Acta Neurochir (Wien) (1998) 140: 161–166

Acta Neurochirurgica
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Printed in Austria

Serum Protein Exudation in Chronic Subdural Haematomas: a Mechanism for Haematoma Enlargement?

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Summary

A study was conducted to investigate the role of serum protein exudation in the aetiology of chronic subdural haematoma (SDH). Scintigraphy after intravenous injection of ^{99m}Tc-labelled human serum albumin (HSA) was performed in three patients with chronic SDH and a patient with subdural effusion. In another 60 haematomas, the amounts of total protein and albumin as indices of serum exudation were measured, and then compared among low-density, iso-density and high-density haematomas. Accumulation of ^{99m}Tc-HSA in the haematoma cavity was seen 6 h after isotope injection and became more evident at 24 h. However, the protein concentrations and albumin ratios in the haematomas exhibited a reciprocal relationship, suggesting that not all the protein in the haematomas was derived from serum exudation. The higher the total protein concentration in the haematoma became, the higher the haematoma density which was observed on CT. The albumin concentration in low-density haematomas was lower than that in iso-density and high-density haematomas, whereas no significant difference was seen between the latter two haematoma types. These results provide morphological evidence for serum protein exudation into the haematoma cavity, and therefore it is possible that serum protein exudation plays a role in the progression of chronic SDH and is related to changes in haematoma density on CT.

Keywords: Chronic subdural haematoma; serum albumin; scintigraphy; CT.

Introduction

Enlargement of chronic subdural haematoma (SDH) has been attributed to repetitive haemorrhage from the highly vascularized subdural outer membrane [5]. Although several theories such as local hyperfibrinolysis [4] and an osmotic or oncotic pressure gradient [3, 11, 12] have been proposed to explain the enlargement of chronic SDH, the actual pathogenesis remains unknown. In some patients with chronic SDH, the haematoma density on serial CT scans gradually increases to reach a stage where surgical treatment becomes necessary. Therefore, the causative factors related to these changes are involved in the development of chronic SDH. Haematomas contain a high concentration of protein [1], and we have speculated that serum protein exudation is responsible for this and, in part, for the changes in haematoma density. In the present study, scintigraphy using intravenous injection of ^{99m}Tc-labelled human serum albumin (^{99m}Tc-HSA) was performed in patients with chronic SDH, and the protein fraction of the haematomas was analysed in relation to the density evident on CT. The possible role of serum protein exudation in the aetiology of chronic SDH was then evaluated.

Clinical Materials and Methods

In three patients with chronic SDH and a patient with subdural effusion, serum protein exudation into the haematoma cavity was investigated pre-operatively. For this purpose, ^{99m}Tc-HSA (740 MBq) was injected intravenously, and scintigrams were obtained at 3, 6 or 24 h after injection of the isotope.

In another 60 haematomas and 37 plasma samples from 51 patients with chronic SDH, the protein fraction was analysed. The patients ranged in age from 36 to 85 years (average 65.8 years), and had not received previous treatment for chronic SDH. Pre-operative CT examination was performed in all the patients, and the haematomas were classified into 5 types according to their CT appearance: low, iso, high and mixed density, and layering. Haematomas were aspirated during surgery by puncture through the dura mater with a plastic syringe. Protein concentrations in the haematomas and plasma were measured, and their fractions analysed. Each protein fraction (i. e. albumin, and alpha 1-, alpha 2-, beta- and gamma-globulin) was measured as a percentage of the total protein concentration, and the absolute value of albumin as an index of serum protein exudation was calculated. The red blood cell counts and haemoglobin concentrations in the haematomas as indices of haemorrhage were also measured. These parameters were

