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Impact of the selected inflammatory biomarekrs and their genetic polymorphism on the clinical and neuroradiological aspects of the human spontaneous intracerebral hemorrhage.

Promotionsfach: Neurologie

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This study was designed as a prospective monocentric clinical observational study with the objective to investigate the role of inflammatory agents in the secondary brain injury after spontaneous intracerebral hemorrhage (SICH) in man.
We assessed blood concentration and genetic polymorphism of specific biomarkers and its relation to the clinical and radiographic outcome.
Consecutive patients admitted to the Neurological Department of the University Hospital in Heidelberg with the diagnosis of SICH or OAT-related SICH who fulfilled all the inclusion criteria were eligible for the study. As a benchmark for inflammatory pattern in SICH patients the levels of the studied biomarkers were assayed in the healthy control group.
Blood samples were collected within 12 hours from symptom onset and were worked out by means of zymography and ELISA to determine the concentration of MMP-9, MMP-2, MMP-12, TIMP-1, TIMP-2, IL-1β, IL-6 and TNFα. The genetic polymorphism in the promoter region of genes coding MMP-9, MMP-2, IL-1β, IL-6 and TNFα was analyzed. CRP, WBC and fibrinogen as well as S100 and NSE were tested as a routine workout of the stroke patients. All the biomarkers were measured at baseline and then on day 2, 3 and 7. Neurological deficit and consciousness of the patients was evaluated by means of NIHSS and GCS, respectively at the same time. All patients underwent one brain CT scanning on admission and then were controlled within 24 hours. Some of the patients had 3rd CT within the first week. The functional outcome was assessed by using mRS at discharge, after 1 and 3 months.
A total of 55 patients entered the study. Eventually 44 patients were considered for the final analysis.
CRP, WBC, fibrinogen, IL-6, S100 and NSE were increased in SICH patients compared with controls. Above all CRP and fibrinogen increase significantly during the first week after SICH. S100 protein peaked immediately after SICH onset and decreased afterwards. The increased level of S100 persisted during the first 7 days.
Common inflammatory biomarkers, IL-6 and S100 correlated with the level of consciousness disturbance, neurological deficit, the bleeding volume and perifocal edema volume during the first week after SICH onset. CRP, NSE and IL-6 blood concentration correlated with the bleeding volume increase within 48 hours, but only NSE correlated with the secondary hematoma and PHE volume increase (within 3-7 day from SICH onset).
CRP, IL-6, S100, proMMP-2 and MMP-9 level ware associated with the presence of intraventricular blood (IVH). CRP, fibrinogen and S100 ware higher in patients with mass effect on baseline CT.

MMP-9 and NSE were associated with neurological decline within 48 hours. CRP, fibrinogen and IL-6 were related to the neurological decline within 72 hours.
CRP, fibrinogen, S100 were associated with the early and long-term mortality. CRP level measured on day 3 was an independent predictor of the early and long-term mortality. There was a relation between MMP-9, MMP-2 levels and the very early mortality. WBC, CRP, fibrinogen, S100 and NSE were related to mRS score at discharge, within 1 and 3 moths. Additionally, IL-1 and TNF were associated with good recovery after 3 months.
Some relations were found between the studied genetic polymorphism of the inflammatory cytokines, MMPs and blood concentration of the studied biomarkers, clinical and neuroradiological outcome.
In conclusion, we have found a specific pattern of biomarkers release after SICH. There were some significant relations between the blood concentration of the biomarkers as well as their genetic variations and the clinical and neuroradiological outcome. CRP level predicted early mortality in SICH patients. Nevertheless, this study was meant to be a pilot study shedding more light on this little investigated issue. Larger cohort studies are needed to expound the role of inflammation in the secondary brain injury after in intracerebral hemorrhage.