Interleukin 6 in the Cerebrospinal Fluid as a Biomarker for Onset of Vasospasm and Ventriculitis After Severe Subarachnoid Hemorrhage

Markus Lenski1, Volker Huge2, Josef Briegel2, Jörg-Christian Tonn1, Christian Schichor1, Niklas Thon1

OBJECTIVE: The aim of the study was to investigate the diagnostic potential of interleukin 6 (IL-6) and other soluble biomarkers in serum and cerebrospinal fluid (CSF) for early diagnosis of cerebral vasospasm (cVSAH) and external ventricular drain–associated ventriculitis (VCSAH) and to separate these conditions from aneurysmal subarachnoid hemorrhage (aSAH) without further complication (SAHw/o/c).

METHODS: The concentrations of serum biomarkers and markers in the CSF were collected in 63 consecutive patients with aSAH and external ventricular drainage. Arithmetical means and standard deviations, area under the curve (AUC), cutoff values (C-OFF), sensitivity (SE), and specificity (SP) were calculated for markers and their correlation with SAHw/o/c, cVSAH, and VCSAH.

RESULTS: Clinical courses included 27 patients with cVSAH, 17 with VCSAH, and 19 with SAHw/o/c. Mean ± standard deviation CSFIL-6 values were 7588 ± 4580 pg/mL at onset of VCSAH and 4102 ± 4970 pg/mL for cVSAH and higher than 234 ± 239 pg/mL in SAHw/o/c( P < 0.001). CSFIL-6 showed excellent diagnostic potential for differing between VCSAH and SAHw/o/c (AUC, 1.00; C-OFF, 707; SE, 100%; SP, 100%), and a moderate diagnostic potential for differing VCSAH from cVSAH (AUC, 0.757; C-OFF, 3100 pg/mL; SE, 86.7%; SP, 70.6%). The concentration of CSFIL-6 within the cVSAH group was significantly increased compared with SAHw/o/c (AUC, 0.937; C-OFF, 530 pg/mL; SE, 87.5%; SP, 91.7%).

CONCLUSIONS: CSFIL-6 is increased after aSAH in patients with cVSAH or VCSAH. Patients with aCSFIL-6 level higher than a C-OFF of 3100 pg/mL have an increased likelihood for VCSAH; patients with CSFIL-6 levels between 530 and 3100 pg/mL have an increased posttest probability for cVSAH.

INTRODUCTION

Aneurysmal subarachnoid hemorrhage (aSAH) is a neurosurgical emergency that causes only 5% of strokes but leads to 25% of stroke-related mortalities worldwide. The incidence of aSAH varies between populations from 2.0/10^5 patient-years in China up to 22/10^5 patient-years in Finland. The incidence in Germany is approximately 6–8/10^5 adults annually. Cerebral vasospasm (cVSAH) and external ventricular drain (EVD)-associated infections contribute significantly to the high

Key words
- Aneurysm
- Cerebral vasospasm
- Cerebrospinal fluid
- EVD-associated infection
- Interleukin 6
- Subarachnoid hemorrhage

Abbreviations and Acronyms
- aSAH: Aneurysmal subarachnoid hemorrhage
- AUC: Area under the curve
- CRP: C-reactive protein
- CSF: Cerebrospinal fluid
- CT: Computed tomography
- CTA: Computed tomography angiography
- cVSAH: Cerebral vasospasm
- DSA: Intra-arterial digital subtraction angiography
- EVD: External ventricular drain
- GOS: Glasgow Outcome Scale
- ICU: Intensive care unit
- IL-6: Interleukin 6
- iLR: Interval likelihood ratio
- ILR: Positive likelihood ratio
- MRA: Magnetic resonance angiography
- CSFPMN%: Percentage of polymorphonuclear cells
- SAH: Subarachnoid hemorrhage
- SAHw/o/c: Aneurysmal subarachnoid hemorrhage without further complication
- TCD: Transcranial Doppler
- VCSAH: EVD-associated ventriculitis
- WFNS: World Federation of Neurosurgical Societies