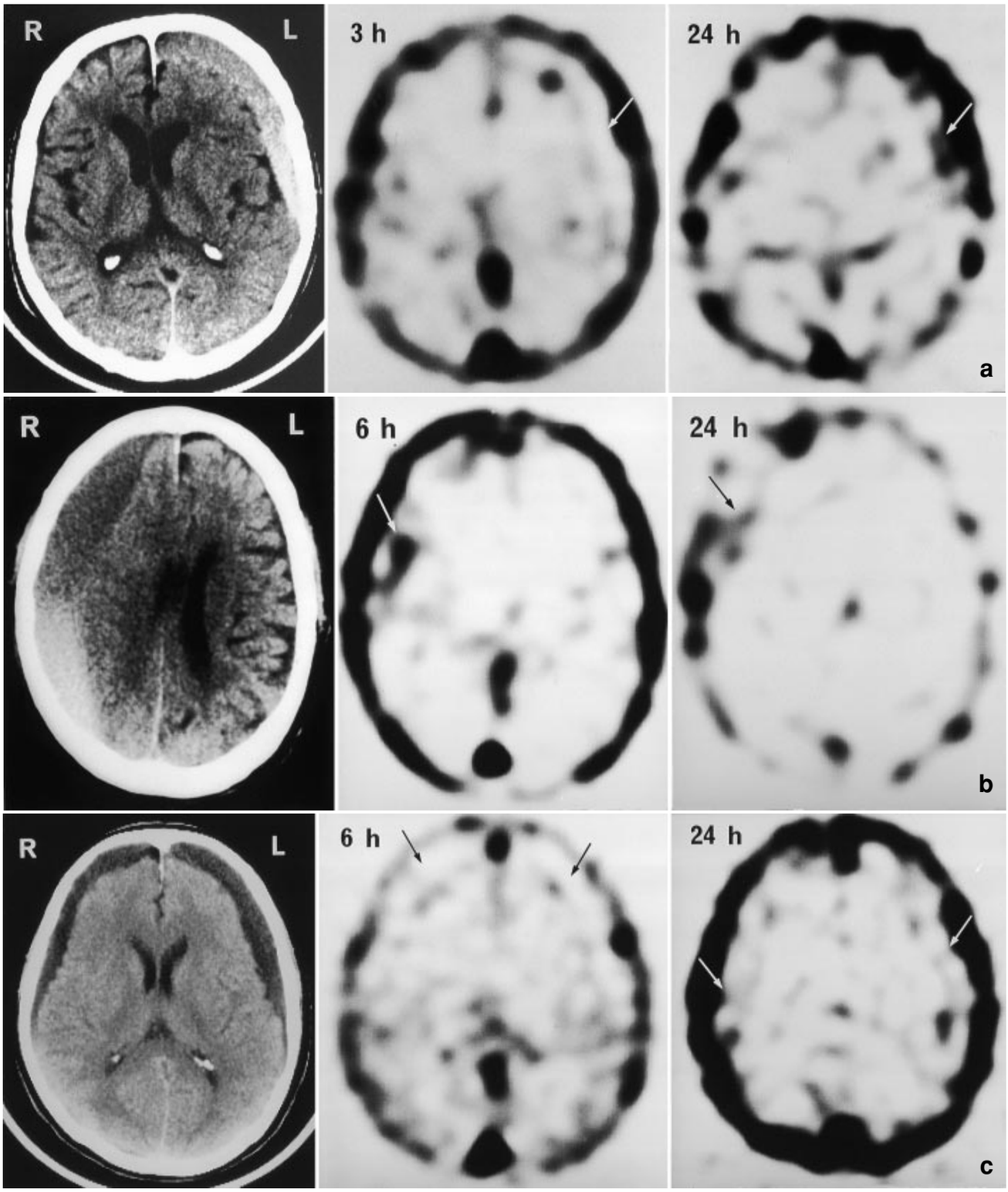

Fig. 1. Left: CT; Center: Scintigram 3 or 6 h after intravenous [^{99m}Tc]-HSA injection; Right: Scintigram 24 h after intravenous [^{99m}Tc]-HSA injection. (a) Case 1; 64-year-old man. Accumulation of ^{99m}Tc-HSA in the haematoma cavity was not evident 3 h after isotope injection, but was seen at 24 h (arrows). (b) Case 2; 85-year-old man (c) Case 4: 73-year-old man with bilateral subdural effusion. Accumulation of ^{99m}Tc-HSA in the haematoma cavities is indicated by arrows

