Inflammation markers and risk factors for recurrence in 35 patients with a posttraumatic chronic subdural hematoma: a prospective study

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Object. To evaluate the role of local inflammation in the pathogenesis and postoperative recurrence of chronic subdural hematoma (CSDH), the authors conducted an investigation in a selected group of patients who could clearly recall a traumatic event and who did not have other risk factors for CSDH. Inflammation was analyzed by measuring the concentration of the proinflammatory and inflammatory cytokines interleukin (IL)-6 and IL-8. The authors also investigated the possible relationship between high levels of local inflammation that were measured and recurrence of the CSDH.

Methods. A prospective study was performed between 1999 and 2001. Thirty-five patients who could clearly recall a traumatic event that had occurred at least 3 weeks previously and who did not have risk factors for CSDH were enrolled. All patients were surgically treated by burr hole irrigation plus external drainage.

The concentration of inflammatory cytokines was very high in the lesion, whereas it was normal in serum. In five cases in which recurrence occurred, concentrations of both IL-6 and IL-8 were significantly increased (p < 0.01) in comparison with cases without a recurrence. In a layering hematoma, the IL-6 and IL-8 concentrations were significantly higher (p < 0.05). Layering CSDHs were also significantly correlated with recurrence. Trabecular hematoma had the lowest cytokine levels and the longest median interval between trauma and clinical onset. The interval from trauma did not significantly influence recurrence, although it did differ significantly between the trabecular and layering CSDH groups. Concentrations of IL-6 and IL-8 in the CSDHs did not differ significantly in relation to either the age of the hematoma (measured as the interval from trauma) or the age of the patient.

Conclusions. Brain trauma causes the onset of an inflammatory process within the dural border cell layer; high levels of inflammatory cytokines were significantly correlated with recurrence and layering CSDH. A prolonged postoperative antiinflammatory medicine given as prophylaxis may help prevent the recurrence of a CSDH.

KEY WORDS • chronic subdural hematoma • interleukin-6 • interleukin-8 • hematoma recurrence • computerized tomography scanning

C HRONIC subdural hematoma is a common disease in elderly persons and its incidence is highest (seven/100,000 individuals) in persons older than 70 years of age. In approximately 60 to 80% of cases a mild traumatic event is reported to have preceded the hemorrhage; however, a mild traumatic episode may sometimes go unreported or unrecognized. Risk factors are not limited to the age of the patient; instead they also include the following: alcoholism; concomitant diseases such as liver dysfunction, kidney diseases, diabetes, dementia, or coagulopathy; hemodialysis; usage of antiagulant, antithrombotic, or chemotherapeutic agents; and the previous presence of a ventriculoperitoneal shunt.

For the last several years the pathophysiology of CSDH has been a controversial topic in the literature. Recently, several papers concerning the ultrastructural anatomy of the meninges and the neomembrane of the hematoma, and the role of inflammatory (cytokines, bradykinin, and kinin), fibrinolytic (tissue plasminogen activator, plasminogen, and fibrin degradation products), angiogenic (VEGFs), and coagulation-system factors have really clarified this complicated topic. Currently, CSDH is considered a chronic self-perpetuating inflammatory process that involves the dura mater.

Surgery is the treatment of choice. Several different modalities of surgery have been suggested: craniotomy, burr hole with or without irrigation and/or a closed drainage system, and twist drill trephination directly into the hematoma.
Inflammatory cytokines in chronic subdural hematoma

at the site of its maximum thickness. 19,28,29,42,43,45 Concomitant diseases are frequently associated with CSDH and can impair both its prognosis and surgical outcome. In fact, death and recurrence are sometimes influenced more by the patient’s poor preoperative clinical status or complications caused by concomitant diseases than by complications or failure of surgical treatment. The rate of recurrence of CSDH after surgery is between 3.7 and 30%. 6,18,28,39,40

These risk factors for recurrence have been discussed in several papers in which controversial findings are not uncommon and have been found to be related to patient age, poor clinical status on admission, concomitant diseases, thickness and neuroimaging features of the hematoma on CT or MR images (layering hematoma compared with other types), as well as to the different modalities of surgical treatment (burr hole, craniotomy, and twist drill trephination) that are performed with or without irrigation. 18,28,31,33,38–40,42,43,53 The presence and location of an external drainage system and the postoperative drainage volume have also been considered as possible risk factors for recurrence. 29,39,40,54