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Citation: World Neurosurg. (2017) 99:132-139.
http://dx.doi.org/10.1016/j.wneu.2016.11.131
Journal homepage: www.WORLDNEUROSURGERY.org
Available online: www.sciencedirect.com
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morbidty and mortality of this disease. The exact pathomechanism for the occurrence of cVSSAH is not completely understood. The extravasation of red blood cells into the subarachnoid space and their subsequent lysis lead to an activation of the immune response, resulting in increased proinflammatory cytokine levels in the cerebrospinal fluid (CSF). A causal relationship between increased cytokine levels and cVSSAH has never been identified, but they correlate with adverse clinical outcome in patients with aSAH. Therefore, current research concentrates on biomarkers in serum and CSF for diagnosing cVSSAH at an early stage to treat cVSSAH effectively from the beginning. Increased interleukin 6 (IL-6) levels in the CSF (CSF-IL-6) have also been reported in patients with bacterial meningitis, in particular in association with an EVD. The aim of this study was to investigate the diagnostic potential of IL-6 and other inflammatory markers in serum and CSF for early diagnosis of cVSSAH and EVD-associated ventriculitis (VCSAH) and to separate these conditions from clinical courses after severe aSAH but without further complications (SAHw/o/c).

METHODS

Study Population

For this retrospective single-center analysis, all 63 consecutive adult patients (>18 years of age) were included who were treated on our neurosurgical intensive care unit (ICU) for severe aSAH with an EVD between 1 January 2013 and 15 October 2015. Existence and severity of aSAH was determined on admission by using the Fisher grade for SAH appearance on computed tomography (CT) scans and the World Federation of Neurosurgical Societies (WFNS) classification system. The bleeding source was identified by CT angiography (CTA) and routine intra-arterial digital subtraction angiography (DSA) as well as magnetic resonance angiography (MRA), if indicated. Early treatment of ruptured aneurysm was performed by neurosurgical clipping or neuroradiologic intervention according to an interdisciplinary decision-making process. This retrospective analysis was accepted by our institutional ethics committee.

Biomarkers in Serum and CSF

Indications for EVD were aSAH with intraventricular hemorrhage and hydrocephalus and/or with clinically not assessable neurologic status. EVD was routinely implanted under strictly aseptic conditions and antibiotic prophylaxis (single shot of 3 g cefuroxime intravenously) in the emergency room under CT control or in the operating theater. The hair was shaved in the area of the Kocher point (2.5 cm from the midline and approximately 12 cm posterior to the nasion) followed by skin disinfection with a povidone-iodine solution. The skin incision was performed on the Kocher point, followed by a drill hole with a gimlet and catheter implantation into the lateral ventricle. Correct positioning was confirmed and an acute bleeding excluded by a control CT scan. No subcutaneous tunneling was routinely performed. The EVD was connected to a closed CSF collection system. A purse-string stitch sutured the wound and secured the position of the catheter. The wound and the exit point of the EVD were covered with sterile dressings.

CSF was aspirated in a strictly sterile fashion by a physician via the proximal 3-way stopcock. According to our clinical routine in SAH management, the serum markers IL-6, C-reactive protein, and white blood cell count were determined daily. Serum procalcitonin levels were measured twice a week or more frequently if a bacterial infection or sepsis had to be followed up. The CSF biomarkers CSF-IL-6 and percentage of polymorphonuclear cells (CSF-PMN%) were determined daily from the installation until the removal of the EVD. All serum and CSF analyses were measured in the Department of Laboratory Medicine of our hospital. Quantification of biomarker levels were performed according to the manufacturer’s instructions and quality control was ensured. No blood or CSF specimen was obtained solely for the purpose of this study.