Table 1. *Protein Fractions in the Haematomas and Plasma (%)*

	n	Protein (g/dl)	Albumin (%)	Globulin (%)			
				Alpha 1	Alpha 2	Beta	Gamma
Haematomas	39	8.3 ± 0.5^b	48.9 ± 3.0^b	2.9 ± 0.2^a	17.0 ± 3.6^a	23.0 ± 3.9^a	10.3 ± 0.7^b
Plasma	22	6.2 ± 0.1	62.3 ± 1.0	3.6 ± 0.2	9.9 ± 0.5	9.6 ± 0.4	14.1 ± 0.4

Values are the mean $\pm$ SEM. [a]Indicates a significant difference from plasma (Student's t test), $p < 0.05$; [b]$p < 0.005$ (Student's t test).

then compared among the low-density (n = 8), iso-density (n = 17) and high-density haematomas (n = 14). Mixed-density haematoma and layering haematomas were excluded from these analyses because of their heterogeneous nature, preventing complete aspiration through the dura mater, which therefore made it impossible to know whether the samples obtained were derived from an area of the same density.

Values were expressed as mean $\pm$ standard error of the mean (SEM). Differences and correlations between two parameters were tested using Student's t test and Spearman's rank correlation test, respectively. Differences among multiple parameters were tested by one-way analysis of variance (ANOVA), followed by Scheffé's F-test for multiple comparisons.

Results

^{99m}Tc-HSA Scintigraphy

Case 1 was a 64-year-old man with a left chronic SDH (Fig. 1 a). Accumulation of ^{99m}Tc-HSA in the haematoma cavity was not evident 3 h after isotope injection, but was seen at 24 h. Case 2 was a 85-year-old man with a right chronic SDH (Fig. 1 b), and case 3 was a 68-year-old man with bilateral chronic SDH. In both patients, accumulation of ^{99m}Tc-HSA in the haematoma cavities was seen 6 h after isotope injection, and became more evident at 24 h. Case 4 was a 73-year-old man with bilateral subdural effusion (Fig. 1 c). No isotope accumulation was seen in the subdural fluid 3 h and 6 h after isotope injection, but was seen slightly at 24 h.

Protein Concentrations

The total protein concentration in the haematomas was significantly higher than that in plasma (Table 1). The protein fraction in chronic SDH showed a unique

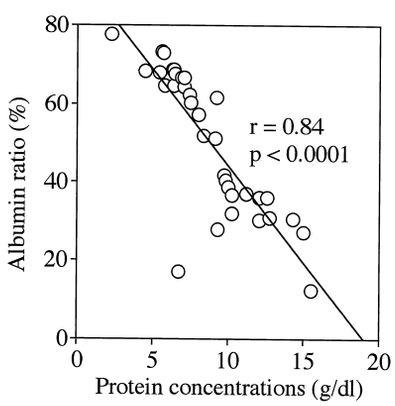

Fig. 2. Correlation between total protein concentration and albumin ratio in haematomas. The higher the protein concentration in the haematoma became, the lower the observed albumin ratio ($r = 0.84$, $p < 0.0001$ by Spearman's rank correlation test