In our study, not only did we analyze these factors but we also focused our attention on the role of inflammation in CSDH, specifically on the proinflammatory and inflammatory cytokines IL-6 and IL-8, because they have already been used as inflammatory markers in patients with severe neurological diseases such as meningitis, subarachnoid hemorrhage, head injury, brain tumor, and CSDH. 1,4,50,53 In addition, these cytokines are produced in the nervous system in response to trauma and infection. 13

The levels of IL-6 and IL-8 were evaluated in the subdural fluid collections of patients in whom trauma was clearly the cause of the bleeding and who did not present other risk factors for CSDH.

On the whole, the main aims of this paper were the following: 1) to analyze the correlation among brain trauma, dural inflammation, and CSDH; 2) to correlate the levels of cytokines with the age of both the CSDH and the patients; and 3) to evaluate the importance of local inflammation in the recurrence of a CSDH, also considering possible correlations between cytokine levels in the hemorrhage and other risk factors for recurrence.

Clinical Material and Methods

Patient Population

The following features excluded patients from the study: 1) current use of thrombolytic, antiaggregant, anticoagulant, and antiinflammatory therapy or hemodialysis; 2) a history of alcohol abuse; 3) concomitant infective, inflammatory, hematological, or neoplastic disease, liver dysfunction, dementia, coagulopathy, or diabetes mellitus; 4) presence of a ventriculoperitoneal shunt; and 5) an MGS score greater than 3. Only patients who had been referred to the hospital for a traumatic event that had occurred at least 3 weeks previously, as suggested by McKissock and associates, 35 and who had coagulation values within the normal range were considered. Thirty-five patients were included in the study. For each of these patients the interval between trauma and hospital admission was also considered. The ESR and the presence of C-reactive protein on the day of the operation were also evaluated in all patients.

Neurological Assessment

Patients were neurologically classified according to the MGS. 31,32 Grade 0 indicates no neurological symptoms; Grade 1, mild symptoms such as headache and a mild neurological deficit such as reflex asymmetry; Grade 2, drowsiness and disorientation with a neurological deficit such as hemiparesis; Grade 3, stupor, presence of a motor response to painful stimuli, and a severe neurological deficit such as hemiplegia; and Grade 4, coma, absence of a motor response to painful stimuli, and decerebrate or decorticate posturing.

Classification of the CSDHs

Initially, the CSDHs were differentiated, on the basis of CT scanning, according to the classification suggested by Nomura, et al. (high density, isodensity, low density, mixed density, and layering type of hematoma). 42 Later, all cases were reviewed and reclassified in the light of the categories suggested by Nakaguchi, et al., 39 who defined four neuroimaging groups of hematomas on the basis of CT scanning as follows: 1) homogeneous density type; 2) laminar type, defined as a subtype of homogeneous density, with a high-density layer along the inner membrane; 3) layering or separated type, containing two components of different densities with a boundary lying between them; and 4) trabecular density type, in which a high-density septum between the inner and the outer membranes appeared against a low-density to isodense background. Hence, we classified the hematomas into four different groups, taking into consideration both classifications: Group 1, the separated or layering type; Group 2, the laminar or mixed-density type; Group 3, the trabecular type (classified by Nomura, et al., within the group of mixed-density hematomas); and Group 4, a high-density, low-density, or isodense type described by Nomura, et al., which is also defined as the homogeneous-density type by Nakaguchi, et al. The thicknesses of the CSDHs were evaluated on the basis of preoperative and postoperative CT scans.

