The Journal of Neurological and Neurosurgical Nursing
Pielęgniarstwo Neurologiczne i Neurochirurgiczne

Wydawnictwo Państwowej Akademii
Nauk Stosowanych we Włocławku
ul. Mechaników 3, pok. 20
87-800 Włocławek

eISSN 2299-0321 ISSN 2084-8021
https://apcz.umk.pl/PNIN

DOI: 10.15225/PNN.2023.12.1.1 JNNN 2023;12(1):3–8 **Original**

# Evaluation of the Selected Parameters of Inflammation in Patients with Haemorrhagic Stroke

## Ocena wybranych parametrów stanu zapalnego u chorych z udarem krwotocznym

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### Abstract

**Introduction.** In the acute phase of stroke, the development of inflammation within the stroke focus can be observed. Therefore, in response to the inflammatory process in the brain, an inflammatory reaction occurs in the peripheral blood.
**Aim.** The aim of the study was to assess the parameters of inflammation in peripheral blood in a group of patients with haemorrhagic stroke.
**Material and Methods.** The study included 64 patients with haemorrhagic stroke hospitalized at the Stroke Centre of the Department of Neurology, University Hospital no. 1 in Bydgoszcz. The type and location of the stroke were verified by a head CT scan performed on the first day of hospitalization. On the first day of stroke, together with routine laboratory tests, the level of CRP1, WBC1, PCT, OB and fibrinogen1 was determined. CRP2, WBC2 and fibrinogen2 levels were repeated on the 14$^{th}$ day of stroke. Patients with infection were excluded from the study. Non-parametric statistical methods were used in the analysis: the Mann–Whitney test, the Kruskal–Wallis test and the Spearman correlation coefficient.
**Results.** Subcortical localization of the haemorrhagic focus was found in the majority of patients. Both baseline and control CRP and WBC values were outside the laboratory range. There were no statistically significant differences between the baseline and control CRP and WBC values, while the control fibrinogen level was significantly higher than baseline ($p<0.041$). Patients who died and/or those with impaired consciousness had statistically significantly higher values of inflammatory parameters (except OB, PCT and FIBR1) compared to patients who survived and were conscious.
**Conclusions.** In our study, we observed a significant increase in fibrinogen levels 14 days after the onset of the stroke. In addition, the control level of fibrinogen correlated with the size of the haemorrhagic focus and the clinical condition of the patients. Further research is needed in this area. **(JNNN 2023;12(1):3–8)**
**Key Words:** clinical status, functional capacity, haemorrhagic stroke, inflammation

### Streszczenie

**Wstęp.** W ostrej fazie udaru mózgu zaobserwować można rozwój stanu zapalnego w obrębie ogniska udarowego. W związku z powyższym w odpowiedzi na proces zapalny w mózgu, dochodzi do reakcji zapalnej we krwi obwodowej.
**Cel.** Celem pracy była ocena parametrów stanu zapalnego we krwi obwodowej w grupie chorych z udarem krwotocznym.
**Materiał i metody.** Do badania włączono 64 chorych z udarem krwotocznym hospitalizowanych w Centrum Udaru Mózgu Kliniki Neurologii Szpitala Uniwersyteckiego nr 1 w Bydgoszczy. Typ i lokalizację udaru weryfikowano badaniem KT głowy wykonywanym w pierwszej dobie hospitalizacji. W pierwszej dobie udaru wraz z rutynowymi badaniami laboratoryjnymi oznaczano poziom CRP1, WBC1, PCT, OB oraz fibrynogenu1. Badanie poziomu CRP2, WBC2 i fibrynogenu2 powtarzano w 14 dobie udaru. Z badania wyłączono pacjentów z infekcją. W analizie zastosowano nieparametryczne metody statystyczne: test Manna–Whitneya, test Kruskala–Wallisa oraz współczynnik korelacji Spearmana.