Definitions of Vasospasm and Ventriculitis After aSAH

VCSAH was defined as proven ventriculitis with a positive microbiological CSF culture combined with clinical signs of infection or as suspected ventriculitis with abnormal CSF parameters such as low CSF glucose levels (<40 mg/dL, or <50% of serum glucose), high CSF protein levels (>50 mg/dL), CSF pleocytosis (100/mm³), positive CSF Gram stain, and organism cultured from the blood or EVD tip in the absence of a positive CSF culture. These criteria are inspired by the modified 2008 criteria for nosocomial infections from the U.S. Centers for Disease Control and Prevention for diagnosing VCSAH. Onset of infection was defined as the day that antibiotic treated was initiated.

cVSSAH was diagnosed when at least 1 of the following 3 criteria was fulfilled: 1) new neurologic deficit without competing cause in a clinically assessable patient; 2) mean middle cerebral artery or anterior cerebral artery blood flow higher than 120 cm²/second and a positive Lindegaard Index with a mean middle cerebral arterial/ internal carotid artery flow ratio higher than 3 measured by transcranial Doppler (TCD) ultrasonography or 3) vasospasm on CTA, MRA orDSA.

Statistical Analysis

We used the biomarker concentrations at the time of first diagnosis of VCSAH or cVSSAH. For the biomarker levels in the SAHw/o/c group, we used the biomarker levels of the seventh day after SAH, because mean day for a complication after SAH was 7.2 ± 2.7 days. Main outcome parameters of this study were the positive likelihood ratio (+LR), negative likelihood ratio (−LR), interval likelihood ratio (ILR), sensitivities, and specificities. Receiver operating characteristic curves and corresponding area under the curve (AUC) were calculated to determine the diagnostic potential of each biomarker. A significant difference of the arithmetical mean of biomarker concentrations in patients with VCSAH, cVSSAH, and SAHw/o/c was identified using a 1-way analysis of variance. Significance level was set at P < 0.05. Youden J statistic was used to identify the cutoff value with maximized sensitivity and specificity. SPSS 17.0 (SPSS Inc., Chicago, Illinois, USA) and 23.0 for Windows were used to perform statistical analysis.

RESULTS

Mean age of the study participants was 55.2 ± 12.5 years (range, 16–80 years), and 42 (66.7%) were women. Patient data including...
clinical scores on admission and Fisher grading of aSAHs are presented in Table 1. Twenty-nine patients (46%) presented with a poor WFNS score of IV or V. Fifty-five patients (87.3%) had massive bleeding (Fisher grade ≥III), with an intraventricular and/or intraparenchymal hemorrhage in 17 cases (Fisher grade IV, 27%). The bleeding source was an aneurysm in 62 patients, in 5 of whom (8%) the aneurysm was associated with an arteriovenous malformation. Aneurysm localizations are outlined in Table 1. In 1 patient with poor clinical status (WFNS 4) and fulminant basal SAH, no bleeding source could be identified by repeated DSA and MRI investigation. Forty-one patients were treated by clipping, 14 by endovascular intervention, and 8 with poor clinical performance by conservative treatment only. During the course of the disease, 27 patients (42.8%) developed CVSAH, which occurred on average 5.6 ± 4.2 days after the bleeding. SAH WFNS ≥ IV was statistically significantly associated with an increased incidence of vasospasm (P < 0.01, 2 test). In 17 patients (27%), a VCSAH was diagnosed. Ventriculitis developed on average 7.8 ± 2.3 days after aSAH. In 10 patients with VCSAH (58.8%), a causative pathogen was defined and included coagulase-negative staphylococci (n = 6), Propionibacterium acnes (n = 2), Burkholderia (n = 1), and Bacillus simplex (n = 1), respectively (EVD tip, n = 5; wound swab, n = 2; CSF, n = 3). In 19 patients, no CVSAH or VCSAH was diagnosed (SAHw/o/c). Overall, 9 patients (14.3%) died during the course of the disease including all patients who received conservative treatment because of poor clinical condition on admission; in none of these patients was death caused by an event of rebleeding. Six of the 9 deceased patients belonged to the group with CVSAH or VCSAH (P = 0.026). At the time of discharge from the ICU, 10 patients (15.9%) had a Glasgow Outcome Scale (GOS) score of 2, 12 patients a GOS score of 3, 3 patients (4.8%) a GOS score of 4, and 9 patients a GOS score of 5.