Treatment of Patients

All patients commenced prophylactic antibiotic treatment 24 hours before surgery and continued on this regimen until 24 hours after surgery. After they had received a sedative and a local anesthetic agent all patients were surgically treated by Burr hole craniostomy with repeated irrigation plus external closed-system drainage. Patients with bilateral CSDHs received two burr holes. In all patients the drainage tip was placed frontally. To prevent an influx of air into the hematoma cavity, the patient’s head was elevated and the subdural space was filled with sterile saline solution. The external drain was removed after 3 days. Patients were kept in bed until the drain had been removed and were mildly hyperhydrated. All patients underwent postoperative brain CT scanning at 24 hours and 1 week postoperatively. Patients in whom a significant amount of subdural air was evident underwent CT or MR imaging of the brain every 24 to 48 hours, depending on their neurological status, until the air had disappeared. All patients underwent follow-up MR imaging of the brain just before being discharged from the hospital and at 1 month, 3 months, and 1 year after surgery. Patients were discharged as soon as symptoms related to the
CSDH had disappeared and a CT or MR image had documented a total or significant reduction in the thickness of the CSDH. Recurrence was believed to have occurred if there was evidence within 1 year after surgery of increased thickness of the residual hematoma or an increase in the size of the subdural space on CT or MR images when compared with the CT scan obtained 24 hours postoperatively.

### TABLE 1

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<th>Case No.</th>
<th>Recurrence</th>
<th>Age (yrs)</th>
<th>MGS Score</th>
<th>CSDH Type on CT Scans (group no.)</th>
<th>CSDH Thickness (mm)</th>
<th>Site</th>
<th>Bilat</th>
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* F = frontal; FP = frontoparietal; FPO = frontoparietooccipital; FPT = frontoparietotemporal; FT = frontotemporal; I = interhemispheric; P = parietal; PO = parietooccipital; TP = temporoparietal; TPO = temporoparietooccipital.
† Appearance of CSDH on CT scan: Group 1, layering density; Group 2, mixed density; Group 3, trabecular; Group 4, homogeneous (isointense, hypointense, or hyperintense).
‡ Group A, interval from trauma was less than 60 days; Group B, interval from trauma was at least 60 days.

### TABLE 2

**Difference in the concentrations of IL-6 and IL-8 between recurrent and nonrecurrent cases of CSDH**

<table>
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<tr>
<th>Cytokine &amp; Group</th>
<th>No. of Patients</th>
<th>Mean (pg/ml)</th>
<th>SD</th>
<th>SEM</th>
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<td>1870.33</td>
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<td>2674.00</td>
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<td>nonrecurrent cases</td>
<td>30</td>
<td>1170.67</td>
<td>548.48</td>
<td>100.14</td>
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</table>

* SD = standard deviation.

Samples were collected directly from the CSDH at the time of surgical treatment. After the external membrane had been opened, approximately 10 ml of the subdural fluid collection was aspirated into siliconized vacuum tubes containing protamine sulfate and ethylenediamine tetraacetic acid. Control samples were collected from venous blood at the same time. All samples were centrifuged at 2500 to 3000 rpm for 10 minutes, and the supernatants were stored in sealed polypropylene tubes at −70°C until analysis. The concentrations of the inflammatory cytokines IL-6 and IL-8 were evaluated using enzyme-linked immunosorbent assay kits (Cellbio; Euroclon, Milan, Italy). Normal serum levels of IL-6 and IL-8 were considered to be less than 15 pg/ml and less than 6 pg/ml, respectively.

Laboratory analyses were performed at the Department of Pathology and Experimental Medicine of the University “La Sapienza” of Rome.

### Statistical Analysis

The Student parametric t-test was used to analyze the role of the following covariates in hematoma recurrence: patient...
Inflammatory cytokines in chronic subdural hematoma

Results

Thirty-five patients were enrolled in the study and their main characteristics are summarized in Table 1.

Five (14%) of 35 patients presented with a recurrence. Four of these patients were affected by layering hematoma.

The serum levels of IL-6 and IL-8 were normal or slightly elevated in all patients (IL-6, 9 ± 7.8 pg/ml; IL-8, 5 ± 4.6 pg/ml [means ± SEMs]). The ESR and concentration of C-reactive protein were normal as well. No patients presented with significant fever on admission, because patients with a recent concomitant infective disease had been excluded from this study. Only one patient (Case 17) reported having a mild fever episode, unrelated to any specific disease, some weeks before admission. Postoperatively, only two patients had a temperature that was higher than 38°C. One of them was the patient who had a fever earlier (Case 17) and the new fever was still unrelated to any specific cause. In the other patient (Case 26) the fever was due to an infection of the skin incision. In both patients prolonged antibiotic therapy was successful.