**Wyniki.** U większości chorych stwierdzono podkorową lokalizację ogniska krwotocznego. Zarówno wyjściowe, jak i kontrolne wartości CRP i WBC przekraczały zakres normy laboratoryjnej. Nie stwierdzono istotnych statystycznie różnic pomiędzy wyjściowymi i kontrolnymi wartościami CRP i WBC, natomiast kontrolny poziom fibrynogenu był istotnie wyższy od wartości wyjściowych (p<0,041). Pacjenci, którzy zmarli oraz osoby z zaburzeniami przytomności mieli istotnie statystycznie wyższe wartości parametrów stanu zapalnego (z wyjątkiem OB, PCT i FIBR1) w porównaniu z chorymi, którzy przeżyli i byli przytomnymi.
**Wnioski.** W naszym badaniu obserwowaliśmy istotny wzrost poziomu fibrynogenu po 14 dniach od początku udaru. Dodatkowo kontrolny poziom fibrynogenu korelował z wielkością ogniska krwotocznego i stanem klinicznym chorych. Niezbędne jest dalsze prowadzenie badań w tym obszarze. **(PNN 2023;12(1):3–8)**
**Słowa kluczowe:** stan kliniczny, wydolność funkcjonalna, udar krwotoczny, stan zapalny

## Introduction

Stroke is one of the most common causes of disability and death [1]. The course of stroke depends on many factors and mechanisms, however, recently there is more and more evidence suggesting that the inflammatory process may affect the extent of stroke and prognosis. In the acute phase of stroke, inflammation develops within the ischemic focus. In response to the inflammatory process of the brain, an inflammatory reaction also arises in the peripheral blood. In the first days of the stroke, elevated levels of CRP, WBC, interleukin 6 and other markers of inflammation in peripheral blood were observed. It was found that the level of CRP on the first day of ischemic strike correlates with the severity of the stroke and influences the prognosis [2–9]. However, few studies on the peripheral inflammatory response in haemorrhagic stroke have been conducted so far, and their results are inconclusive.

The aim of the study was to assess the parameters of inflammation in peripheral blood in a group of patients with haemorrhagic stroke.

## Material and Methods

The study included patients with haemorrhagic stroke hospitalized at the Stroke Centre of the Department of Neurology. The type and location of the stroke were verified by a head CT scan performed on the first day of hospitalization. On the basis of the CT scan of the head, the volume of the haemorrhagic focus was calculated. The clinical condition of the patients was monitored using the Bydgoszcz General Motor and Body Scale (BSMOC) and ADL; due to immobilization of patients in the first days of haemorrhagic stroke (bed regime), measurements on the day of discharge were used for statistical calculations, excluding patients who died. On the first day of stroke, together with routine laboratory tests, the level of CRP1, WBC1, PCT, OB and fibrinogen1 was determined. CRP2, WBC2 and fibrinogen 2 levels were repeated on the 14$^{th}$ day of stroke. Patients with infection were excluded from the study.

## Statistical Methods

Analyses were performed using the R software. Tests were performed at a significance level of 0.05. Fulfilment of the assumptions about the normality of variables was tested on the basis of the Shapiro–Wilk test. Due to the fact that not all variables met the assumptions of normal distribution, non-parametric statistical methods were used in the analysis: the Mann–Whitney test, the Kruskal–Wallis test and the Spearman correlation coefficient. The study was conducted with the consent of the Bioethics Committee of the Collegium Medicum of the Nicolaus Copernicus University in Bydgoszcz.

## Results

The study included 64 patients (29 men and 35 women) with haemorrhagic stroke. The average age was 71.23 years, men were slightly older than women. Consciousness was impaired in 23 patients and 21 patients died. Data on the study group of patients are presented in Table 1.