### Table 1. Characteristics of Patients with Subarachnoid Hemorrhage and External Ventricular Drain

<table>
<thead>
<tr>
<th>Aneurysm localizations</th>
<th>No such complication (aneurysmal subarachnoid hemorrhage without further complication)</th>
<th>Clipping (external ventricular drain—associated ventriculitis)</th>
<th>Coilng</th>
<th>Conservative</th>
<th>Embolization</th>
<th>VCSAH</th>
<th>CVSAH</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>18 (28.6)</td>
<td>16 (25.4)</td>
<td>8 (12.7)</td>
<td>3 (4.8)</td>
<td>9 (14.3)</td>
<td>1 (1.6)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Anterior cerebral artery</td>
<td>1 (1.6)</td>
<td>7 (11.1)</td>
<td>1 (1.6)</td>
<td>1 (1.6)</td>
<td>9 (14.3)</td>
<td>1 (1.6)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Vertebral artery</td>
<td>37 (58.7)</td>
<td>8 (12.7)</td>
<td>11 (17.5)</td>
<td>11 (17.5)</td>
<td>10 (15.9)</td>
<td>12 (19.0)</td>
<td>12 (19.0)</td>
</tr>
<tr>
<td>Posterior inferior cerebellar artery</td>
<td>18 (28.6)</td>
<td>1 (1.6)</td>
<td>1 (1.6)</td>
<td>1 (1.6)</td>
<td>1 (1.6)</td>
<td>1 (1.6)</td>
<td>1 (1.6)</td>
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<tr>
<td>Medial cerebral artery</td>
<td>8 (12.7)</td>
<td>1 (1.6)</td>
<td>11 (17.5)</td>
<td>1 (1.6)</td>
<td>12 (19.0)</td>
<td>12 (19.0)</td>
<td>12 (19.0)</td>
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<tr>
<td>Internal carotid artery</td>
<td>37 (58.7)</td>
<td>8 (12.7)</td>
<td>11 (17.5)</td>
<td>11 (17.5)</td>
<td>10 (15.9)</td>
<td>12 (19.0)</td>
<td>12 (19.0)</td>
</tr>
<tr>
<td>Anterior communicating artery</td>
<td>8 (12.7)</td>
<td>1 (1.6)</td>
<td>11 (17.5)</td>
<td>1 (1.6)</td>
<td>12 (19.0)</td>
<td>12 (19.0)</td>
<td>12 (19.0)</td>
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<tr>
<td>Basilar artery</td>
<td>8 (12.7)</td>
<td>1 (1.6)</td>
<td>11 (17.5)</td>
<td>1 (1.6)</td>
<td>12 (19.0)</td>
<td>12 (19.0)</td>
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<tr>
<td>Penicillalos artery</td>
<td>8 (12.7)</td>
<td>1 (1.6)</td>
<td>11 (17.5)</td>
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<td>12 (19.0)</td>
<td>12 (19.0)</td>
<td>12 (19.0)</td>
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<tr>
<td>Arteriovenous malformation</td>
<td>5 (7.9)</td>
<td>8 (12.7)</td>
<td>11 (17.5)</td>
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<td>12 (19.0)</td>
<td>12 (19.0)</td>
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</table>

### Table 2. Characteristics of Patients with Subarachnoid Hemorrhage and External Ventricular Drain

<table>
<thead>
<tr>
<th>Treatment groups</th>
<th>Treatment groups</th>
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</thead>
<tbody>
<tr>
<td>Clipping (external ventricular drain—associated ventriculitis)</td>
<td>17 (27.0)</td>
</tr>
<tr>
<td>Coilng</td>
<td>11 (17.5)</td>
</tr>
<tr>
<td>Conservative</td>
<td>8 (12.7)</td>
</tr>
<tr>
<td>Embolization</td>
<td>3 (4.76)</td>
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</table>

