Interleukin-6 Levels in Cerebrospinal Fluid and Plasma in Patients with Severe Spontaneous Subarachnoid Hemorrhage

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■ BACKGROUND: **Inflammatory processes play a key role in the pathophysiology of subarachnoid hemorrhage (SAH). This study evaluated whether different temporal patterns of intrathecal and systemic inflammation could be identified in the acute phase after SAH. The intensity of the inflammation was also assessed in clinical subgroups.**

■ METHODS: **Cerebrospinal fluid (CSF) and blood samples were collected at days 1, 4, and 10 after ictus in 44 patients with severe SAH. Interleukin-6 (IL-6) was analyzed by a routine monoclonal antibody-based method. Median IL-6 values for each day were calculated. Day 4 IL-6 values were compared in dichotomized groups (age, sex, World Federation of Neurosurgical Societies [WFNS] grade, Fisher scale grade, outcome, vasospasm, central nervous system infection and systemic infections).**

■ RESULTS: **CSF IL-6 levels were significantly elevated from day 1 to days 4 and 10, whereas plasma IL-6 showed a different trend at lower levels. Median CSF IL-6 concentrations for days 1, 4, and 10 were 876.5, 3361, and 1567 ng/L, whereas plasma was 26, 27.5, and 15.9 ng/L, respectively. No significant differences in CSF concentrations were observed between the subgroups, with the most prominent one being in day 4 IL-6 in the WFNS subgroups (grades 1–3 vs. 4–5, 1158.5 vs. 5538 ng/L; $P = 0.056$). Patients with systemic infection had significantly higher plasma IL-6 concentrations than patients without infection (31 vs. 16.05 ng/L, respectively; $P = 0.028$).**

■ CONCLUSIONS: **Distinctly different inflammatory patterns could be seen intrathecally compared with the systemic circulation. In plasma, a significant difference in the intensity of the inflammation was seen in cases with systemic infection. No other subgroup showed statistically significant differences.**

INTRODUCTION

Spontaneous subarachnoid hemorrhage (SAH) is a common neurosurgical emergency caused mainly by the rupture of intracranial aneurysms. Overall, mortality rates of 25%–40% have been reported. Among the survivors, 40% present with permanent neurologic deficits.[1] Factors significantly associated with unfavorable outcome after SAH are advanced age, worse clinical status at admission (based on the World Federation of Neurosurgical Societies [WFNS] grade), and higher amount of blood on the admission computed tomography (CT) scan measured with the Fisher scale.[2]

The outcome not only depends on the bleeding itself but also on complications that can occur shortly after ictus, such as rebleeding, vasospasm, acute hydrocephalus, cardiovascular or respiratory problems, and infections. Outcome has changed over the years because of the improvements in aneurysm treatment modalities and the introduction of dedicated neurointensive care units (NICUs).[3-5] Neurointensive care is directed at avoiding and treating secondary insults to reduce the development of secondary brain injury.[6,7]

Key words
- Inflammatory response
- Interleukin-6
- Neuroinflammation
- SAH
- Subarachnoid hemorrhage

Abbreviations and Acronyms
AVM: Arteriovenous malformation
CNS: Central nervous system
CSF: Cerebrospinal fluid
CT: Computed tomography
GOS: Glasgow Outcome Scale
IL-6: Interleukin-6
NICU: Neurointensive care unit
SAH: Subarachnoid hemorrhage
WFNS: World Federation of Neurosurgical Societies

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There is substantial evidence that inflammatory processes play a key role in the pathophysiology of SAH and the development of secondary brain injury.[8] Numerous studies have elucidated the role of inflammatory mediators leading to complications, such as vasospasm, delayed cerebral ischemia, or hydrocephalus, affecting the outcome.[9-13] Potential biomarkers that have been studied include oxidative stress molecules such as nitric oxide, inflammatory cytokines such as interleukin-1, interleukin-6 (IL-6), and tumor necrosis factor-alpha, brain injury biomarkers such as S100B and glial fibrillary acidic protein, and vascular pathology molecules such as endothelin-1.[1] A major goal has been the identification of biomarkers that can be used to characterize the course of the disease, predict the development of complications, and potentially be useful as therapeutic targets.[14]