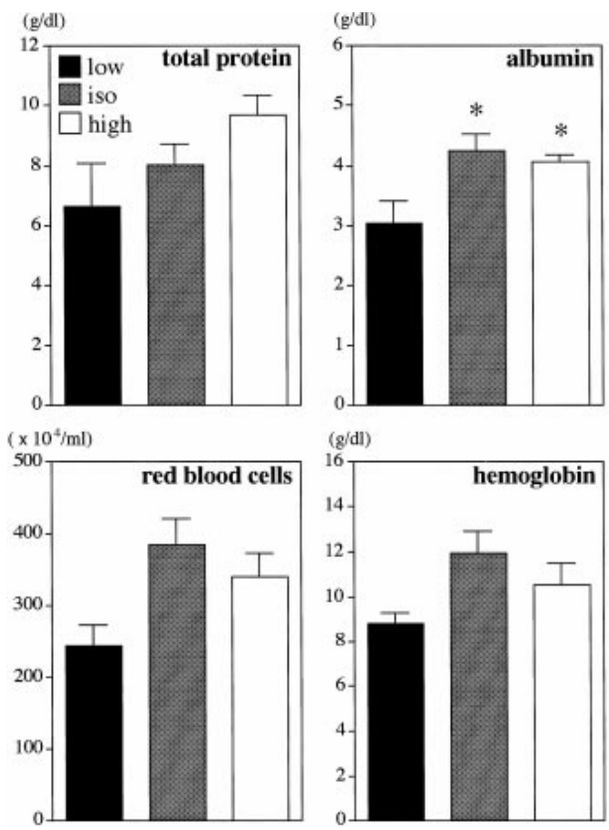

Fig. 3. Comparisons of the amounts of total protein, albumin, red blood cells and haemoglobin among three density types of haematomas. *$p < 0.05$ by one-way analysis of variance (ANOVA), followed by Scheffé's F-test for multiple comparisons

Table 2. *Protein Fractions in the Low-Density, Iso-Density and High-Density Haematomas (%)*

	n	Albumin (%)	Globulin (%)			
			Alpha 1	Alpha 2	Beta	Gamma
Low-density	8	57.4 ± 8.5	0.2 ± 0.02	1.0 ± 0.8	2.1 ± 1.7	0.5 ± 0.1
Iso-density	17	48.1 ± 4.9	0.3 ± 0.04	2.4 ± 0.9	1.2 ± 0.3	0.6 ± 0.1
High-density	14	44.9 ± 3.6	0.3 ± 0.03	2.1 ± 0.8	2.8 ± 0.7	0.6 ± 0.1

Values are means ± SEM.

pattern: a low albumin ratio, and high alpha 2- and beta-globulin ratios. Figure 2 shows the relationship between the protein concentration in the haematomas and the ratio of albumin: the higher the protein concentration, the lower the albumin ratio.

Figure 3 shows comparisons of the total protein and albumin concentrations, and the amounts of red blood cells and haemoglobin among the three types of haematomas. Haematomas with higher protein concentrations showed a higher density on CT. The albumin concentration in low-density haematomas was significantly lower than those in iso-density and high-density haematomas. However, there was no significant difference in albumin concentration between the latter two haematoma types. The red blood cell counts and haemoglobin concentrations of the low-density haematomas tended to be lower than those of the iso-density and high-density haematomas. The albumin ratio in the haematomas became lower as the haematoma density on CT increased (Table 2). There was no significant correlation between albumin concentration and red blood cell count or haemoglobin concentration in the haematomas.

Discussion

Albumin labelled with specific markers such as radiotisotopes and Evans blue dye has been used as an index of serum protein exudation into certain pathological areas, and such exudation is known to be caused by increased vascular permeability. The present results of ^{99m}Tc-HSA scintigraphy provided morphological evidence for serum protein exudation into the haematoma cavity. The haematoma cavity is encapsulated by the inner and outer membranes. Since the inner membrane consists of collagen bundles and is non-vascular, the highly vascularized outer membrane must be the source of serum protein exudation.

Within the haematoma, however, the higher the protein concentration became, the lower the albumin ratio observed, suggesting that all the protein in the haematoma was not derived from serum protein exudation. Subdural effusion or hygroma following minor head injury sometimes develops into chronic SDH [7, 8], and neurosurgeons often encounter patients in whom the haematoma density on CT gradually increases to reach a stage where surgical irrigation of the haematoma becomes necessary. Although haemorrhage into the haematoma cavity may play a role in this change, the actual factors responsible have not been fully determined. In fact, the present study demonstrated that the amounts of red blood cells and haemoglobin in high-density haematomas were lower than those in iso-density haematomas. Therefore, haemorrhage *per se* is not the only factor responsible for the changes in CT findings. On the other hand, the present finding that protein concentrations were higher in haematomas showing higher density on CT indicates that haematoma density is related to the protein concentration present. Although the albumin concentration in low-density haematoma was lower than those in iso-density and high-density haematomas, there was no significant difference between the latter two haematoma types. Furthermore, the albumin ratio became lower as the haematoma density increased on CT. Therefore, serum protein exudation also is not entirely responsible for the changes seen in haematoma density. Haemorrhage into the haematoma cavity, in turn, results in haemolysis within the cavity. We speculate that such haemolysis is another factor responsible for both the high protein concentration in the haematoma and the changes in haematoma density.