### Table 3. Characteristics of Patients with Subarachnoid Hemorrhage and External Ventricular Drain

<table>
<thead>
<tr>
<th>Glasgow Outcome Scale score</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean ± standard deviation</td>
<td>55.2 ± 12.5</td>
<td>42 (66.7)</td>
<td>37 (58.7)</td>
<td>11 (17.5)</td>
<td>12 (19.0)</td>
</tr>
<tr>
<td>Sex female</td>
<td>42 (66.7)</td>
<td>37 (58.7)</td>
<td>11 (17.5)</td>
<td>12 (19.0)</td>
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### Table 4. Characteristics of Patients with Subarachnoid Hemorrhage and External Ventricular Drain

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<th>World Federation of Neurosurgical Societies grades</th>
<th>Fisher grades</th>
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<tr>
<td>1</td>
<td>12 (19.0)</td>
</tr>
<tr>
<td>2</td>
<td>9 (14.3)</td>
</tr>
<tr>
<td>3</td>
<td>7 (11.1)</td>
</tr>
<tr>
<td>4</td>
<td>17 (27.0)</td>
</tr>
<tr>
<td>5</td>
<td>12 (19.0)</td>
</tr>
</tbody>
</table>

### Table 5. Characteristics of Patients with Subarachnoid Hemorrhage and External Ventricular Drain

<table>
<thead>
<tr>
<th>Aneurysm localizations</th>
<th>Arteriovenous malformation associated</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>5 (7.9)</td>
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</tbody>
</table>

 Scatterplots of IL-6 and other inflammatory markers in serum and CSF of patients with CVSAH, VCSAH, and SAHw/o/c are provided in Figure 1. At the time of first diagnosis, the mean/standard deviation concentration of CSFIL-6 in VCSAH was 7588 ± 4580 pg/mL, 4102 ± 4970 pg/mL in CVSAH (P = 0.57), and 233.8 ± 238.8 pg/mL in patients without these complications (P < 0.01). The respective AUC was 0.852 with an optimized cutoff value of 3100 pg/mL to indicate VCSAH compared with CVSAH and SAHw/o/c (sensitivity, 86.7%; specificity, 82.1%; +LR, 4.8; −LR, 0.16) (Figure 2, Table 2). CSFIL-6 showed excellent diagnostic potential for differing between CVSAH and SAH alone (AUC, 1.00; cutoff, 707 pg/mL; sensitivity, 100%; specificity, 100%; +LR, ∞; −LR, 0) and a moderate diagnostic potential for differing VCSAH from CVSAH alone (AUC, 0.757; cutoff, 3100 pg/mL; sensitivity, 86.7%; specificity, 70.6%; +LR, 2.9; −LR, 0.19) (Figure 3). The concentration of CSFIL-6 in the CVSAH group was also significantly increased compared with the SAH− group (AUC, 0.937; cutoff, 530 pg/mL; sensitivity, 87.5%; specificity, 91.7%; +LR, 10.5; −LR, 0.14) (Figure 3). The iLRs of CSFIL-6 for predicting ventriculitis and vasospasm are shown in Table 3. However, no difference was found in serum levels of IL-6 between patients with VCSAH and those with CVSAH (P = 0.63) or SAH− (P = 0.93). Accordingly, the mean ratio of IL-6 in CSF versus serum (CSFIL-6/SIL-6) was significantly increased.
during EVD-associated infections, with 247 ± 176 compared with SAH− with 16.9 ± 29.4 (P = 0.001) but showed no significant difference compared with VCSAH, with 148 ± 151 (P = 0.16). The IL-6 ratio had a moderate diagnostic potential for predicting VCSAH (AUC_{IL-6 ratio} = 0.798), and the optimized threshold was 50 (sensitivity, 86.7%; specificity, 67.9%; +LR, 2.7; −LR, 0.20).

