

Ukr Neurosurg J. 2023;29(4):35-41
doi: 10.25305/unj.287723

Determination of inflammatory mediator levels in cerebrospinal fluid during the formation of cerebral vasospasm and delayed cerebral ischemia after subarachnoid hemorrhage

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Received, 19 September 2023

Accepted, 03 November 2023

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Introduction. Delayed cerebral ischemia (DCI) and cerebral vasospasm (CV) lead to poor outcomes in patients after aneurysmal subarachnoid hemorrhage (aSAH). The pathophysiology of these complications is not fully understood, preventing the adoption of a single definition. Reliable diagnostic tests and effective evidence-based treatment are lacking.

Objective: to determine the relationship between the concentration of interleukin-6 (IL-6), IL-10, IL-17, tumor necrosis factor- α (TNF- α) in cerebrospinal fluid and formation of delayed complications of subarachnoid hemorrhage.

Materials and methods. The study involved 45 patients with aSAH who were treated in Kharkiv Regional Hospital (18 men and 27 women aged 32 to 73 years (mean age – 45.9 \pm 8.5 years). The control group consisted of 20 healthy individuals (8 men and 12 women aged from 32 to 73 years (mean age - 59.2 \pm 10.6 years). The occurrence of DCI or CV was recorded. The level of IL-6, IL-10, IL-17 and TNF- α in the cerebrospinal fluid (CSF) was measured in all subjects of the study using enzyme-linked immunosorbent assay.

Results. Levels of IL-6, TNF- α , IL-17, and IL-10 in the CSF of patients with aSAH were higher than in control subjects. In patients with CV, the values of IL-6, IL-17 and TNF- α in CSF exceeded those of patients without CV. The concentration of IL-6 and TNF- α was also increased in the cerebrospinal fluid of patients with DCI.

Conclusions. The obtained results indicate that IL-6 and TNF- α in CSF may be early markers for predicting vasospasm and DCI on the 3rd day after subarachnoid hemorrhage before clinical onset. The content of IL-17 correlates with the formation of cerebral vasospasm, but there is no connection between its level in the CSF and DCI. The concentration of IL-10 in the CSF on the 3rd day after aSAH had no prognostic value either for CV or for DCI formation.

Keywords: cerebral vasospasm; delayed cerebral ischemia; subarachnoid hemorrhage; IL-6; TNF- α ; IL-17; IL-10

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a debilitating condition, accounting for 5% of all strokes. The incidence is reported at 9 cases per 100,000 population per year [1–2]. Cerebral vasospasm (CV) and delayed cerebral ischemia (DCI) develop in 30–40% of aSAH patients, leading to poor clinical outcomes in half of these cases. Approximately 70% of aSAH patients either die or subsequently require assistance in daily life [3].

Many studies have identified that the prognosis of aSAH patients depends on the neurological status at admission, stratified by the Hunt-Hess and World Federation of Neurological Surgeons (WFNS) scales and the occurrence of DCI due to the development of CV, correlated with the initial bleeding volume on brain computed tomography using the modified Fisher scale [4]. Despite numerous investigations of significance of various markers for early diagnosis of CV development and consequences of SAH, but their substantial prognostic significance on the development

of CV, monitoring its progression and formation of DCI has not been proved.

The onset and etiology of CV is difficult to determine. Patients with aSAH often experience a delayed onset of CV, leading to cerebral ischemia [6]. Although the exact pathophysiology of aSAH has not been established, prior studies have identified that infiltration of red blood cells into the subarachnoid space and cerebral cisterns, accompanied by their lysis, induces a distinct immune response mediated by proinflammatory cytokines [7–8]. Currently, there are no validated biomarkers to diagnose or monitor preclinical predictors of vasospasm, but two areas of research have been identified for discovery of new biomarkers – neuroimaging and biochemical markers in body fluids such as serum/plasma and cerebrospinal fluid (CSF) [9]. Activation of the inflammatory response, mediated by increased cytokine release in the CSF and plasma, correlates with adverse clinical outcomes in patients with aSAH. Levels of cytokines and cytokine receptors are significantly increased in the CSF after

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aSAH, but the exact relationship between disease progression and inflammatory markers in the CSF has not been clarified. Thus, the identification of a diagnostic biomarker would be an important step forward in the treatment of CV and DCI.