IL-6 is a proinflammatory cytokine of low molecular weight (24 kD) secreted by mononuclear phagocytes, T cells, and endothelial cells in response to acute brain injury, but also many other conditions such as trauma, infection, and cardiovascular diseases.[15,16] In the context of SAH, the secretion of IL-6 is mainly triggered by mononuclear leukocytes that are found within the blood clot in the subarachnoid space.[17,18] Several studies have demonstrated elevated IL-6 levels in cerebrospinal fluid (CSF) and in the interstitial space of patients with SAH and a positive correlation between increased IL-6 and vasospasm.[19-25]

In the present prospective study, we assessed the time course of the inflammatory response in the acute phase of the SAH by measuring IL-6 levels at days 1, 4, and 10 after ictus. Samples were taken from ventricular CSF and arterial blood to see in which fluid compartment the inflammatory response was most strongly activated. Furthermore, we compared the IL-6 patterns based on parameters describing the severity of the bleeding and the course of the acute disease.

METHODS

Patient Population

Forty-four patients with SAH who were admitted to the NICU, Uppsala University Hospital between May 2013 and July 2016 were prospectively enrolled in the study. Patients with SAH not requiring insertion of external ventricular drainage, those considered terminally ill from the SAH (i.e., Glasgow Coma Scale score of 3 with bilaterally fixed dilated pupils), and those with previous conditions treated with steroids were not included. **Table 1** summarizes the basic characteristics of the population. There were 17 men and 27 women, and the mean age was 58 years (range, 37–81). All patients were admitted within 24 hours of ictus, and the SAH diagnosis was confirmed by CT and lumbar puncture (in 1 case). The median Hunt and Hess grade at admission was 3, and the median Glasgow Coma Scale score was 10.[26,27] The WFNS grade was extracted from Glasgow Coma Scale scores (median, 4).[28] Diagnostic CT scans were evaluated and categorized according to Fisher classification scale (median grade, 4).[29] Functional outcome using the Glasgow Outcome Scale (GOS) was assessed 1 year after ictus by a research nurse.[30]

Bleeding Source and Treatment

All patients underwent CT angiography and, if necessary, 3-dimensional rotational digital subtraction angiography for identification of the bleeding source. Forty patients were found to have aneurysms (27 anterior circulation, 13 posterior circulation), and 1 patient was found to have an arteriovenous malformation (AVM) with feeders from the posterior inferior cerebellar artery. In 3 patients, no bleeding source was identified on the initial or the subsequent angiographic examinations. Endovascular techniques were used for the treatment of 37 aneurysms (including the AVM), whereas the remaining 4 were surgically clipped (**Table 1**).

Table 1. Baseline Characteristics of the Patient Population (N = 44)

Characteristic	Value
Sex	
Male	17 (38.6)
Female	27 (61.4)
Age (years)	58 (37–81)
Bleeding source*	
Anterior circulation	27
Posterior circulation	13
AVM	1
Not identified	3
Treatment	
Endovascular occlusion	37
Surgical clipping	4
No treatment	3
Clinical status at admission	
WFNS grade 1	4
WFNS grade 2	12
WFNS grade 3	2
WFNS grade 4	19
WFNS grade 5	7
Fisher grade on admission CT scan	
Grades 1–3	15
Grade 4	29
Functional outcome (GOS) 1 year post-SAH	
Favorable (4–5)	13
Poor (1–3)	31

Values are number of participants, mean (range), or number of participants (%).
AVM, arteriovenous malformation; WFNS, World Federation of Neurosurgical Societies; CT, computed tomography; GOS, Glasgow Outcome Scale; SAH, subarachnoid hemorrhage.
*Forty aneurysms and 1 AVM with feeders from the posterior inferior cerebellar artery (included in posterior circulation).