In patients who presented with a recurrent CSDH, the concentrations of IL-6 and IL-8 were significantly higher (p < 0.001) than those in patients who did not experience a recurrence (Table 2 and Figs. 1 and 2). The other covariates analyzed using the Student t-test were not significantly correlated with recurrence (p > 0.05). In comparison with other types of CSDHs observed on CT scans, the layering type was significantly associated with recurrence (odds ratio, 16; 95% CI, 1.5–170.6).

Concentrations of IL-6 and IL-8 significantly differed among the four neuroimaging groups (p < 0.01 and p = 0.04) (Table 3 and Fig. 3). The differences in IL-6 and IL-8 concentrations were significant between Groups 1 and 3, 1 and 4, and 2 and 3. In the group of layering hematomas, the concentrations of these cytokines were higher than those in the other groups (IL-6, 3013 ± 214; IL-8, 1841 ± 204 [means ± SEMs]), whereas in trabecular hematomas the concentrations of cytokines were lower than those in...
Fig. 3. Graph showing a significant difference in the concentration of IL-6 in the CSDH among the neuroimaging Groups 1 and 3, 1 and 4, and 2 and 3. The Bonferroni test was used to compare couples of means. Group 1, layering-density hematoma; Group 2, mixed-density hematoma; Group 3, trabecular hematoma; Group 4, homogeneous-density hematoma.

The other groups (IL-6, 1137 ± 277; IL-8, 705 ± 263.6 [mean ± SEM]).

The interval from trauma did not influence the risk of recurrence, although it varied significantly among the various neuroimaging groups (p = 0.047) (Table 4 and Fig. 4). In fact, it was longer in trabecular hematomas than in the other CSDHs (mean interval 75 days).

Levels of IL-6 and IL-8 in CSDHs did not differ significantly with respect to the age of the hematoma or the age of the patient (p > 0.05). The levels of IL-6 were 2202 ± 1030 pg/ml and 1936 ± 1810 pg/ml in Groups A and B, respectively; the levels of IL-8 were also similar in both groups (1431 ± 809 pg/ml in Group A and 1316 ± 1150 pg/ml in Group B).

**Discussion**

In 1857 Virchow described CSDH as a specific dural inflammatory disease called “pachymeningitis hemorrhagica interna or proliferative hemorrhagic pachymeningitis.” He was the first to stress the importance of inflammation for the onset and development of this disease, because he believed that inflammation was related to a specific cause such as the bacteria responsible for meningitis, syphilis, or tuberculosis, and involved the entire dura mater. Later, several studies demonstrated that this process is a local inflammatory reaction of the dura mater in response to injury or external stimuli such as trauma, blood, CSF, fibrin, or fibrin degradation products.8,31,32,39,58 Furthermore, Friede and Schachenmayr47 and later Haines16 demonstrated that the simple cleavage of the inner dural layer (also known as the dural border cell layer) by a traumatic event, can create a virtual space inside that layer, the so-called subdural space. Overall, the complex pathophysiology of CSDH can be summarized in the following manner. After trauma, once the aforementioned space has been created, CSF or blood frequently collects within the dural border cell layer.16,31,32,40 Blood collection may be caused by the tearing of bridging veins subsequent to trauma. In elderly patients, as a result of brain atrophy, both the dural border cell layer and the bridging veins are stretched and can be very easily damaged by a traumatic event.16,43 Once this intradural space has been created, cells in the dural border begin to proliferate, representing the first step in the pathogenesis of CSDH.20,31,32,40,58

In fact, as these mesenchymal cells proliferate and differentiate, they form a sort of inflammatory capsule or membrane around the blood clots or CSF, called the external or outer membrane.29,31,32,38,42 The outer membrane of the CSDH is composed of a sort of granulation tissue in which several types of inflammatory cells—mast cells, eosinophils, neutrophils, monocytes, macrophages, endothelial cells, and fibroblasts—are continuously activated and recruited.8,10,16–18,20,22,44,53 This membrane also contains immature vessels and connective fibers and, on the whole, constitutes a source of inflammatory, angiogenic, fibrinolytic, and coagulation factors.19–22,25,33,46,49–51,55,57,58 Immunohistochemical analysis recently demonstrated a strong expression of the cytokine VEGF in most inflammatory cells infiltrating the neomembranes of CSDH, mainly in plasma cells and tissue macrophages.55 Furthermore, the role of VEGF in neovascularization and vascular hyperpermeability has been documented, confirming previous studies in which it was stated that inflammation is responsible for angiogenesis of the outer membrane.50,51

