Interleukin 6 after aneurysmal subarachnoid hemorrhage

After rupture of a intracranial aneurysm, high CSF Interleukin 6 levels were found to associate with vasospasm [1) 2) 3)].

This aneurysmal subarachnoid hemorrhage (SAH) has been reported to induce an intrathecal inflammatory reaction reflected by cytokine release, particularly interleukin 6 (IL-6), which correlates with early brain damage and poor outcome.

Results provide strong evidence that IL-6 and TNF-α CSF levels are elevated in SAH patients and may participate in SAH development. Thus, these two cytokines could be important biomarkers for early diagnosis and disease monitoring in SAH patients [4)].

Higher early IL6 serum levels after aSAH are associated with poor outcome at discharge. In addition, involvement of leukemia inhibitory factor (LIF) in the early inflammatory reaction after aSAH has been demonstrated [5)].

CSF IL-6 values of ≥10,000 pg/ml in the early post-SAH period may be a useful diagnostic tool for predicting shunt dependency in patients with acute posthemorrhagic hydrocephalus. The development of shunt-dependent posthemorrhagic hydrocephalus remains a multifactorial process [6)].

Case series

2017

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, cVSSAH, and VCSAH. RESULTS: Clinical courses included 27 patients with cVSSAH, 17 with VCSAH, and 19 with SAHw/o/c. Mean ± standard deviationCSFIL-6 values were 7588 ± 4580 pg/mL at onset of VCSAH and 4102 ± 4970 pg/mL for cVSSAH 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 cVSSAH (AUC, 0.757; C-OFF, 3100 pg/Ml; SE, 86.7%; SP, 70.6%). The concentration of CSFIL-6 within the cVSSAH group was significantly increased compared with SAHw/o/c (AUC, 0.937; C-OFF, 530 pg/mL; SE, 87.5%; SP, 91.7%).

CSFIL-6 is increased after aSAH in patients with cVSSAH or VCSAH. Patients with a CSFIL-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 cVSSAH [7)].

2015

Kao et al. prospectively included 53 consecutive patients treated with platinum coil embolization of the ruptured intracranial aneurysm. Plasma IL-6 levels were measured in the blood samples at the orifices of the aneurysms and from peripheral veins. The outcome measure was the modified Rankin

Scale one month after SAH. Multiple logistic regression analyses were used to evaluate the associations between the plasma IL-6 levels and the neurological outcome.

Significant risk factors for the poor outcome were old age, low Glasgow Coma Scale (GCS) on day 0, high Fisher grades, and high aneurysmal and venous IL-6 levels in univariate analyses. Aneurysmal IL-6 levels showed modest to moderate correlations with GCS on day 0, vasospasm grade and Fisher grade. A strong correlation was found between the aneurysmal and the corresponding venous IL-6 levels ($\rho = 0.721$; $P<0.001$). In the multiple logistic regression models, the poor 30-day mRS was significantly associated with high aneurysmal IL-6 level (OR, 17.97; 95% CI, 1.51-214.33; $P = 0.022$) and marginally associated with high venous IL-6 level (OR, 12.71; 95% CI, 0.90-180.35; $P = 0.022$) after adjusting for dichotomized age, GCS on day 0, and vasospasm and Fisher grades.

The plasma level of IL-6 is an independent prognostic biomarker that could be used to aid in the identification of patients at high-risk of poor neurological outcome after rupture of the intracranial aneurysm [8].

A complete data set (DHEAS and IL-6 serum levels for days 0, 1, 4, 7, 10 and 14 after aSAH) and outcome assessment at discharge according to modified Rankin Scale score (mRS) was available for 53 patients of the initially screened cohort (n = 109). Outcome assessment six months after aSAH was obtained from 41 patients. Logarithmized levels of DHEAS and IL-6 were related to dichotomized functional outcome either assessed at discharge or at six months. A mixed between-within subjects ANOVA was applied for statistical analysis (SPSS 21.0).

DHEAS and IL-6 levels across time were related to functional outcome. Regarding outcome assessment at discharge and at six months after aSAH, DHEAS levels (transformed to square root for statistical purposes) were considerably higher in patients with favorable outcome (mRS 0-2) ($p = .001$; $p = .020$). Inversely, in patients with favorable outcome either at discharge or six months after aSAH, lower IL-6 levels (logarithmized for statistical purposes) were observed across time (both $p < .001$).

Höllig et al. provide new evidence that DHEAS is associated with protective properties resulting in improvement of functional outcome after aSAH, possibly by influencing the inflammatory response after aSAH shown in the decreasing IL-6 serum levels. But the results for outcome six months after SAH are limited due to a high drop-out rate [9].

2011

Daily systemic IL-6 levels were measured in the acute phase in 11 patients with non-aneurysmal perimesencephalic SAH (pmSAH), with bleeding strictly located around the midbrain, and in nine patients with non-aneurysmal non-perimesencephalic (non-pmSAH), with hemorrhage extending into adjacent cisterns (group 1). IL-6 levels were compared with those from patients suffering from aSAH with cerebral vasospasm (CVS) (group 2) and without CVS (group 3). The mean IL-6 level (±standard error of the mean) was significantly lower in group 1 compared to group 2 (9.9±1.9 vs. 29.1±6.7 pg/mL, $p=0.018$). The difference in mean IL-6 level between group 1 and 3 fell short of significance (9.9±1.9 vs. 14.9±1.1 pg/mL, $p=0.073$). Patients in group 1 had a significantly better outcome (Glasgow Outcome Scale score 4-5) compared to group 2 ($p<0.001$) and a trend towards better outcome compared to group 3 ($p=0.102$). A subgroup analysis revealed a higher mean IL-6

concentration in patients with non-pmSAH compared to patients with pm-SAH (p=0.001). We concluded that systemic IL-6 concentration reflects the severity of the inflammatory stress response and course of the illness. The more benign illness and good prognosis of patients with pmSAH or non-pmSAH in contrast to patients with aSAH is reflected by the lower concentrations of IL-6 [10].

2010

A total of 38 consecutive aSAH patients were studied prospectively within 14 days after admission and classified as asymptomatic (n = 9; WFNS grade 1 (1-2), median and quartiles) and symptomatic (n = 29; WFNS grade 4 (2-5)); the latter presenting with acute focal neurological deficits (AFND) (n = 13), delayed cerebral ischemia(DCI). (n = 10) or both (n = 6). Levels of pro-inflammatory cytokine IL-6 were determined in cerebral extracellular fluid (ECF, using cerebral microdialysis), cerebrospinal fluid (CSF) and plasma for 10 days after aSAH. Additionally, C-reactive protein (CRP) levels were measured in plasma.

High IL-6 levels in CSF, ECF and plasma were found in all patients, reflecting a pronounced local inflammatory response after aSAH, followed only in symptomatic patients by a delayed systemic inflammation (CRP $P < 0.025$, days 7-9 after aSAH). In all compartments, IL-6 levels appeared to be higher in symptomatic patients, accompanied also by a higher ECF lactate-pyruvate ratio ($P = 0.04$). Cerebral, but not plasma IL-6, levels were indicative of the development of DCI in symptomatic patients (ECF $P = 0.003$; CSF $P = 0.001$).

A pronounced initial cerebral inflammatory state was observed in patients of all WFNS grades, suggesting that IL-6 elevations are not necessarily detrimental. Cerebral, but not plasma IL-6, levels were predictive of the development of delayed ischemic deficits in symptomatic patients, suggesting that CSF or ECF are the best sampling media for future studies [11].

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