NICU Treatment Protocol

All patients were operated within 24 hours of ictus with insertion of external ventricular drainage. Early aneurysm treatment (within

48 hours from ictus) was performed in all cases. Standardized NICU treatment protocols were applied with maintenance of normovolemic state, nimodipine administration, sedation, and mechanical ventilation when needed.[31] Routine monitoring included continuous intracranial pressure and cerebral perfusion pressure registration, arterial and central venous lines, continuous electrocardiography, daily transcranial Doppler examinations, regular CT scans including Xenon CTs (CereTom, Neurologica, Boston, Massachusetts, USA) for bedside cerebral blood flow measurements, and regular wake-up tests 3–6 times daily for assessment of neurologic status. Additional studies such as electroencephalography, magnetic resonance imaging, angiography, and perfusion CT scan were performed when indicated.

Blood and CSF Samples

Arterial blood plasma and ventricular CSF samples were obtained within the first 24 hours and at day 4 and day 10 after admission. CSF samples were collected intermittently from the ventricular drain and centrifuged at 20°C before analysis. Blood samples were collected intermittently through the arterial line and were sent directly for analysis. IL-6 was preferred in this study as a routine biomarker that is easy to detect and measure in both compartments. IL-6 concentrations were analyzed in both compartments by a routine monoclonal antibody-based method at the clinical chemistry department, Uppsala University Hospital (Roche CobasE 602 (Roche, Basel, Switzerland); reference interval for plasma <7 ng/L; for CSF not available). Blood and CSF samples were sent for cultures to confirm possible bacterial infections. Bacterial cultures were also performed, when indicated, in urine and tracheal secretions.

Definitions

In this study, a clinical definition of vasospasm was used: 1) new focal neurologic deficit and/or decrease in the level of consciousness not attributable to new hemorrhage or hydrocephalus that required pharmacologic and/or endovascular treatment and 2) delayed cerebral ischemia seen on CT scan. Patients were considered to have infection only when positive bacterial cultures were confirmed and not based on symptoms or elevation of white blood cells or other inflammatory parameters in blood and/or CSF.

Analysis and Statistics

Statistical analyses and graphical presentations were performed using the Statistica software (StatSoft, Inc., Tulsa, Oklahoma, USA). Medians and 25th and 75th percentiles were chosen because the values were not normally distributed (distribution of data tested visually with histograms). Wilcoxon matched pairs test was used for comparison of median IL-6 values between days 1, 4, and 10. Mann-Whitney U test was used for comparison of the day 4 IL-6 values between the different groups. Results were considered significant at the $P < 0.05$ level.

The median IL-6 values in CSF and plasma were calculated for days 1, 4, and 10 to estimate the temporal intrathecal and systemic inflammatory response. Day 4 median IL-6 values were then isolated and compared between groups based on dichotomization of age (≥60 vs. <60 years), sex (men vs. women), amount of blood on the admission CT scan based on the Fisher scale (grades 1–3 vs. 4), WFNS grade at admission (grades 1–3 vs. 4–5), functional outcome based on GOS score (favorable vs. unfavorable), and presence or absence of vasospasm/delayed cerebral ischemia. We also monitored presence or not of culture-verified central nervous system (CNS) infection and systemic infection.

RESULTS

Inflammatory Trend and Intensity

The temporal intrathecal and systemic inflammatory response estimated by ventricular CSF and arterial plasma levels of IL-6 are shown in Figures 1 and 2, respectively. In general, the inflammatory response seemed to be more intense intrathecally than systemically. In CSF, the initial IL-6 levels on day 1 were followed by significantly increased IL-6 values on day 4 that had decreased on day 10, but still remained significantly higher than the day 1 values (Table 2). In plasma, a different pattern of inflammatory reaction was noticed. The IL-6 values were above the reference interval already from day 1, remained stable until day 4, and decreased on day 10. The differences in plasma IL-6 between day 1 and day 4 versus day 10 were statistically significant (Table 2).