The levels of cytokines in body fluids are influenced by various factors. Interleukins (IL)-6 and 17 are cytokines that are actively involved in inflammation and the body's response to infections, and also play an important role in the regulation of metabolism, tissue regeneration, and nervous system development. Tumor necrosis factor- α (TNF- α) is a critically important cytokine that is involved in the initiation of inflammatory reactions and may play a leading role in the occurrence of oxidative stress and apoptosis of endothelial cells observed in aSAH. An increase in the level of IL-6 in the CSF is associated with elevation in the incidence of CV and worse outcomes for patients [10-11]. In several previous studies, which tried to compare the level of IL-6 and TNF- α in the SCF with consequences of aSAH, contradictory results were obtained [12]. Anti-inflammatory cytokines such as IL-4 and IL-10 have also been associated with ischemia, but their involvement in aSAH is less explored.

Objective: to determine the relationship between the concentration of IL-6, IL-10, IL-17, TNF- α in cerebrospinal fluid and formation of delayed complications of subarachnoid haemorrhage.

Materials and methods

Study participants

Throughout the study, demographic, clinical, and laboratory parameters of patients were prospectively recorded.

From September 2021 to March 2023, 45 patients undergoing treatment in the neurosurgery department of Kharkiv Regional Hospital for aneurysmal subarachnoid hemorrhage (aSAH) were enrolled in the study. The participants included 18 males and 27 females, aged 32 to 73 years (mean age: 45.9 ± 8.5 years). The control group consisted of 20 healthy individuals (8 men and 12 women aged 32 to 73 years (mean age – 59.2 ± 10.6 years)) who did not take steroid and immunosuppressive drugs. There were no statistically significant differences between the groups in terms of age, sex ratio, and body mass index.

Written informed consent was obtained from all patients or their legal representatives. The Bioethical Committee of Kharkiv National Medical University approved the conduct of this study.

Inclusion and exclusion criteria

The criteria for inclusion in the study were verified cases of aSAH according to computed tomography (CT) data with the presence of an intracranial aneurysm confirmed by computed tomographic angiography (CTA) and/or intraarterial digital subtraction angiography (DSA) and hospitalization within the first 48 hours after the onset of the disease. Patients were excluded from the study if they had infections, heart disease, autoimmune disorders, malignancy, pregnancy, were taking drugs or receiving treatment affecting immune

function. In addition, patients hospitalized later than 3 days after the onset of bleeding were not included in the study.

Patient management

The diagnosis of aSAH was confirmed using CT scans. All patients were diagnosed with an intracranial aneurysm according to CTA and DSA. The severity of the disease was assessed upon admission using the Hunt-Hess scale, neurological examination results, the onset of headache, and the modified Fisher scale.

Angiography was performed as a standard admission procedure, as a postoperative follow-up procedure, and/or in case of neurological deterioration.

All patients underwent surgical clipping or endovascular embolization within 24–48 h after the onset of the disease. Patients received nimodipine for 21 days and a standard neurointensive care.

Angiographic vasospasm was detected on cerebral angiograms analyzed by neuroradiologists blinded to the patient's identity. Cerebral vasospasm was determined based on transcranial dopplerography results (mean blood flow velocity in the middle cerebral or anterior cerebral artery >120 cm/s and Lindegaard index >3). Delayed cerebral ischemia was defined as imaging confirmation of secondary infarcts unrelated to aneurysm occlusion procedure or other interventions (CT) and/or development of neurological symptoms after ruling out other causes of response to induced hypertension with or without secondary infarcts [13].

Patients were divided into two subgroups - those with or without cerebral vasospasm, as well as those with or without delayed cerebral ischemia.

Patients were examined on an outpatient basis 3 months after hemorrhage or through telemedicine consultations. Clinical outcome was evaluated according to the modified Rankin scale (mRS).

Collection, processing, and analysis of cerebrospinal fluid samples

Cerebrospinal fluid (CSF) samples (3 mL) from aSAH patients were collected from the ventriculostomy port, lumbar drains, or by routine lumbar puncture on day 3 after the onset of hemorrhage. Samples were centrifuged at 800g for 10 min to remove cells and stored at -70 °C until further analysis. The level of IL-6, IL-17, TNF- α , and IL-10 in the CSF was measured by solid-phase enzyme-linked immunosorbent assay (ELISA) using commercially available ELISA kits (Elabscience, USA) and following all manufacturer's instructions.

