonstrated that cytokine vascular endothelial growth factor, which is responsible for the neovascularization and vascular hyperpermeability, appears in the outer membrane.3 Substances such as bradykinin and IL-6 also play role in hyperpermeability of the vascular network of the outer membrane.2,3

Watanabe et al.21 showed that the growth content of experimental chronic SDH was proportional to the thickness of the layer of macrocapillaries and also to the degree of leakage. Glover and Labadie6 found that the enlargement of an experimental chronic SDH was strongly correlated with increased capillary permeability, and dexamethasone inhibited its growth. Bender1 also reported using corticosteroid treatment in a series of patients with chronic SDH. Recently, Frati et al.3 thought that antiinflammatory medicine could be given to prevent the recurrence of a chronic SDH. Positive brain scintigraphy using protein-bound radioactive substances and higher protein concentration than serum detected in chronic subdural fluids are further evidence of exudation in chronic SDH.2,5 Therefore, exudation from macrocapillaries in the outer membrane of the chronic
SDH may play an important role in the lesion’s enlargement.

However, this vascular leakage was described as exudation, transudation, or both. At the beginning of the inflammation, blood vessels dilate and become leaky as a result of increased local blood pressure forcing a filtrate of plasma without large protein molecules. This process is known as transudation. Soon after, changes in the blood vessel endothelial cells occur, and plasma with large protein molecules including clotting and immunological proteins escapes. The increased volume of proteins accumulating in the extravascular space also further increases the escape of plasma by increased osmotic pressure. This, the exodus of protein-rich plasma, is considered exudation. Therefore, transudation is a short-lived event characteristic of the escape of protein-deficient plasma, whereas exudation is a long-lasting event characteristic of extravascular accumulation of protein-rich plasma. The definition of transudation and exudation in pleural effusions is clear, and if the rate of effusion of the protein level to the plasma level is higher than 0.5, the effusion is considered exudation.

The aim of this study was to measure the exudation in chronic SDH and search for a correlation between the exudation and appearance on CT scans, recurrence rate, and clinical grade of the patient. In our previous study, we assessed the exudation of plasma into chronic SDH by an indirect method in which the protein-bound antiepileptic phenytoin penetrated into the hematoma. However, in the present study direct measurement of exudation was achieved using $^{99m}$Tc bonded to HSA. We found that the average exudation rate was 13.24% after 4 hours. We also found that the average exudation rates were higher in patients older than 60 years of age and in women, although these results were statistically insignificant.

Exudation rates in patients with high neurological grades (Grade 2 or 3) were significantly higher than in patients with a low grade (Grade 0 or 1). This finding could be attributed to the expanding capacity of the hematoma-related exudation rate that resulted in more severe findings.

The natural history of chronic SDH has not been fully described. In a recent study Nakaguchi et al. reported the results of CT monitoring of 18 patients without neurological deficits. They examined the density changes in the cavity and internal architecture of the chronic SDH. According to these authors hypodense and isodense hematomas develop continuously into hyperdense hematomas. They termed this stage the homogeneous stage. The laminar stage, in which a hyperdense laminar structure runs along the inner membrane, is considered a subtype of the homogeneous stage. As the hematoma matures, it separates into two components that head motion cannot homogenize. This stage
is described as the separated stage. If mild head movement causes homogenization of the hematoma, the hematoma is not completely separated and is thought to be between the homogeneous and separated stages. Later, hyperdense septated structures develop and the hematoma density changes from an isodense to a hypodense signal on CT scans. This stage is considered the trabecular stage.

In our study we used the CT classification described by Nomura et al.16 According to these authors trabecular and laminar types are mixed-density type in their classification. In this classification, chronological appearances of chronic SDH are as follows: hypodense, isodense, hyperdense, layered, and mixed-density lesions. Our study clearly showed that exudation rates increase as the chronic SDH matures. Mixed-density hematomas were encountered more in patients with Grade 2 (three patients) and Grade 3 (five patients) neurological conditions, whereas hypodensity hematomas were more frequently seen in patients with Grade 0 (two patients) and Grade 1 (five patients) (Fig. 3). These findings correlated well with the chronological appearances of chronic SDH.

Fujisawa et al.3 found that protein concentrations were higher in chronic SDHs showing greater density on CT scans, and the hematoma density was related to the protein concentration. Frati et al.1 showed that layered and mixed-density hematomas had a higher IL-6 concentration, which is an inflammatory cytokine causing increased vascular permeability. These findings correlate well with our results.

Several studies on the prediction of recurrence, based on CT appearance have been reported. Lesions classified as layered on CT scans have been found to be associated with a higher risk of recurrence by some authors, although Tsutsumi et al.19 could not find a positive correlation between CT classification and recurrence. Unfortunately in our study, the number of the layered-appearing chronic SDHs was too small (only one) to compare statistically, and this was added to the mixed-density group. In our series, mixed-density lesions had a high exudation rate. Nomura et al.16 reported that these lesions had a tendency to recur. According to Nakaguchi et al.15 the laminar type also had a high recurrence rate. Most likely the laminar type described by Nakaguchi and colleagues was included in the mixed-density group in our series. Also Frati et al.3 demonstrated that inflammatory cytokines (IL-6 and -8) were high in layered and mixed-density hematomas; therefore, this finding supported our results on mixed-density chronic SDH.

Statistically, in our series the exudation rate was higher in the patients who experienced reaccumulation than in those who did not. Thus, these results are in accordance with the increased inflammatory cytokine levels found in cases of recurrent chronic SDH.5 Most of the clinical studies on chronic SDH focused on recurrence.17 The following are considered risk factors for recurrence of a chronic SDH: advanced patient age, poor clinical status at admission, bilateral lesions, alcohol intake, anticoagulant use, renal and liver diseases, and a layered-type appearance on CT scans.11 However, patients with renal or liver disease and those using anticoagulants and alcohol were excluded from our study.

Advanced patient age has been considered to be a risk factor for recurrence by some authors. It is usually thought that the older the patient, the longer it takes for the brain to recover function. In our study, the reaccumulation rates were similar between the patients older than 60 years and the younger ones. Nakaguchi et al.15 and Tsutsumi et al.19 also found no significant difference in recurrence rates between younger and older patient groups.

We also detected reaccumulation in all three patients with bilateral lesions; however, in two the exudation rates were high. Therefore, the bilateral nature of the lesions may not be responsible for reaccumulation in all of them.

Conclusions

Local inflammatory reaction of the dura mater (within the dural border layer), which can be considered as the origin of chronic SDH, causes the abnormally permeable macrocapillaries. Protein-rich plasma can then exudate through these macrocapillaries.

The rate of exudation is correlated with a severe neurological condition (Markwalder Grade 2 or 3) of the patient, the appearance of the lesion on CT scans, and reaccumulation. Exudation from the macrocapillaries of the outer membrane of chronic SDH probably plays an important role in the pathophysiology and the growth of chronic SDH.

References


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