Day 4 IL-6 Values in Subgroups

Day 4 IL-6 concentrations were used as an indicator of the intensity of the inflammatory response. Median day 4 IL-6 values in CSF and plasma were compared between different subgroups as shown in Table 3. In general, larger numerical between-group variations were noticed in CSF compared with plasma IL-6

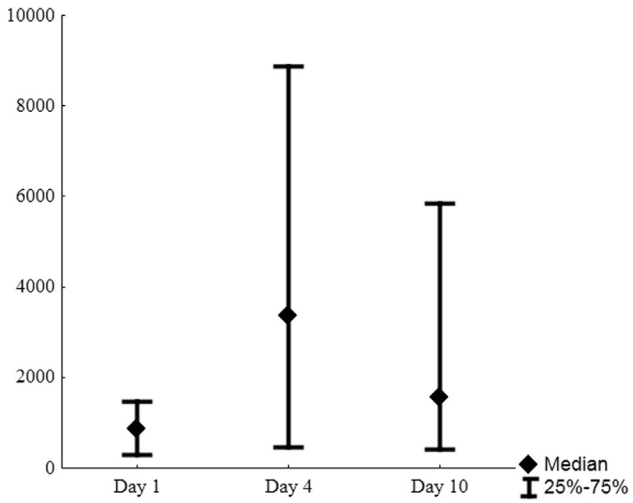

Figure 1. Temporal pattern of the intrathecal inflammatory response estimated by ventricular cerebrospinal fluid interleukin-6 values (ng/L). The initial response on day 1 was followed by significantly higher values on day 4 that had decreased on day 10, but still remaining significantly higher than day 1 values (Table 2). Medians and 25th and 75th percentiles are shown for days 1, 4, and 10.

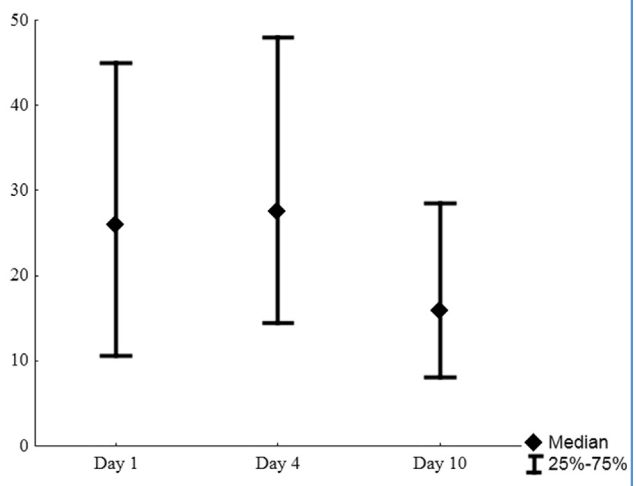

Figure 2. Temporal pattern of the systemic inflammatory response estimated by arterial plasma interleukin-6 (IL-6) values (ng/L). The initial day 1 response was above the reference interval (<7 ng/L) for plasma IL-6, remained stable to day 4, and decreased significantly toward day 10 (Table 2). Medians and 25th and 75th percentiles are shown for days 1, 4, and 10.

values. Older patients, men, patients with larger hemorrhage (Fisher grade 4), patients with worse clinical status at admission (WFNS grade 4–5), patients with unfavorable outcome, patients with vasospasm/delayed cerebral ischemia, patients with CNS infection, and patients with systemic infection had higher numerical IL-6 concentrations in CSF, but not statistically significant. Regarding plasma values, the largest difference, which was also statistically significant, was noticed between patients with and without systemic infection (31 vs. 16.05 ng/L; P = 0.028).

Infections

Culture-verified systemic infections (pneumonia, urinary tract infection, septicemia, and clostridium colitis) were found in 32 patients, and meningitis was found in 8 patients. Five patients had both systemic and CNS infections. A total of 39 patients were treated with antibiotics during the first 10–12 days of the NICU stay. The number of patients who received antibiotics for meningitis based on the development of fever and the inflammatory reaction in CSF was 24.