Statistical analysis

Graph Pad Prism 5.0 software (USA) was used for statistical analysis of the data obtained in the study. Data were evaluated using the Mann-Whitney U-test. Data are presented as median and interquartile range (IQR; 25%–75%), categorical data as arithmetic mean and standard deviation. A value of $p \leq 0.05$ indicated statistical significance.

Results and discussion

The mean modified Fisher scale and the Hunt-Hess scale scores at hospital admission were 2.22 ± 0.97 and 2.43 ± 1.20 , respectively.

This article contains some figures that are displayed in color online but in black and white in the print edition

Aneurysms were located predominantly in the anterior semicircle of blood circulation (76.2%), less often in the posterior semicircle (23.8%). The mean aneurysm size from dome to neck was 7.0 ± 3.6 mm. Aneurysms were treated mainly by clipping (66.7%), less frequently by endovascular techniques (33.3%). Cerebral vasospasm was documented in 20 (38.0%) patients, DCI in 27 (47.6%). The mRS score after 3 months of treatment was 2.95 ± 1.56 (**Table 1**).

Data on the content of the studied cytokines are presented in **Table 2**.

Cytokine levels of IL-6, IL-10, IL-17, and TNF- α in the cerebrospinal fluid of SAH patients

Statistically significant differences ($p < 0.001$) were observed in the concentrations of IL-6, IL-10, IL-17, and TNF- α in the cerebrospinal fluid (CSF) between SAH patients and individuals in the control group (**Fig 1**).

Association of IL-6, IL-10, IL-17, and TNF- α levels in the CSF with CV.

The results demonstrated that concentration of IL-6, TNF- α , and IL-17 in the cerebrospinal fluid (CSF), measured on the 3rd day after bleeding in patients with CV, was significantly higher than that in patients without CV ($p < 0.0001$, $p = 0.0005$, $p = 0.0005$, respectively). No statistically significant difference in the level of IL-10 between patients with and without CV was observed ($p = 0.3295$) (**Fig. 2**).

Association of IL-6, IL-10, IL-17, and TNF- α levels in the CSF with DCI

Analysis of the CSF study results in patients after aSAH revealed a difference between groups with and without DCI in the concentration of IL-6 ($p = 0.0433$) and TNF- α ($p = 0.0468$). No statistically significant association was found between the levels of IL-10 and IL-17 in the CSF and the development of DCI ($p = 0.7966$, $p = 0.1941$, respectively) (**Fig. 3**).

Aneurysmal SAH most often occurs as a result of the rupture of a cerebral artery aneurysm, resulting in the entry of blood into the subarachnoid space. This leads to early and delayed neurological complications [14-15]. Post-subarachnoid CV is a major cause of morbidity and mortality. Many patients are finally diagnosed

Table 1. Patient, treatment and outcome data

Parameter	Number of patients
Gender	
M	19
W	26
Hunt-Hess scale score	
1	8
2	12
3	15
4	7
5	3
Fisher scale score	
1	7
2	9
3	17
4	10
Localization of aneurysm	
ACA	16
PCA	9
ICA	5
MCA	10
BA and VA	5
Method of surgical treatment	
Clipping	30
Coiling	15
Consequences (mRS)	
0-2	28
3-6	17

Note. ACA – anterior communicating artery; BA – basilar artery; ICA – internal carotid artery; MCA – middle cerebral artery; PCA – posterior communicating artery; VA – vertebral artery.

Table 2. Concentration of cytokines IL-6, TNF- α , IL-10, IL-17 (pg/ml) in the cerebrospinal fluid of patients after subarachnoid haemorrhage

Group	n	IL-6	TNF- α	IL-10	IL-17
SAH	45	295,7	133,2	84,4	1374,5
Control group	20	13,9	12,7	7,7	21,3
CV	20	366,0	141,0	89,4	1654,0
Without CV	25	225,0	125,3	79,5	1095,0
DCI	27	349,3	140,8	79,5	1582,0
Without DCI	18	310,14	133,6	89,4	1350,0