**Table 1.** Demographic and clinical characteristics of the study group

| Parameter | |
|---|---|
| Age, mean (SD) | 71.23 (13.33) |
| Gender, N | |
| Women | 35 |
| Men | 29 |
| Prognosis, N | |
| Dead | 21 |
| Survived | 43 |
| Disorders of consciousness, N | 23 |
| Functional status, mean (SD) | |
| ADL | 9.42 (7.48) |
| BSMOC | 17.98 (7.76) |

SD — standard deviation; N — number of observations

Subcortical localization of the haemorrhagic focus was found in the majority of patients. The mean size of the haemorrhagic focus was 56.53 cm³ (Table 2).

Data on baseline and control values of inflammation parameters and scores in the ADL and BSMOC scales are presented in Table 3. Both baseline and control CRP and WBC values were outside the laboratory normal range.

There were no statistically significant differences between baseline and control CRP and WBC values, while control fibrinogen levels were significantly higher than baseline ($p<0.041$) (Table 4).

Patients who died and those with impaired consciousness had statistically significantly higher values of inflammatory parameters (except for OB, PCT and FIBR1) compared to the surviving and conscious patients. There were no significant differences between the above values between the group of women and men (Table 5).

A significant, moderate, positive correlation was found between the parameters of inflammation (except for the baseline of fibrinogen, PTC and OB) and the size of the haemorrhagic focus. A significant, moderate, negative correlation was also found between some parameters of inflammation (CRP, FIBR2, PTC) and the BSMOC

**Table 2.** Location and size of the haemorrhagic focus

| Location of the haemorrhagic focus | Number of patients | Average focus size (cm³) | Maximum focus size (cm³) | Minimum focus size (cm³) |
|---|---|---|---|---|
| Cortical | 10 | 63.26 | 8 | 196 |
| Subcortex | 40 | 57.05 | 1.2 | 402 |
| Cerebellum | 4 | 18.44 | 4.76 | 45 |
| Brainstem | 5 | 17.26 | 1 | 29 |
| Plural | 5 | 108.72 | 3.6 | 236 |
| All locations | 64 | 56.53 | 1 | 402 |

**Table 3.** Baseline and control values of inflammation parameters and ADL and BSMOC scores

| Variable | $\bar{x}$ | SD | Min | Quantile 25% | Me (quantile 50%) | Quantile 75% | Max | N |
|---|---|---|---|---|---|---|---|---|
| CRP1 mg/l | 23.36 | 27.32 | 0.60 | 4.90 | 10.76 | 34.26 | 134.80 | 62 |
| CRP2 mg/l | 26.17 | 28.95 | 0.70 | 5.13 | 11.10 | 34.85 | 112.20 | 62 |
| WBC1 t/ul | 9.39 | 3.90 | 4.40 | 6.18 | 8.59 | 11.93 | 24.57 | 64 |
| WBC2 t/ul | 9.75 | 4.18 | 4.17 | 6.65 | 8.63 | 11.65 | 21.73 | 64 |
| FIBR1 g/l | 3.81 | 0.91 | 1.75 | 3.24 | 3.65 | 4.47 | 6.65 | 63 |
| FIBR2 g/l | 4.26 | 1.48 | 1.47 | 3.23 | 3.89 | 5.10 | 9.27 | 62 |
| PCT ng/ml | 0.20 | 0.73 | 0.02 | 0.04 | 0.05 | 0.08 | 4.51 | 39 |
| OB mm/h | 21.75 | 18.75 | 2.00 | 9.25 | 15.50 | 25.25 | 72.00 | 40 |
| BSMOC | 17.98 | 7.76 | 0.00 | 12.00 | 21.00 | 25.00 | 25.00 | 42 |
| ADL | 9.42 | 7.48 | 0.00 | 2.00 | 9.00 | 16.50 | 20.00 | 43 |

$\bar{x}$ — mean; SD — standard deviation; Min — minimum value; Me — median; Max — maximum value; N — number of observations

**Table 4.** Comparison of baseline and control parameters of inflammation

| Variable | $\bar{x}$ | Test | Test statistics | p-value |
|---|---|---|---|---|
| CRP1 | 23.36 | Mann–Whitney test | 791.00 | 0.269 |
| CRP2 | 26.17 | | | |
| WBC1 | 9.39 | Mann–Whitney test | 976.50 | 0.674 |
| WBC2 | 9.75 | | | |
| FIBR1 | 3.81 | Mann–Whitney test | 685.00 | 0.041 |
| FIBR2 | 4.26 | | | |