In summation, after trauma the sequence of events in the natural course of the CSDH consists of local inflammation, angiogenesis, vasopermeability (due to immature neovessels), bleeding, hypercoagulative activity, hyperfibrinolytic activity, and increased vasopermeability (due to bradykinin, which is activated by plasmin from high-molecular-weight kinogen). This leads to further inflammation caused by the release of proinflammatory factors such as cytokines and bradykinin, creating a self-enhancing vicious circle that is responsible for frequent rebleeding and enlargement of the CSDH.10,11,38–41,50,51,55

As important mediators as well as markers of the inflammation process, IL-6 and IL-8 are of particular interest. Interleukin-6 and -8 are produced by many different cell types, such as stimulated monocytes, macrophages, fibroblasts, endothelial cells, T-cells, B-lymphocytes, granulocytes, smooth muscle cells, eosinophils, chondrocytes, osteoblasts, mast cells, and glial cells.1–4,6,13,26,34,44,54,55

Interleukin-6 is a pleiotropic cytokine that influences immune and inflammatory responses and is one of the major physiological mediators of the acute phase reaction.26,44 With regard to IL-6 inflammation in the nervous system, very high levels of IL-6 frequently can be observed in the CSF of patients with bacterial or viral meningitis, as well as in those harboring gliomas.30,34,44,48 Normal levels of
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IL-6 were reported to be approximately 2 ± 1.9 pg/ml in the control group of a study in which CSF levels of IL-6 were evaluated in patients with psychiatric diseases.2 Recently, intracerebral overexpression of IL-6 in transgenic mice has been shown to be associated with neurological syndromes, the severity of which shows a correlation with levels of IL-6 expression.1,4,12,26,34,44,48 These mice are characterized by stunted growth, tremor, neurodegeneration, astrocystosis, and angiogenesis, from which we may infer a direct pathogenic role of IL-6 in inflammatory angiogenesis and in infectious and neurodegenerative diseases of the central nervous system. An extensive breakdown of the blood–brain barrier has also been demonstrated in these mice.26,34,44,48 Interleukin-6 can cause enlargement of the gap junction between endothelial cells and increase vascular permeability.50,59

With regard to IL-8, its role in the inflammation process is well established. It differs from all other cytokines in its specific ability to enhance adhesion molecule affinity on neutrophil granulocytes, activate them, and mediate their chemotaxis; for this last function, IL-8 is the prototype of the new class of cytokines called chemokines, and it is chemotactic for all known types of migratory immune cells.2,34,48,60 In addition, IL-8 supports angiogenesis and may play a role in angiogenesis-dependent processes such as granulation tissue, wound healing, and tumor growth.2,34,48,60 For all these functions IL-8 plays a pivotal role in acute and chronic inflammatory disorders.

Chronic subdural hematoma seems to present the typical features of chronic inflammatory processes. In this hematoma, the cytokines IL-6 and IL-8 are secreted by fibroblasts and by endothelial and inflammatory cells that are infiltrating the outer membrane. Production of IL-6 and IL-8 is increased by proinflammatory factors that are released after bleeding, such as platelet-activating factor, bradykinin, and thrombin.16,17,20,21,25,26,32 On the whole, it is not surprising that both IL-8, as a potent angiogenic and chemotactic factor, and IL-6, as a factor that increases inflammation and vaso-permeability, and causes the gap enlargement between endothelial cells and breakdown of the blood–brain barrier, are involved in the pathogenesis of CSDH.9,50,59 This is the complex context in which our study was performed. We observed that, in all patients, the concentrations of inflammatory cytokines were significantly elevated (p < 0.01) in the hematoma, whereas they were normal in serum, and that the serum coagulation parameters were normal both pre- and postoperatively. The level of C-reactive protein and the ESR were normal in all patients. Because its production is controlled by IL-6, C-reactive protein may be a serum marker of IL-6 production and activity in a systemic inflammatory process. Hence, the initial conclusion of our analysis is that a CSDH is a local, circumscribed inflammatory process.