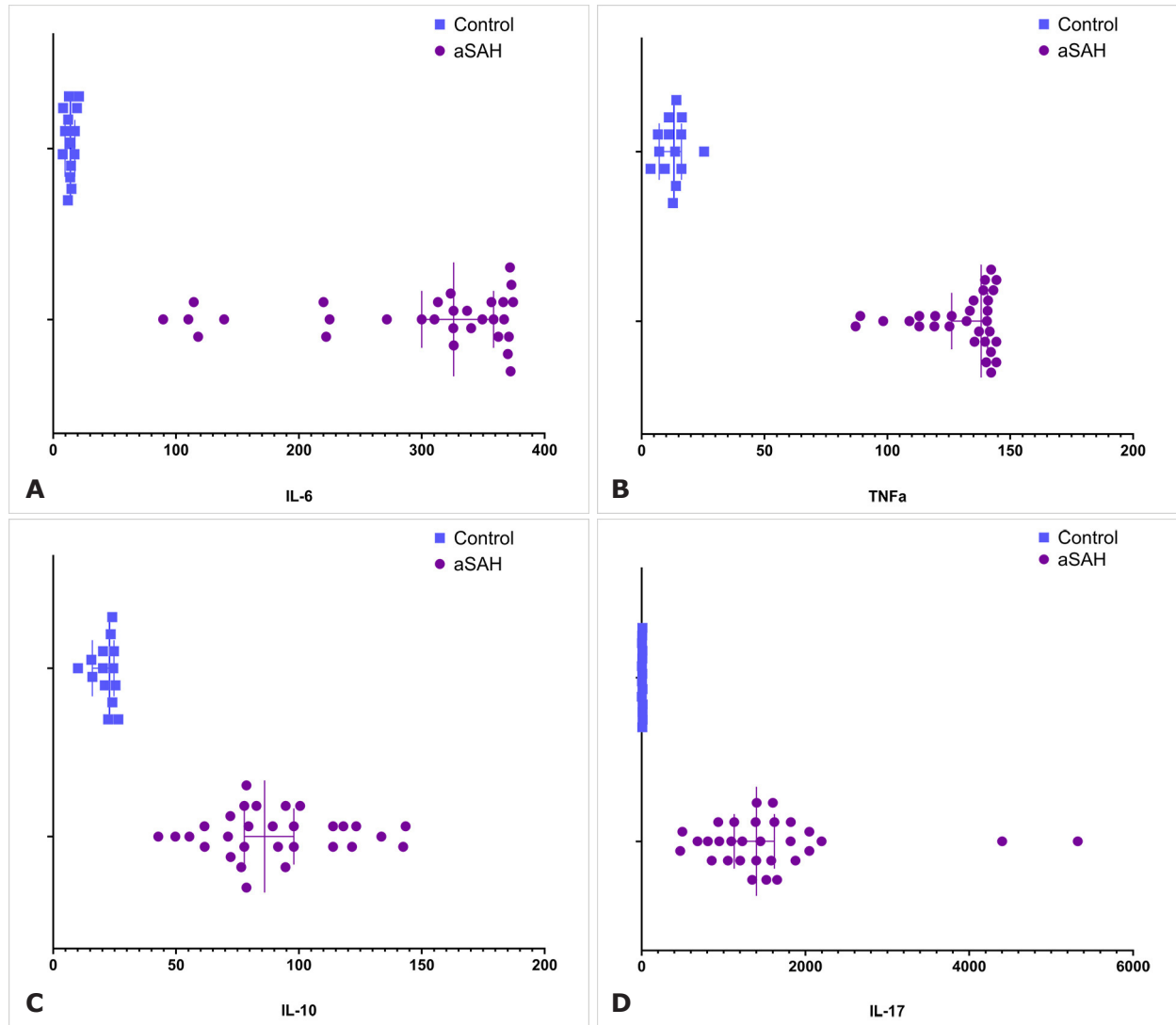
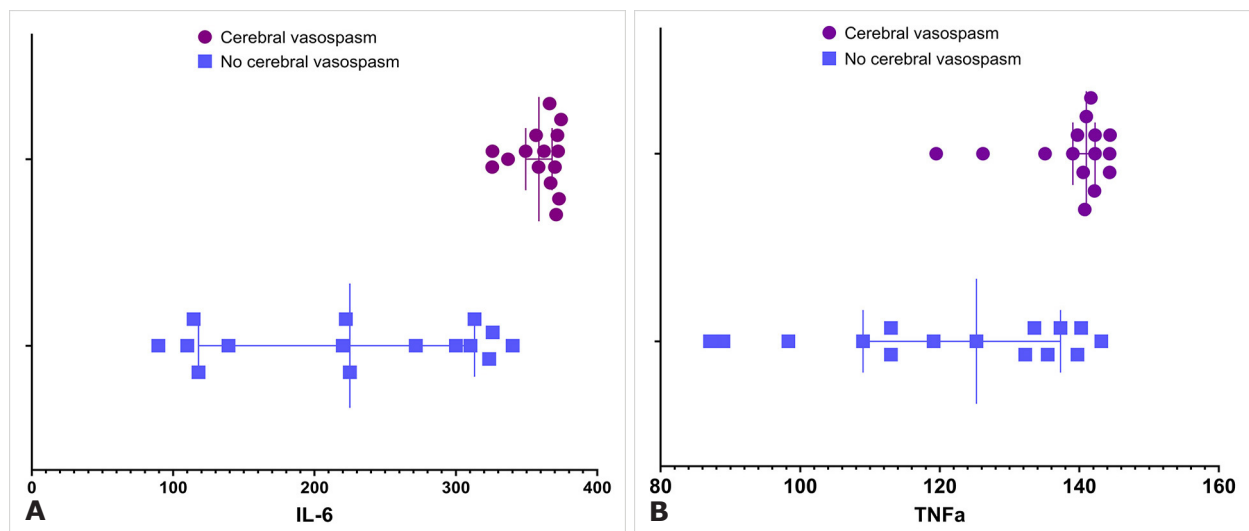