Table 2. Comparison of Median IL-6 Values in CSF and Plasma Between Different Days

Days	Compartment	Values	*P* Value
Day 4 vs. day 1	CSF	3361 vs. 876.5	<0.01
	Plasma	27.5 vs. 26	0.77
Day 10 vs. day 1	CSF	1567 vs. 876.5	<0.01
	Plasma	15.9 vs. 26	<0.01
Day 10 vs. day 4	CSF	1567 vs. 3361	0.14
	Plasma	15.9 vs. 27.5	<0.01

In CSF, significantly higher interleukin-6 values (ng/L) were seen on day 4 and day 10 compared with day 1. In plasma, no difference was seen between day 1 and 4 values, whereas day 10 values were significantly lower than both day 1 and 4 values. A Wilcoxon matched pairs test was used for the comparison of interleukin-6 values.
CSF, cerebrospinal fluid.

Table 3. Median Day 4 Interleukin-6 Values in Ventricular Cerebrospinal Fluid and Arterial Plasma in Dichotomized Clinical Groups

Groups	Median Day 4 IL-6 Values (ng/L)		*P* Value
Age	<60 years (n = 22)	≥60 years (n = 22)	
CSF	2406	3923.5	0.841
Plasma	30	26	0.823
Sex	Female (n = 27)	Male (n = 17)	
CSF	2955	4080	0.781
Plasma	31	24	0.311
Fisher grade	1–3 (n = 15)	4 (n = 29)	
CSF	960	4502	0.193
Plasma	30	24	0.372
WFNS grade	1–3 (n = 18)	4–5 (n = 26)	
CSF	1158.5	5538	0.056
Plasma	29.5	26	0.990
Outcome	4–5 (n = 13)	1–3 (n = 31)	
CSF	960	4928	0.132
Plasma	26	30	0.315
Vasospasm	No (n = 28)	Yes (n = 16)	
CSF	1607	4791	0.550
Plasma	28	26.5	0.912
CNS infection	No (n = 36)	Yes (n = 8)	
CSF	2942.5	3517.5	0.637
Plasma	29.5	21.4	0.493
Systemic infection	No (n = 12)	Yes (n = 32)	
CSF	917.5	4578	0.196
Plasma	16.05	31	0.028

Higher numerical CSF IL-6 values, although not statistically significant, were noticed in older patients, men, patients with larger hemorrhage, patients with worse WFNS grade on admission, patients with unfavorable outcome, patients with vasospasm, and patients with infection, suggesting a positive correlation between the severity of the bleeding and the intensity of the inflammation. Plasma IL-6 values were more consistent between the groups and did not suggest a similar correlation, with the exception of systemic infections where the presence of infection was associated with significantly higher day 4 IL-6 values. Mann-Whitney *U* test was used for comparison of IL-6 values.
IL-6, interleukin-6; CSF, cerebrospinal fluid; WFNS, World Federation of Neurosurgical Societies; CNS, central nervous system.

DISCUSSION

In this study, we measured IL-6 in ventricular CSF and arterial plasma at days 1, 4, and 10 after SAH to compare the intrathecal and systemic inflammatory response in the acute phase of the disease. We found distinctly different temporal patterns of inflammatory response in the 2 compartments (Figures 1 and 2 and Table 2). Moreover, the intrathecal inflammation appeared to be considerably more intense than the systemic inflammation. This suggests that an endogenous production and/or secretion of inflammatory cytokines takes place within the CNS after SAH. Those cytokines may later cross the disrupted blood-brain barrier into the bloodstream, leading to a systemic inflammatory response syndrome and subsequent systemic complications.[32-34]

Significantly higher IL-6 concentrations in CSF were noticed on day 4 and day 10 compared with day 1. The higher values on day 4 coincide with the time window observed in clinical practice when patients are more susceptible to vasospasm, whereas the concentrations decreased toward day 10 when the patients are usually more stable. We found numerically higher IL-6 levels, although not statistically significant, suggesting more intense intrathecal inflammatory response in patients with higher Fisher grade SAH, patients with worse clinical status at admission, patients with complications (vasospasm and infections), patients with unfavorable outcome, and in men and older patients (Table 3). This is in line with the hypothesis that the severity of the bleeding correlates with the intensity of the inflammation.