The arithmetical mean of CSF PMN% was also statistically higher in the case of VCSAH (72.2% ± 16.1%) than in SAH− (43.6%...
The calculated AUC was 0.786 (sensitivity, 81.3%; specificity, 71.4%; +LR, 2.8; −LR, 0.26). C-reactive protein (CRP) values in serum did not differ between groups. All other parameters did not show any correlation with clinical courses of the disease.

**DISCUSSION**

VCSAH and vasospasm contribute significantly to the morbidity and poor outcome in patients with severe SAH. However, early diagnosis can be difficult and cause a significant delay in treatment. Patients are often intubated and deeply sedated, and therefore, clinical symptoms and new neurologic deficits play only a minor role in detecting those pathologic conditions. No soluble biomarker for clinical assessment of cVSSAH or VCSAH has been established for routine diagnosis. Bleeding-induced inflammatory processes and degradation of red blood cells in CSF further complicate the differentiation of these complications from the physiologic biomarker course in patients with SAH. Here, we show that determination of CSF IL-6 can support early diagnosis of both VCSAH and cVSSAH with respective cutoff values.

Our study population is representative for patients with severe aSAH and EVD in the ICU setting. Clinical parameters including WFNS and Fisher grading distribution were similar to previous reports. 

Figure 2. Receiver operating characteristic curves with corresponding area under the curve (AUC) of several inflammatory markers of patients with ventriculitis compared with vasospasm and no complication after subarachnoid hemorrhage and external ventricular drain insertion. cf IL-6, cerebrospinal fluid interleukin-6, cf PMN%, percentage of polymorphonuclear cells in the cerebrospinal fluid; IL-6, interleukin 6; sIL6, serum interleukin 6; sCRP, serum C-reactive protein.
of VCSAH and/or cVSSAH. A special focus was set on IL-6 in the biomarkers in serum and CSF and correlation with early diagnosis between VCSAH and cVSSAH: CSFIL-6 levels greater than 3100 pg/mL were measured more frequently in patients with cVSSAH (iLRVS, 5.06; iLR VC, 0.373), but VC SAH was not associated with the presence of IL-6 and CRP in serum. In the literature, vasospasm was found to affect up to 47% of patients with SAH.3,12,21 However, comparability between studies is limited because of different diagnostic criteria. Usually, TCD sonography is broadly available and used as a bedside test but it has low intraobserver and interobserver reproducibility.16,27 CTA-based and MRA-based assessments are not sufficiently standardized and impractical for everyday use18 and could further endanger patients with cVSSAH by transportation and examination risks. Here, clinical-based, TCD-based, and/or imaging-based criteria showed cVSSAH in 27 patients (42.9%). Occurrence of risks. Here, clinical-based, TCD-based, and/or imaging-based diagnosing VCSAH compared with SAH severe SAH and showed good diagnostic potential for patients with SAH.1,32 Accordingly, the causing pathogen was identified only in a subset of patients with VCSAH in our study, too. However, the spectrum with coagulase-negative staphylococci and Propionibacterium acnes, was representative for EVD-associated infections.13 There is no standard management for EVD-associated infections13 and treatment options derive from expert opinion and case series.23 Some investigators advocate a minimal handling procedure,23 whereas others favor a close monitoring of CSF inflammatory parameters for monitoring success with antibiotic therapy. Here, antibiotic treatment with a combination of vancomycin and meropenem was initiated and the EVD was replaced within 24 hours in every case of VCSAH.

In the literature, vasospasm was found to affect up to 47% of patients with SAH.1,5,24,25 However, comparability between studies is limited because of different diagnostic criteria. Usually, TCD sonography is broadly available and used as a bedside test but it has low intraobserver and interobserver reproducibility.16,27 CTA-based and MRA-based assessments are not sufficiently standardized and impractical for everyday use18 and could further endanger patients with cVSSAH by transportation and examination risks. Here, clinical-based, TCD-based, and/or imaging-based criteria showed cVSSAH in 27 patients (42.9%). Occurrence of cVSSAH correlated with both Fisher grade and with worse clinical outcome scores.