Fig. 1. Levels of IL-6 (A), TNF- α (B), IL-10 (C), IL-17 (D) (pg/ml) in SAH patients



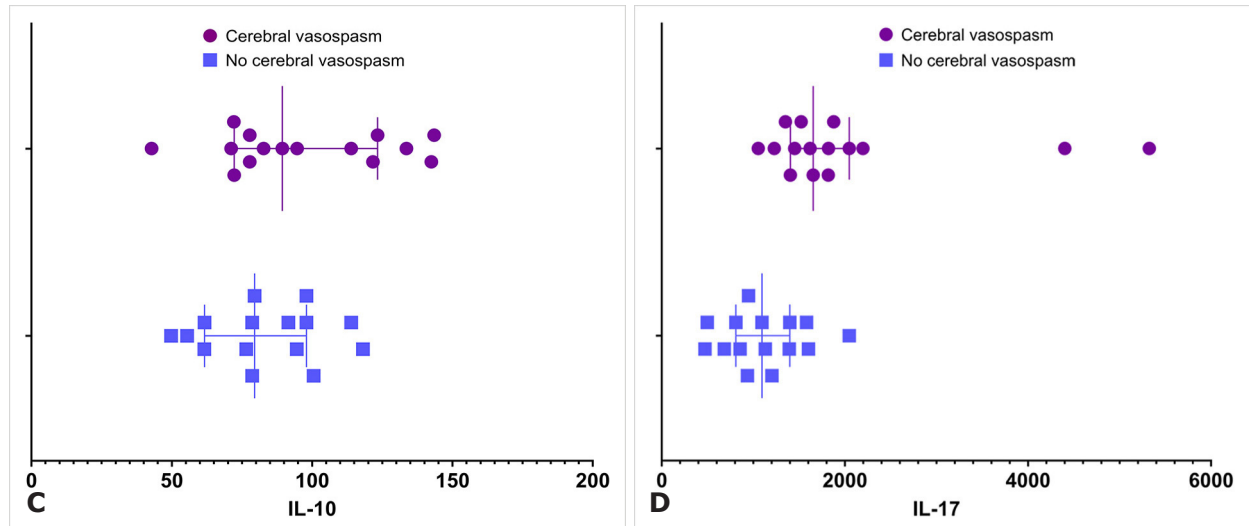


Fig. 2. Levels of IL-6 (A), TNF- α (B), IL-10 (C), IL-17 (D) (pg/ml) in patients with and without cerebral vasospasm