$\bar{x}$ — mean

**Table 5.** Comparison of baseline and control values of inflammation parameters in selected groups of patients

| Variable | Women | Men | p | Dead | Survived | p | Disturbance of consciousness | No disturbance of consciousness | p |
|---|---|---|---|---|---|---|---|---|---|
| CRP1 | 20.37 | 27.23 | 0.79 | 30.99 | 19.72 | 0.00 | 34.98 | 16.96 | 0.00 |
| CRP2 | 24.32 | 28.57 | 0.94 | 52.22 | 13.76 | 0.00 | 48.84 | 13.70 | 0.00 |
| WBC1 | 8.89 | 10.00 | 0.58 | 11.30 | 8.46 | 0.02 | 10.55 | 8.74 | 0.05 |
| WBC2 | 9.37 | 10.20 | 0.61 | 13.83 | 7.75 | 0.00 | 12.49 | 8.20 | 0.00 |
| FIBR1 | 3.92 | 3.66 | 0.13 | 3.97 | 3.73 | 0.21 | 3.96 | 3.72 | 0.24 |
| FIBR2 | 4.38 | 4.10 | 0.19 | 4.96 | 3.92 | 0.00 | 5.16 | 3.76 | 0.00 |
| PCT | 0.28 | 0.05 | 0.08 | 0.68 | 0.06 | 0.22 | 0.63 | 0.05 | 0.03 |
| OB | 24.96 | 17.41 | 0.16 | 21.23 | 22.00 | 0.99 | 21.15 | 22.04 | 0.95 |

p — test probability

and ADL scores. There was a significant positive correlation between CRP and PTC and the age of the patients (Table 6).

**Table 6.** Spearman's correlation matrix (including the results of the significance test) for the parameters of inflammation and selected clinical parameters

| Variable | Size of haemorrhagic focus | BSMOC | ADL | Age |
|---|---|---|---|---|
| CRP1 | 0.35 | –0.43 | –0.37 | 0.39 |
| CRP2 | 0.56 | –0.54 | –0.46 | 0.36 |
| WBC1 | 0.32 | | | |
| WBC2 | 0.47 | | | |
| FIBR2 | 0.40 | –0.36 | –0.35 | |
| PCT | | –0.54 | –0.57 | 0.43 |

## Discussion

In contrast to ischemic stroke, the inflammatory process does not play a key role in haemorrhagic stroke, probably because the inflammatory reaction is secondary to bleeding. The presence of intracranial bleeding triggers an acute cerebral and peripheral inflammatory reaction. In response to acute brain injury, interleukin 6 is secreted, which is the main factor that stimulates the production of CRP. On the other hand, the peripheral inflammatory reaction triggered by intracerebral haemorrhage leads to an intensification of brain damage.

C-reactive protein is a glycoprotein produced by the liver. The presence of acute inflammation and tissue destruction stimulates its production. Di Napoli et al. [10] showed that on the first day of stroke, the CRP level is higher than in the control group, correlated with the size of the stroke focus and influences the prognosis. Roudbary et al. [11] noted that in patients with ischemic stroke on the first day the level of CRP is significantly higher than in patients with haemorrhagic stroke; according to the authors, CRP may be a marker helpful in determining the type of stroke. It is believed that the inflammatory reaction in ischemic stroke proceeds faster than in haemorrhagic stroke, hence the differences in CRP levels between types of strokes, especially if CRP measurement is performed in the first hours after the onset of stroke symptoms. Whiteley et al. [12] found that the high level of CRP and WBC on the first day of stroke was an independent factor influencing the prognosis 6 months after the stroke.