### Diagnostic Potential of IL-6 in CSF and Serum After SAH

The major aim of this study was to evaluate soluble inflammatory biomarkers in serum and CSF and correlation with early diagnosis of VCSAH and/or cVSSAH. A special focus was set on IL-6 in the CSF, which has been associated with many pathologic conditions, such as SAH, intracerebral bleeding, brain trauma, and meningitis.19 In our study, cSFIL-6 level was increased in patients with severe SAH and showed good diagnostic potential for diagnosing VCSAH compared with SAH17 but also to separate between VCSAH and cVSSAH: cSFIL-6 levels greater than 3100 pg/mL were highly suggestive for VCSAH (iLRVC, 4.85), cSFIL-6 levels between 530 and 3100 pg/mL were measured more frequently in patients with cVSSAH (iLRVS, 5.06; iLRVC, 0.373), but VCSAH cannot be excluded. Here, additional clinical and markers are necessary to assess final diagnosis.

Our data are in line with the literature and support the notion that cSFIL-6 could serve as a biomarker for ventriculitis and vasospasm in patients with SAH.19 Wu et al.1 recently reported higher mean cSFIL-6 concentrations in patients with SAH and cVSSAH 362.56 ± 30.14 pg/mL than in those without cVSSAH 291.79 ± 21.67 pg/mL (P < 0.05). However, these differences were smaller than in our study. Schoch et al.10 also described statistically significant higher median values of cSFIL-6 in patients’ cVSSAH on day 4 after bleeding (1380 pg/mL) compared with patients without vasospasm and introduced cSFIL-6 as an early marker for predicting VS after SAH. The diagnostic potential of cSFIL-6/IL-6 in patients with SAH alone and not improve diagnostic assessment. This finding might have been to the result of altered levels of systemic markers including IL-6 and CRP after SAH and bias by systemic inflammation, infections, and other complications.1,38 Accordingly, both serologic screening parameters were not useful for further diagnosis. Possible explanations are that VCSAH is a local, circumscribed infection without systemic involvement. It remains unclear whether an untreated ventriculitis may lead to meningitis and therefore to an increase of levels of IL-6 and CRP in serum during the course of the disease. In these patients, sIL-6 and serum CRP might be useful for monitoring the success of antibiotic treatment.

### Table 2. Inflammatory Markers in Serum and Cerebrospinal Fluid for Diagnosing Ventriculitis

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Mean ± Standard Deviation</th>
<th>Area Under the Curve (95% CI)</th>
<th>Cutoff</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Positive Likelihood Ratio (95% CI)</th>
<th>Negative Likelihood Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSFIL-6 (pg/mL)</td>
<td>15 7588 ± 4580</td>
<td>0.852 (0.738–0.967)</td>
<td>3100</td>
<td>86.7 (62.1–96.3)</td>
<td>82.1 (64.4–92.1)</td>
<td>4.8 (2.14–11.0)</td>
<td>0.16 (0.04–0.60)</td>
</tr>
<tr>
<td>CSFPMN (%)</td>
<td>16 72.2 ± 16.1</td>
<td>0.786 (0.638–0.933)</td>
<td>62.0</td>
<td>81.3 (57.0–93.4)</td>
<td>71.4 (45.4–82.8)</td>
<td>2.8 (1.27–6.47)</td>
<td>0.26 (0.10–0.82)</td>
</tr>
<tr>
<td>CSF/IL-6 Ratio</td>
<td>15 247 ± 176</td>
<td>0.798 (0.665–0.930)</td>
<td>50.0</td>
<td>86.7 (62.1–96.3)</td>
<td>67.9 (49.3–82.1)</td>
<td>2.7 (1.52–4.79)</td>
<td>0.20 (0.05–0.73)</td>
</tr>
<tr>
<td>sIL-6 (pg/mL)</td>
<td>16 80.5 ± 151</td>
<td>0.579 (0.417–0.741)</td>
<td>10.1</td>
<td>100 (80.6–100)</td>
<td>22.5 (12.3–37.5)</td>
<td>1.29 (1.08–1.53)</td>
<td>0</td>
</tr>
<tr>
<td>sCRP (mg/dL)</td>
<td>17 8.8 ± 9.5</td>
<td>0.685 (0.543–0.828)</td>
<td>5.5</td>
<td>58.8 (36.0–78.4)</td>
<td>75.0 (59.8–85.8)</td>
<td>2.35 (1.21–4.59)</td>
<td>0.55 (0.30–1.00)</td>
</tr>
</tbody>
</table>