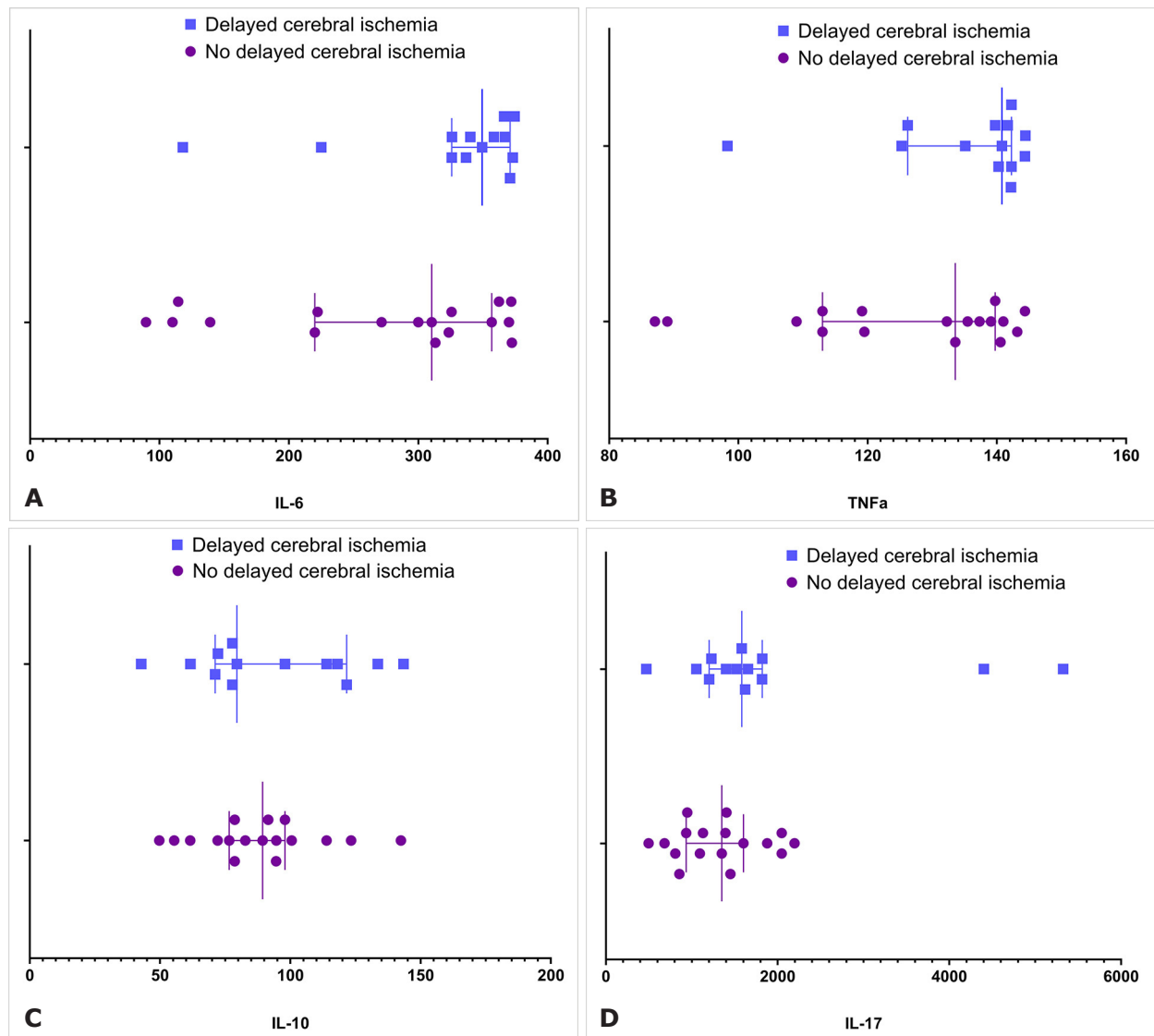


Fig. 3. IL-6 (A), TNF- α (B), IL-10 (C), IL-17 (D) (pg/ml) in patients with and without delayed cerebral ischemia

after ischemic complications, when the pathogenetic state is difficult to change. Predicting the occurrence of vasospasm is a key point in the treatment of vasospasm. The pathophysiology of DCI and secondary infarcts has not been elucidated, but the inflammatory response induced by cerebral hemorrhage may play a significant pathogenetic role.

The pathology of aSAH is due to the entry of extravasated blood into the subarachnoid space. After aSAH, hematoma components enter the brain parenchyma together with the CSF, leading to a series of destructive reactions resulting in neuronal death. Hematoma components consist predominantly of erythrocytes, their lysate and hemoglobin. Hemoglobin and molecular fragments released from erythrocytes are associated with the lesion and have a strong cytotoxic effect that causes neuronal death.

Interleukin-6 and TNF- α are pro-inflammatory cytokines that regulate numerous physiological processes [16]. Studies suggest that IL-6 and TNF- α play an important role in brain tissue damage, but the underlying mechanism is poorly understood [17-18]. We conducted a case-control study to investigate the relationship between the development of SAH complications and the levels of IL-6, IL-10, IL-17, and TNF- α in the CSF.