Actually, this conclusion is not novel, because several authors have reported that different direct or indirect inflammatory markers such as fibrinogen degradation products, platelet-activating factor, VEGF, bradykinin, tissue plasminogen activator, IL-6, IL-8, and tumor necrosis factor are present at a higher concentration in a hematoma than in serum.7,8,11,19,23,33,37,58,41,43,46,49,51,55,57,60 Nevertheless, several of these papers differed from our study in that they also included patients with risk factors for CSDH, such as concomitant diseases.9,10,19,19,49,54

In the five patients in our series who presented with a recurrence, significantly (p < 0.01) higher levels of IL-6 and IL-8 were found in the CSDH than in hematomas of patients who did not experience a recurrence (Table 2 and Figs. 1 and 2). Four of these five patients had layering hematoma, and the other a mixed-density hematoma. The layering aspect observed on CT scans is also associated with a higher risk of recurrence, as already noted in other series.56,42 The time interval between trauma and hospital admission was not found to be a significant risk factor for recurrence, although the median interval in patients with layering hematomas was shorter than the overall median interval (of all groups, the longest median interval between trauma and onset of symptoms was found in the trabecular hematoma group). On the other hand, in the series reported by Nakaguchi, et al.,9 an interval shorter than 60 days proved to be a significant risk factor for recurrence. Nakaguchi, et al., also provided a neuroimaging-based definition

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**Means and 95.0 Percent Bonferroni Intervals**

**Fig. 4.** Graph showing differences in the interval from trauma among the various neuroimaging groups. On ANOVA the difference was significant. The Bonferroni test was used to compare couples of means; the difference was significant between Groups 1 and 3 and Groups 3 and 4. See legend to Fig. 3 for an explanation of groups.

Interestingly, the recurrence rate (14%) in our series was fairly high, considering that patients with concomitant disease had been excluded. Because the best modality of surgical management of CSDH has always been a controversial issue, at the moment we cannot exclude that this rate of recurrence was related to the modality chosen.18,39,43,54 In fact, it has been suggested in some recent papers that the best treatment for CSDH is a burr hole closed drainage system without irrigation.28,32,33,43 Authors of these papers reported lower recurrence rates (1–5%) in comparison with the rates reported in patients treated by burr hole irrigation (recurrence rate 10–20%), stating that the decrease in intracranial pressure that is obtained by the latter is so rapid that it damages the transverse vein severely enough to cause further bleeding. Moreover, this procedure increases the risk of air entering the cavity of the hematoma, which is also considered a risk factor for recurrence.28,40,43 On the other hand, to avoid recurrence, some authors prefer copious irrigation of the subdural fluid collection, so that fibrin clots and fibrin degradation products, which represent a source of angiogenic and inflammatory factors, are completely eliminated.9,10,21,23,39,42
of the different phases of hematoma development, starting with the traumatic event and followed chronologically by a homogeneous stage (Stage 1), a separated or multilayered stage (Stage 2), and a trabecular stage (Stage 3); these authors attempted to define the temporal boundaries of each of these stages.  

In this context, it should be remembered that the interval between trauma and the onset of symptoms from CSDH can vary according to the patient’s individual clinical condition, including the amount of brain atrophy, blood pressure levels, or the presence of concomitant diseases. Regarding the pathophysiology of CSDH, classification of the hematoma into different temporal stages, as suggested by Nakaguchi, et al., is acceptable. In fact, during the initial phase (Stage 1 or a homogeneous-density hematoma), there is not much bleeding because the balance between fibrinolysis and coagulation is maintained; in Stage 2 (layering-density hematoma) when hyperfibrinolysis takes place, there is considerable bleeding of the neomembrane. This ceases in Stage 3 ( trabecular hematoma) because the membrane has a large fibrous component (appearing hyperdense on the CT scan) and, therefore, exhibits an extremely low tendency to bleed. In our series, the values of IL-6 and IL-8 were significantly higher in patients with layering hematoma and significantly lower in the trabecular type (Table 3 and Fig. 3). Nevertheless, the cytokine levels were not influenced by the age of the hematomas, probably because the interval between trauma and onset of symptoms also depends on several individual factors (as already mentioned), which differ from one patient to another (p = 0.4).  