Most patients with chronic SDH can be cured by surgical irrigation of the haematoma cavity. This leads to the question of why such a simple treatment can achive complete cure, since the source of haemorrhage and protein exudation (i.e. from the outer membrane)

remains after the treatment. The same question can be applied to spontaneous resolution of the haematoma observed in some patients. It has been suggested that local hyperfibrinolysis in the outer membrane is a major aetiological factor of chronic SDH [2, 4, 6]. Intermittent cycles of bleeding, coagulation and fibrinolysis have been suggested to cause haematoma enlargement [9]. In addition, we have reported previously that the increase of vascular permeability and consequent serum exudation caused by activation of the kallikrein-kinin system may also play a role in the progression of chronic SDH [1]. Morphologically, the outer membrane is composed of granulation tissue containing many vessels [10]. Irrigation of the haematoma cavity may restore a normal haemostatic balance [2, 9] to facilitate absorption of the residual haematoma or fluid in the cavity and organisation of the outer membrane. During such a process, haemorrhage and protein exudation into the haematoma cavity may decrease. In cases of spontaneous resolution of chronic SDH, a normal haemostatic balance may be restored spontaneously and the process described above may therefore occur.

In this study, we have obtained morphological evidence for serum protein exudation into chronic SDH and a difference in the protein fractions between the haematoma and plasma. We speculate that serum protein exudation caused by increased vascular permeability in the outer membrane is one of the mechanisms responsible for the clinical progression of chronic SDH and subdural effusion or hygroma. However, it may be necessary to perform a further quantitative study on the effects of inhibition of such exudation on the clinical stability of chronic SDH.

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Comments

The authors have studied the protein contents of chronic subdural haematoma fluid in a large number of patients, including protein electrophoresis. They have equated protein content with CT appearances. The illustrations of this phenomenon are convincing. They have also studied the extravasation of radio-labelled albumin into the subdural fluid in four other patients prior to evacuation of the dural fluid with scintigraphy. In three of the four, there was relatively convincing evidence that labelled albumin actually accumulated within the subdural fluid compartment within 24 hous of intravenous injection. This too is new information.

J. T. Hoff

The authors of this study test the hypothesis that serum protein exudation is a mechanism for the clinical evolution of chronic subdural haematomas (SDHs). Using an in vivo morphometric study, they show that ^{99m}Tc-labelled human serum albumin (HSA) accumulates in the chronic SDHs of three patients. This is shown convincingly in the scintigraphs for Patients 1 and 2. Accumulation of ^{99m}Tc-labelled HSA in Patient 4, who presented with bilateral subdural effusions, is not well visualized (Fig. 2 C).

The authors also speculate that the density of chronic SDHs is a function of total protein concentration. Although low-density chronic SDHs had a lower total protein concentration compared with iso or hyperdense chronic SDHs, no difference was observed among the latter two, suggesting that other mechanisms must be involved in the computerized tomography appearance of chronic SDHs. These comparisons are made between patients and not for and individual patient, whose total protein and albumin levels are unique. A more meaningful analysis would involve several samplings of an evolving chronic SDH; however, this would be unacceptable to most ethics committees.

Distribution of protein fractions in chronic SDHs and plasma differs, and is statistically significant in this study. Surprisingly, the fraction of albumin in the total protein pool of chronic SDHs is less than that found in plasma. This supports the idea that other plasma proteins (Alpha-2 and Beta globulin) may play a greater role than albumin in the clinical progression of chronic SDHs. The authors do not directly test whether these other serum proteins accumulate by means of serum protein exudation.

In summary, the author's main contribution is the observation that the distribution of plasma proteins in chronic SDHs is different than that of plasma. By using scintigraphy the authors also showed that albumin accumulates in chronic SDHs over a twenty-four hour period. This suggests that serum protein exudation may be a mechanism included in the clinical progression of chronic SDHs. However, direct evidence for this is not provided, and the authors would need to show that inhibition of serum protein exudation results in clinical stability of chronic SDHs.

J. Tew

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