Aneurysmal SAH is a common disease causing cerebrovascular damage. After aSAH, inflammation rapidly occurs in the subarachnoid space. According to our results, the levels of IL-6, IL-10, IL-17 and TNF- α in CSF of patients with SAH exceeded those in the control group. The content of cytokines increased with the severity of the disease, indicating an elevated synthesis of pro-inflammatory and anti-inflammatory cytokines in the CSF and may be associated with the progression of complications of aSAH [19].

In our study, the concentration of IL-6 in the CSF was statistically significantly increased in patients with aSAH who developed CV and DCI compared to the group without these complications, suggesting that inflammatory responses mediated by IL-6 may play a crucial role in the progression of aSAH complications. Therefore, an elevated level of IL-6 in the cerebrospinal fluid may influence the progression of aSAH and serve as a predictor of poor clinical outcomes in patients with SAH.

The key cytokine in the inflammatory cascade is TNF- α , which plays an important role in the body's defense against infections. Our case-control study confirmed that a sharply elevated TNF- α level correlates with CV formation and long-term complications of aSAH (DCI) [20]. Modern theories explain the formation of DCI by impaired fibrinolytic activity, activation of the inflammatory cascade and endothelial dysfunction, which leads to the formation of microthrombi, resulting in increased TNF- α activity. Our findings are consistent with previous studies: both TNF- α and IL-6 play an important role in the development of CV and DCI after aSAH and can be used as potential biomarkers for early detection.

IL-17A has been shown to have various functions, particularly inducing pathogenic inflammation and inducing acute innate immune defenses [21]. Thus, IL-17A is not just an inflammatory factor. Its specific mechanism in neurodegenerative diseases has not been

finally elucidated. It is generally recognized that IL-17A causes disease by activating glial cells. The functions of IL-17A have been shown to be more adaptive and diverse than previously predicted. Our finding that IL-17 was markedly elevated in patients with SAH who developed CV but not in those who developed DCI may be related to the timing of the CSF sampling. It is necessary to conduct a study of the CSF samples later after the development of aSAH [22, 23].

Interleukin-10 is an anti-inflammatory cytokine, its elevation in both hemorrhagic and ischemic stroke correlates with the severity of the disease and worse prognosis [24]. It is currently believed that elevated IL-10 levels reflect the balance between pro-inflammatory and anti-inflammatory cytokines. A high concentration of IL-10 is caused by excessive response to inflammatory stimulus [25].

In our study, no correlation was found with the level of IL-10 in the CSF on the 3rd day after the occurrence of hemorrhage and CV and DCI. It is likely that the ability of IL-10 to influence the pro-inflammatory environment differs for different forms of acute brain injury. Delayed IL-10 synthesis may lead to prolonged inflammation that exacerbates secondary brain damage, leading to poorer outcomes.

Limitations of our study include small patient sample size and the single-center nature. The acute inflammatory response after aSAH is a complex and multifactorial cascade with large interindividual variations in cellular and humoral immunity, and cannot be adequately explained by a few cytokines alone. The inflammatory response is a time-dependent process. The elevation of various parameters cannot be described only at the early stage of the disease, they should be studied in dynamics. We plan to conduct multicenter studies to confirm the role of neuroinflammation in the CSF and potential prognostic biomarkers for aSAH and aSAH-related brain injury mechanisms.

Conclusions

In our study, the expression of TNF- α , IL-6, and IL-17 was significantly enhanced after SAH in patients who developed CV and DCI. IL-10 level was reduced, but may also be involved in the development and progression of aSAH at later stages of the disease.

The prognostic value of four cytokines for prognosis in patients with aSAH was evaluated. IL-6 and TNF- α were confirmed to have optimal prognostic value for CV and DCI formation.

Disclosure

Conflict of interest

The authors declare no conflict of interest.

Ethical approval

All procedures performed on patients comply with the ethical standards of institutional and national ethics committees, the 1964 Declaration of Helsinki and its amendments or similar ethical standards. The study was approved by the Ethics Committee of Kharkiv National Medical University (Minutes No. 3 dated September 14, 2021).

Informed consent

Informed consent was obtained from each of the patients.

Funding

The study was funded by the Ministry of Health of Ukraine on the state budget as part of the research work "Develop methods for predicting the consequences of cerebral stroke after SARS-CoV-2 infection based on blood and cerebrospinal fluid study" (state registration number 0122U000120).

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