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

Ki-Su Park, M.D., Seong-Hyun Park, M.D., Sung-Kyoo Hwang, M.D., Chaekyung Kim, M.S., Jeong-Hyun Hwang, M.D.

Department of Neurosurgery, Kyungpook National University School of Medicine, Daegu, Korea

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 to 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/βTP in the serum > 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 those 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 βTP and the ratio of βTP in the subdural fluid/βTP in the serum of the hyperintense group (n = 13) of T2-WI MRI were 7.3 ± 2.9 mg/L and 12.6 ± 5.4, whereas those 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 the non-hyperintense group. And, the hyperintense group on T2-WI MRI exhibited higher concentrations of βTP and the ratio of βTP in the subdural fluid/βTP in the serum than the 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.
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 vacuum 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 (βTP_{ser})20. Samples of subdural fluid with a βTP concentration in the subdural fluid (βTP_{sf}) at least twice as high as the βTP_{ser} (βTP_{sf}/βTP_{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 βTP_{sf}/βTP_{ser} in the subdural fluid was >2, a CSF admixture to the subdural fluid was not considered to be present15. In addition, the concentration of βTP reflected the amount of CSF present in the CSDH17.

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 fluid...
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 mm).

**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        | Homogenous  |
| 3        | 40/F    | No                | None             | No         | 35             | No            | High          | Low        | Homogenous  |
| 4        | 66/M    | Yes               | 40               | No         | 13             | No            | High          | High       | Homogenous  |
| 5        | 58/F    | No                | None             | Yes        | 20             | No            | Low           | Low        | Homogenous  |
| 6        | 62/F    | Yes               | 58               | No         | 22             | No            | Low           | High       | Heterogenous|
| 7        | 59/M    | Yes               | 30               | No         | 20             | No            | High          | Low        | Heterogenous|
| 8        | 68/M    | No                | None             | No         | 21             | No            | High          | High       | Heterogenous|
| 9        | 74/M    | Yes               | 25               | No         | 16             | No            | High          | Low        | Homogenous  |
| 10       | 73/M    | Yes               | 37               | No         | 15             | No            | High          | High       | Heterogenous|
| 11       | 50/M    | Yes               | 62               | No         | 23             | No            | High          | Low        | Heterogenous|
| 12       | 80/F    | No                | None             | No         | 33             | No            | High          | Low        | Heterogenous|
| 13       | 77/M    | Yes               | 32               | No         | 20             | No            | High          | Low        | Homogenous  |
| 14       | 80/M    | Yes               | 19               | No         | 18             | Yes           | High          | Low        | Heterogenous|
| 15       | 82/F    | Yes               | 21               | No         | 31             | No            | Iso           | Low        | Homogenous  |
| 16       | 86/M    | Yes               | 30               | No         | 10             | No            | High          | High       | Heterogenous|
| 17       | 71/M    | No                | None             | No         | 19             | No            | Low           | High       | Homogenous  |
| 18       | 38/M    | Yes               | 60               | No         | 17             | No            | Iso           | High       | Homogenous  |
| 19       | 76/M    | No                | None             | No         | 24             | No            | High          | Low        | Heterogenous|
| 20       | 72/M    | Yes               | 32               | No         | 20             | No            | High          | High       | Homogenous  |
| 21       | 74/F    | Yes               | 30               | No         | 21             | No            | High          | Low        | Heterogenous|
| 22       | 72/F    | No                | None             | No         | 19             | No            | Iso           | Low        | Homogenous  |
| 23       | 80/F    | Yes               | 45               | No         | 8              | No            | Low           | High       | Homogenous  |
| 24       | 57/M    | Yes               | 64               | No         | 9              | Yes           | Iso           | Low        | Homogenous  |
| 25       | 57/M    | Yes               | 44               | No         | 27             | No            | Iso           | High       | Homogenous  |
| 26       | 64/M    | Yes               | 57               | No         | 26             | No            | High          | Iso        | Heterogenous|
| 27       | 71/M    | Yes               | 30               | Yes        | 22             | No            | Low           | Low        | Homogenous  |
| 28       | 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
mm). Thirteen hematomas (42%) were homogenous and 18 (58%) were heterogeneous on CT scans. According to the MRI, 17 (55%) of hematomas were hyperintense on T1-weighted image and 14 hematomas (45%) were hypointense on T2-WI. There was no statistically significant difference between a hyperintense group and a non-hypointense group in terms of laterality 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 βTP/βTP 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-hypointense 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-hypointense group, respectively (p<0.001 and p=0.004).