Suzuki and colleagues demonstrated that the levels of these cytokines are significantly lower in hygromas when compared with CSDHs. Hygromas also have a traumatic cause and can be considered, in chronological terms, to be precursors of CSDH, because they may evolve into this hematoma if they are not surgically treated.  

Suzuki and colleagues reported that IL-6 and IL-8 concentrations, as well as the levels of the IL-6 activating precursors, namely IL-1β and tumor necrosis factor-α, are significantly higher in the hygroma than in serum (values of IL-6 and IL-8 in the subdural effusion were 256.3 ± 93.7 pg/ml and 129.5 ± 51.9 pg/ml [means ± SEMs], respectively), indicating that the onset of a local inflammatory process within the dura is confined to the subdural fluid collection, without systemic involvement during the early phases (hygroma) of CSDH evolution. This correlates with our observations that only one patient exhibited a fever during the weeks before surgery.  

It seems probable that in all cases of CSDH, the development process of the hematoma across the various stages proposed by Nakaguchi, et al., occurs with time differences according to the intensity of the local inflammatory reaction. Therefore, when this reaction is severe, the hematoma is active with a higher tendency to rebleed and more frequently displays a layering aspect: in such hematomas the levels of inflammatory ILs are very high. On the contrary, in the very early (hygroma) or very late ( trabecular aspect, prevalence of fibrotic phenomena within the neomembrane) phases, during which local inflammation is low, the tendency to bleed is also low and the neuroimaging appearance of the hematoma is predominantly homogeneous (hypo- or isodense according to whether the bleeding is more or less recent) or has a homogeneous matrix and fibrotic high-density septum ( trabecular hematomas). By measuring the inflammatory cytokines within CSDH, it is possible to assess the degree of local inflammation. It would have been particularly interesting to determine the concentrations of IL-6 and IL-8 in the CSF and to assess any possible involvement of the subarachnoid space in this inflammatory process.  

Very high levels (range 15–4485 pg/ml) of IL-6 were also found in patients with an Enterovirus 71 infection of the central nervous system. Moreover, IL-8 was found to be strongly increased (up to ~800 pg/ml) in patients with spinal cord injury due to hypoperfusion and ischemia. On the other hand, with respect to the pathophysiology of CSDH, we believe that the arachnoidal spaces are not involved by inflammation because they are separated from the hematoma by its inner membrane, which does not contain inflammatory cells. Nevertheless, we also believe that in patients with CSDH, drainage of CSF may thwart the therapeutic intention by increasing the risk of new bleeding preoperatively and impairing or slowing down brain expansion postoperatively.  

On the basis of our data it seems likely that in a patient population with an anamnesis that is positive for trauma, but no other risk factors for CSDH, the main prognostic factor for recurrence is the degree of inflammation. We believe that patients with very high cytokine levels should undergo a prolonged antiinflammatory therapy. In any case, additional studies are needed to confirm these data and to evaluate the role of antiinflammatory agents including not only corticosteroid medications, but also cytokines with immunomodulatory effects, such as IL-10, or blocking antibodies, such as the anti–tumor necrosis factor, anti–IL–6, or anti–IL–8 antibody. The possible side effects of these drugs should be considered, particularly in those patients not eligible for this study, such as those suffering from concomitant diseases, who account for a significant number of patients with CSDHs.

Conclusions

On the basis of our results, the following conclusions can be drawn.

1) Trauma can produce the onset of a local chronic inflammatory reaction within the dural border cell layer, which may be considered the origin of a CSDH. Systemic inflammation was not detected either before or after surgery.

2) Local levels of IL-6 and IL-8 are high in a CSDH.

3) High levels of inflammatory cytokines are significantly associated with recurrence.

4) The appearance of a layering hematoma on a preoperative CT scan is also associated with recurrence and is accompanied by significantly higher levels of inflammatory cytokines.

5) The inflammatory cytokines IL-6 and IL-8 are significantly higher in layering hematomas than in trabecular or homogeneous ones. The lowest concentrations of these cytokines are found in trabecular hematomas.

6) The interval between trauma and symptoms is not significantly associated with hematoma recurrence, although this interval does differ significantly between a layering hematoma (Group 1) and a trabecular hematoma (Group 3).
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Of all the groups, the mean interval from trauma was longest in Group 3.

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