CI, confidence interval; CSFIL-6, cerebrospinal fluid interleukin 6; CSFPMN%, percentage of polymorphonuclear cells in the cerebrospinal fluid; sIL-6, serum interleukin 6; sCRP, serum C-reactive protein.
However, with respect to the detection of an VCSAH at early onset, local inflammatory markers in the CSF may have a higher diagnostic potential. This observation supports the need for daily monitoring of CSF inflammatory markers\textsuperscript{22}; systemic markers do not seem to be useful for diagnosing ventriculitis at an early stage.\textsuperscript{22} This finding differentiates a ventriculitis from all other life-threatening infections of critical ill patients.

Besides CSFIL-6, CSFPMN\% was significantly increased during VCSAH and showed moderate diagnostic potential (AUC, 0.786) in our study. It is concluded that despite the physiologic increase of the CSFPMN\% in context with degradation of red blood cells in the subarachnoid space after SAH, this marker has enough diagnostic potential to support the diagnosis of VC in daily clinical practice. Our findings are in contrast to those of Walti et al.,\textsuperscript{13} who did not find any significant difference of the CSF granulocyte count on the day of EVD infection compared with the count on the day of EVD insertion; the AUC was 0.65. Also Liu et al. detected no statistical difference between the mean CSFPMN\% in patients with VC\textsubscript{SAH} (76.0\% ± 6.7\%) and nonmeningitis (49.5\% ± 10.1\%). On the other hand, a study of the diagnostic potential of CSFPMN\% for predicting meningitis after neurologic surgery\textsuperscript{33} reported a sensitivity of 94\% and specificity of 28\%. It was concluded that CSFPMN\% was a useful biomarker for making the diagnosis. Furthermore CSFPMN\% has been a very good parameter for differing bacterial from aseptic meningitis in nonneurosurgical patients (AUC, 0.932; sensitivity, 89.7\%; specificity, 90.6\%; +LR, 9.50; −LR, 0.11).\textsuperscript{34} The CSFPMN\% should be determined in patients with suspicion of EVD-associated VC.

**Limitations**

Our study is limited by several factors. First, the study was designed as a retrospective clinical study. Therefore data acquisition may not have been as accurate as in prospective studies. Furthermore, we included patients with culture-verified and culture-negative ventriculitis. It cannot be excluded that patients with chemical meningitis were integrated in the septic study group. However, we believe that we have captured the biomarker levels in a representative and exactly defined study population that was treated by a strictly standardized operating procedure. Moreover, other inflammatory markers such as tumor necrosis factor α, IL-1 receptor antagonist, and neurofilament proteins were not available.

**CONCLUSIONS**

Diagnosing VCSAH after severe SAH at an early stage is challenging. Because patients are deeply sedated, day-to-day supervision of clinical symptoms and biomarker levels in serum and CSF may be essential. CSFIL-6 is increased after SAH in patients with vasospasm or ventriculitis. Patients with a CSFIL-6 greater than 30\(8^1\) pg/mL have an increased posttest probability for
REFERENCES