In our study, CRP was significantly elevated in all groups of patients both on the first and 14$^{th}$ day from the onset of stroke, and its value correlated with the size of the haemorrhagic focus and clinical status. In the group of patients who died, with disturbances of consciousness and infection, CRP was significantly higher than in the group that survived, in the group without disturbances of consciousness and without infection.

Elevated levels of fibrinogen are one of the risk factors for vascular diseases. Studies have shown that in the acute phase of ischemic stroke, the concentration of fibrinogen, similarly to other indicators of the acute phase, may be elevated. The question of whether an increase in fibrinogen concentration leads to stroke or is a reaction to stroke has still not been answered [13,14]. In studies conducted by Peycheva et al. [15], it was shown that people diagnosed with ischemic stroke were characterized by significantly elevated average fibrinogen levels (>4 g/l). Stroke subtypes were also analysed according to the median fibrinogen concentration. It was observed that people with an undetermined cause of stroke and patients with atherosclerotic stroke had significantly higher median fibrinogen levels compared to patients with other types of stroke. There was no significant relationship between fibrinogen levels and neurological deficit. In turn, Mehta et al. [16] showed that the National Institutes of Health Stroke Scale score at admission (Odds Ratio (OR) 1.152 [95% CI 1.070–1.240], p<0.001), age (OR) 1.034 [95% CI 1.001–

1.069], p=0.046), and fibrinogen (OR 1.011 [95% CI 1.006–1.015], p<0.001) were independent predictors of early neurological deterioration in patients with acute ischemic stroke. Moreover, fibrinogen concentration was also found to be a statistically significant predictor of poor prognosis (OR 1.004 [95% CI 1.000–1.007], p=0.038).

An increase in the level of fibrinogen is associated with an increased risk of ischemic stroke, and according to recent reports — also haemorrhagic. Sturgeon et al. [14] prove that high levels of fibrinogen increase the risk of CNS bleeding. Sato et al. [17] found a relationship between the level of fibrinogen and an increased risk of haemorrhagic stroke, but did not confirm such a relationship with ischemic stroke and subarachnoid haemorrhage. How to explain such results? Fibrinogen levels have been shown to correlate with small vessel atherosclerotic brain damage, such as leukoaraiosis, Biswanger's disease, dementia, and silent stroke. Damage to these vessels is responsible for the occurrence of intracerebral haemorrhages.

In our study, we observed a significant increase in fibrinogen levels 14 days after the onset of the stroke. In addition, the control level of fibrinogen correlated with the size of the haemorrhagic focus and the clinical condition of the patients. It is difficult to explain why fibrinogen levels increased after 14 days if stroke, while WBC and CRP levels did not.

The limitation of the study is the small number of patients, the lack of ADL and BSMOC measurements in the first day of stroke, and the lack of a control OB and PCT test. Another limitation may be the lack of a control group, we could related the obtained values of inflammation parameters only to the laboratory standard.

## Conclusions

It was observed that the level of fibrinogen in the blood increases on the 14$^{th}$ day of the haemorrhagic stroke compared to the measurement on the first day, while the WBC and CRP levels do not change. Moreover, the parameters of inflammation are higher in the group of deceased patients and patients with impaired consciousness compared to the group of patients who survived and patients without consciousness disorders. Most parameters of inflammation (with the exception of baseline fibrinogen level) correlate with the size of the haemorrhagic focus and the clinical status assessed using the ADL and BSMOC scales on the first day of stroke.

## Implications for Nursing Practice

Stroke is considered one of the most common causes of disability and death. The course of stroke correlates with many factors and mechanisms. Moreover, it has been shown that the inflammatory process may affect the extent of the infarct focus, which in turn affects the prognosis. Therefore, in the nursing care of a stroke patient, it is important to monitor for the possibility of inflammation symptoms. Quick diagnosis and initiation of targeted treatment can significantly affect the treatment process and the patient's condition.

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**Conflict of Interest**: None
**Funding**: None
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**Received**: 4.01.2023
**Accepted**: 10.02.2023