The systemic inflammatory response was not as intense as the intrathecal response, nor did it follow a similar temporal pattern. Plasma IL-6 levels have previously been used as a predictor of the severity of the disease and outcome in other conditions where systemic inflammation is activated.[35-37] Our results did not support this. The systemic inflammatory response did not seem to be affected by the severity of bleeding in the same consistent pattern as the intrathecal response. No essential differences were seen between the subgroups except for patients with systemic infections who had significantly higher day 4 median IL-6 concentrations compared with patients without infection.

Our results suggest that the intrathecal inflammatory response seems more suitable to describe the clinical course after SAH than the systemic inflammation. Sarrafzadeh et al.[23] reached the same conclusion in their study of 38 patients with SAH who were collectively divided into 2 groups (symptomatic vs. asymptomatic), and IL-6 levels were measured in the CSF, the cerebral interstitial fluid (samples taken through microdialysis catheters), and plasma throughout a period of 14 days after ictus. The findings of this study (with the additional interstitial measurements) were quite similar with our own regarding the elevated IL-6 levels in all compartments and their temporal patterns; however, this study did not report correlations in specific clinical subgroups as in the present study.

Systemic and CNS infections could influence the course and intensity of inflammation and were therefore studied specifically.[38] The 8 patients with culture-verified meningitis showed a trend of higher day 4 IL-6 concentrations in CSF and lower plasma concentrations compared with those without infection. The fact that the difference was not as profound as in other clinical subgroups may indicate that the intrathecal inflammatory response is already activated post-SAH and not affected significantly by the presence of infection. Systemic infections were far more common (32 of 44 patients) and were correlated with higher day 4 IL-6 values in CSF and plasma (significantly in the latter), perhaps because of the activation of a more extensive inflammatory reaction from the affected organs along with the intracranial compartment.

Unexpected in our results was the large number of patients who received antibiotics for meningitis even in the absence of verified infection. The antibiotics were often given on suspicion of meningitis based on clinical parameters (e.g., fever) and white blood cells and lactate in the CSF, while waiting for results from CSF bacterial cultures. Better methods to separate real infections from the inflammatory response are obviously needed.

We used IL-6 as the only biomarker of inflammation because this is a well described proinflammatory cytokine with important implications in the pathophysiology of SAH and other related neurologic conditions, such as ischemic stroke.[39-41] However, the inflammatory response is a complicated process involving many substances and mechanisms. Activation of immunomodulatory cells within the CNS such as microglia and the following upregulation of cell adhesion molecules is essential.[42-44] Possible mechanisms include direct contact with the smooth muscle cells of cerebral vessels or, indirectly, through the induction of synthesis of vasoconstrictors such as endothelin-1.[38,45] Notably, blood breakdown products are not entirely necessary because data show that injection of proinflammatory materials intracisternally induces vasospasm in the absence of SAH.[8]

Limitations of the Study

Among the shortcomings of this study are the small number of patients included and the fact that the cohort consists of a uniform group of patients with SAH with severe bleeding and poor clinical status at admission requiring NICU care. A larger sample and better distributed throughout the whole SAH clinical spectrum would most probably provide more information. We do not have data to adjust the IL-6 results for levels of white blood cells and erythrocytes in CSF, which may be a limitation even though we consider the inevitable presence of these cells an integral part of the disease process. Finally, the acute inflammatory response after SAH is a complex and multifactorial cascade with great interindividual variations between the molecules involved and cannot be described adequately by one parameter alone (IL-6 in this study). However, this study serves as a pilot supporting a role of neuroinflammation in the pathophysiology of SAH and its complications. More studies where larger numbers of inflammatory cytokines and other biomarkers are examined are clearly needed.

CONCLUSIONS

Distinctly different temporal patterns of inflammatory responses were seen intrathecally and systemically in patients with SAH.

The higher intensity of the inflammatory response observed in the intrathecal compartment suggests endogenous cytokine production within the CNS after SAH. The significant elevation of IL-6 levels in ventricular CSF from day 1 to day 4 may carry valuable prognostic information for the individual patient regarding the risk of secondary complications, such as vasospasm/delayed neurologic deficit development. In plasma, a significant difference in the intensity of the inflammation was seen in cases with systemic infection. No other subgroup showed statistically significant differences.

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