For T2-WI MRI, the mean concentrations of βTP and the ratio of βTP/βTP were higher 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 hypointense group of CSDHs and higher levels of βTP in the T2-WI MRI hypointense 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. In CSDHs, IL-6 and IL-8 were increased. Nomura et al. reported that the concentrations of IL-6 and IL-8 were increased. Nomura et al. reported the presence of the βTP in the subdural hematoma, and suggested that 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. reported that in the trabecular and layering types of CSDHs, the concentrations of IL-6 and IL-8 were increased. Frati et al. 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 hypointense group of CSDHs and higher levels of βTP in the T2-WI MRI hypointense group of CSDHs, and described the association between levels of these markers and findings on MRI.

**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. As a result, many molecular markers for CSDHs have been demonstrated, and they can be classified as follows: 1) tissue plasminogen activator, plasmin-inhibitor complex, thrombomodulin, fibrinogen and D-dimer in relation with coagulation and fibrinolytic activity; 2) IL-6, IL-8, IL-10 and tumor necrosis factor-α in relation with inflammatory process in the neomembrane; and 3) vascular endothelial growth factor, basic fibroblast growth factor and platelet-derived growth factor in relation with angiogenic activity of the neomembrane. And, Kristof et al. 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 CSDHs.
Correlation of Biomolecules with MRI in Chronic Subdural Hematoma

KS Park, et al.

of the subacute intracranial hematoma, is a common observation, which is probably due to repeated hemorrhage\(^2\). 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 \(\beta\)-TP (prostaglandin-D2-synthase) is an ideal marker to identify a CSF admixture into the subdural fluid. More than 99% of \(\beta\)-TP is contained within the CSF, and it is synthesized mainly by the choroid plexus of the CNS, whereas a very small amount of \(\beta\)-TP is synthesized outside the CNS, mainly in the heart and blood. The \(\beta\)-TP concentration is 32–34 times higher in the CSF (8–40 mg/L) compared to the serum (0.3–0.76 mg/L)\(^1,2,8\).

Kristof et al.\(^17\) suggested that \(\frac{\beta\text{-TP}}{\text{CSF}}/\frac{\beta\text{-TP}}{\text{SER}}\) > 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 \(\beta\)-TP reflected the amount of CSF present. Although the mechanism of CSF leakage (and its component \(\beta\)-TP) into the subdural space in CSDHs remains unknown, two hypotheses were suggested in the literature: 1) CSF (and its component \(\beta\)-TP) 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 \(\beta\)-TP) 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 metheglobin, appear hyperintense on such images\(^16\). However, our study demonstrated that the mean concentration of \(\frac{\beta\text{-TP}}{\text{CSF}}/\frac{\beta\text{-TP}}{\text{SER}}\) in the T2-WI MRI hypointense group were significantly higher than in the non-hypointense group, and indicated more CSF admixture to the CSDHs in the T2-WI MRI hypointense group. Therefore, the higher subdural concentrations of \(\beta\)-TP and the higher ratio of \(\frac{\beta\text{-TP}}{\text{CSF}}/\frac{\beta\text{-TP}}{\text{SER}}\) may provide good markers for CSDHs for the hypointense group on T2-WI MRI, and CSF admixture to the CSDHs may provide another possibility for the T2-WI MRI hypointensity 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 hypointense group compared to the non-hypointense group, and we suggested that the subdural concentrations of IL-6 and IL-8 in CS-
DHSs 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 βTPs and the ratio of βTPδ/βTPε 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.

• Acknowledgements
We thank Wade Martin of Medical Research International for his critical review of this manuscript. This work was supported by a Biomedical Research Institute grant, Kyungpook National University Hospital (2014).

References
1. Bachmann G, Peterhi H, Djenah U, Michel O : Predictive values of beta-trace protein (prostaglandin D synthase) by use of laser-nephelometry assay for the identification of cerebrospinal fluid. Neurosurgery 50 : 571-576; discussion 576-577, 2002
2. Bascelli H, Nordmann A, Bucher HC, Gratzi O : Demographics and prevalent risk factors of chronic subdural haematoma : results of a large single-center cohort study. Neurosurg Rev 27 : 263-266, 2004
3. Bradley WG Jr, Schmidt PG : Effect of methemoglobin formation on the MR appearance of subarachnoid hemorrhage. Radiology 156 : 99-103, 1985
4. Fobben ES, Grossman RI, Atlas SW, Hackney DB, Goldberg HJ, Zimmerman RA, et al. : MR characteristics of subdural hematomas and hydroceles at 1.5 T. AJR Am J Roentgenol 153 : 589-595, 1989
5. Frati A, Salvati M, Maniero F, Ippoliti F, Rocchi G, Raco A, et al. : Inflammation markers and risk factors for recurrence in 35 patients with a posttraumatic chronic subdural hematoma : a prospective study. J Neurosurg 100 : 24-32, 2004
6. Fusaiwa H, Nomura S, Tsuchida E, Ito H : Serum protein exudation in chronic subdural haematoma : a mechanism for haematoma enlargement? Acta Neurochir (Wien) 140 : 161-165; discussion 165-166, 1998
7. Gemori JM, Grossman RJ : Mechanisms responsible for the MR appearance and evolution of intracranial hemorrhage. Radiographics 8 : 427-440, 1988
8. Gemori JM, Grossman RJ, Hackney DB, Goldberg HJ, Zimmerman RA, Bilanik LJ : Variable appearances of subacute intracranial hematoma on high-field spin-echo MR. AJR Am J Roentgenol 150 : 171-178, 1988
9. Hirashima Y, Endo S, Hayashi N, Karasawa K, Nojima S, Takaku A : Platelet-activating factor (PAF) and the formation of chronic subdural haematoma. Measurement of plasma PAF levels and anti-PAF immunoglobulin titers. Acta Neurochir (Wien) 137 : 15-18, 1995
10. Hong HJ, Kim YI, Yi HJ, Ko Y, Oh SJ, Kim JM : Role of angiogenic growth factors and inflammatory cytokines on recurrence of chronic subdural hematoma. Surg Neurol 71 : 161-165; discussion 165-166, 2009
11. Hosoda K, Tamaki N, Masumura M, Matsumoto S, Maeda F : Magnetic resonance images of chronic subdural hematoma. J Neurosurg 67 : 677-683, 1987
12. Katagami Y, Ohara H, Satoh H, Onda H, Matsumoto G, Fusa A, et al. : Measurement of inflammatory cytokines and thrombomodulin in chronic subdural hematoma. Neurul Med Chir (Tokyo) 52 : 810-815, 2012
13. Kleine TO, Dam T, Alhass H : Quantification of beta-trace protein and detection of transferrin isoforms in mixtures of cerebrospinal fluid and blood serum as models of diencephale and otoreh diagnosis. Fresenius J Anal Chem 366 : 382-386, 2000
14. Koch AE, Polverini PJ, Runkel SL, Harlow LA, DiPietro LA, Elen S, et al. : Interleukin-8 as a macrophage-derived mediator of angiogenesis. Science 258 : 1798-1801, 1992
15. König SA, Schick U, Döhnert J, Goldammer A, Vitzthum HE : Coagulopathy and outcome in patients with chronic subdural haematoma. Acta Neurochir 107 : 110-116, 2003
16. Krauss JK, Wiegand R : Medical and surgical management of chronic subdural hematomas in Youmans JR, Winn R (eds) : Youmans Neurological Surgery, ed 6. Philadelphia : Elsvier Saunders, 2011, pp535-543
17. Kristof RA, Grimm J, Stoffel-Wagner B : Cerebrospinal fluid leakage into the subdural space : possible influence on the pathogenesis and recurrence frequency of chronic subdural hematoma and subdural hygroma. J Neurosurg 108 : 275-280, 2008
18. Lee KS : The pathogenesis and clinical significance of traumatic subdural hygroma. Brain Inj 12 : 595-603, 1998
19. Lim DJ, Chung YG, Park YK, Song JH, Lee HK, Lee KC, et al. : Relation between tissue plasminogen activator, plasminogen activator inhibitor and CT image in chronic subdural hematoma. J Korean Med Sci 10 : 373-378, 1995
20. Markwalder TM : Chronic subdural hematomas : a review. J Neurosurg 54 : 637-645, 1981
21. Maruo N, Morita I, Shirao M, Murota S : IL-6 increases endothelial permeability in vitro. Endocrinology 131 : 710-714, 1992
22. Nakaguchi H, Yoshimazu N, Tanishima T : Relationship between the natural history of chronic subdural hematoma and enhancement of the inner membrane on post-contrast CT scan. No Shinkei Geka 31 : 157-164, 2003
23. Nomura S, Kashiwagi S, Fusaiwa H, Ito H, Nakamura K : Characterization of local hyperfibrinolysis in chronic subdural hematomas by SDS-PAGE and immunoblot. J Neurosurg 81 : 910-913, 1994
24. Park HR, Lee KS, Shim JH, Yoon SM, Bae HG, Deh JIV : Multiple densities of the chronic subdural hematoma at CT scans. J Korean Neurosurg Soc 54 : 38-41, 2013
25. Park SH, Kang DH, Park I, Hwang JH, Hwang SK, Sung JK, et al. : Fibrinogen and D-dimer analysis of chronic subdural hematomas and computed tomography findings : a prospective study. Clin Neurol Neurosurg 113 : 272-276, 2011
26. Saito K, Ito H, Hasegawa T, Yamamoto S : Plasmin-alpha 2-plasmin inhibitor complex and alpha 2-plasmin inhibitor in chronic subdural hematoma. J Neurosurg 70 : 68-72, 1989
27. Sajantti J, Majamaa K : High concentrations of procollagen propeptides in chronic subdural haematoma and effusion. J Neurosurg Psychiatry 74 : 522-524, 2003
28. Schnabel C, Di Martino E, Gilsbach JM, Riediger D, Gressner AM, Kunz X : Comparison of beta2 transferrin and beta-trace protein for detection of cerebrospinal fluid in nasal and ear fluids. Clin Chem 50 : 661-663, 2004
29. Senturk S, Guzel A, Bulaci A, Tsalimay I, Guzel E, Alacu MU, et al. : CT and MR imaging of chronic subdural hematomas : a comparative study. Swiss Med Wkly 140 : 335-340, 2010
30. Shono T, Inamura T, Morimaki T, Matsumoto K, Suzuki SO, Ikezaki K, et al. : Vascular endothelial growth factor in chronic subdural hematoceles. J Clin Neurosci 8 : 411-415, 2001
31. So SK, Ogawa T, Gerberg E, Sakimura I, Wright W : Tracer accumulation in a subdural hygroma : case report. J Nucl Med 17 : 119-121, 1976
32. Stroobandt G, Fransen P, Thauvoy C, Menard E : Pathogenetic factors in chronic subdural hematoma and causes of recurrence after drainage. Acta Neurochir (Wien) 137 : 6-14, 1995
33. Vaquerio J, Zurita M, Cinca R : Vascular endothelial growth-permeability factor in granulation tissue of chronic subdural hematomas. Acta
Neurochir (Wien) 144 : 343-346; discussion 347, 2002.
34. Weigel R, Schilling L, Schmidek P.: Specific pattern of growth factor distribution in chronic subdural hematoma (CSH): evidence for an angiogenic disease. Acta Neurochir (Wien) 143 : 811-818; discussion 819, 2001.