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Level of fibrinogen, D-dimers and C-reactive protein, and correlations between these parameters in ischemic and haemorrhagic stroke

Poziom fibrynogenu, D-dimerów i białka C-reaktywnego oraz korelacja pomiędzy tymi parametrami w udarze krwotocznym i niedokrwiennym mózgu

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Abstract

Introduction and objective. Fibrinogen (FIB) and C-reactive protein (CRP) play an important role in any inflammatory response. FIB levels may be higher in stroke patients compared to non-stroke patients. CRP is used to detect inflammation due to its high sensitivity in aseptic inflammation. Blood levels of d--dimer (DD) are used to determine the amount of fibrin formed and distributed. Inflammation may play an important role in the pathogenesis of haemorrhagic stroke causing primal damage, and in ischemic stroke causing secondary damage due to a decrease in perfusion in the brain. The aim of the study is to prove the hypothesis that the inflammatory process is involved in the pathogenesis of ischemic and haemorrhagic stroke.

Materials and method. The study used data from a retrospective study conducted on a group of 402 stroke patients, among which the levels of FIB, CRP and DD were compared. The patients were hospitalized in the Department of Neurology of the Medical University (MU) in Białystok from 1 January – 31 December 2016. Patients' data was obtained from medical records. The diagnosis of stroke was confirmed by CT of the head. Patients with other brain injuries were excluded from the study. The study was approved by the Bioethics Committee of the MU of Bialystok. The applied research method was the statistical method.

Results. A positive moderate correlation was found between CRP and FIB. In the group of patients with ischemic stroke it was higher (0.59) than in the group of patients with haemorrhagic stroke(0.22). Moreover, in the group of patients with ischemic stroke, a correlation was found between DD and CRP(0.517).

Conclusions. Inflammatory process is involved in pathogenesis of ischemic and haemorrhagic stroke, but could be associated with comorbid diseases. Increased CRP correlates with higher levels of FIB and DD in the ischemic stroke but not in the haemorrhagic stroke.

Key words

C-reactive protein, fibrinogen, ischemic stroke, D-dimers, haemorrhagic stroke

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Streszczenie

Wprowadzenie i cel pracy. Celem pracy jest udowodnienie tezy, że proces zapalny bierze udział w patogenezie udaru niedokrwiennego i krwotocznego. Nasze badanie porównuje poziomy FIB, CRP i DD wśród pacjentów przyjętych do Kliniki Neurologii Uniwersytetu Medycznego w Białymstoku z powodu udaru niedokrwiennego lub krwotocznego. Chcemy odpowiedzieć na pytanie, czy poziomy tych parametrów w dwóch rodzajach udaru różnią się od siebie.

Materiał i metody. Do pracy użyliśmy danych z badania retrospektywnego przeprowadzonego na grupie 402 pacjentów z udarem niedokrwiennym lub krwotocznym. Pacjenci byli hospitalizowani w Klinice Neurologii Uniwersytetu Medycznego w Białymstoku od 1 stycznia do 31 grudnia 2016 roku. Dane demograficzne i kliniczne pacjentów uzyskano z dokumentacji medycznej. Rozpoznanie udaru niedokrwiennego lub krwotocznego potwierdzono badaniem TK głowy. Z badania wykluczono pacjentów z krwotokiem pourazowym i podpajęczynówkowym oraz pacjentów z guzami mózgu. Badanie uzyskało akceptację Komisji Bioetycznej Uniwersytetu Medycznego w Białymstoku. Zastosowaną metodą badawczą była metoda statystyczna.

Wyniki. Stwierdzono dodatnią umiarkowaną korelację między CRP a FIB. Korelacja ta w grupie pacjentów z udarem niedokrwiennym była wysoka (0,59) w porównaniu z grupą

pacjentów z udarem krwotocznym (0,22). Ponadto w grupie pacjentów z udarem niedokrwiennym stwierdzono korelację między DD a CRP (0,517), której nie zaobserwowano w grupie pacjentów z udarem krwotocznym (0,09).
Wnioski. Nasze badanie wykazało, że proces zapalny bierze udział w patogenezie udaru niedokrwiennego i krwotocznego, chociaż może być związany z chorobą współtowarzyszącą. Zwiększone CRP koreluje z wyższymi poziomami fibrynogenu i DD w udarze niedokrwiennym, ale nie w udarze krwotocznym.

Słowa kluczowe

udar niedokrwienny, białko C-reaktywne, udar krwotoczny, fibrynogen, D-dimery

INTRODUCTION

Fibrinogen (FIB) has an important role in haemostasis by being a soluble precursor of insoluble fibrin. It also supports platelet aggregation. A fibrin clot activates the fibrinolytic system which provides a balance between clotting and fibrinolysis[1]. FIB also plays an important role in systemic inflammation. The amplified concentration of FIB may be the result of its increased production or slower degradation. It has been observed as a result of endothelial damage, acute phase reactions, or as an outcome of activation of the coagulation and fibrinolytic systems. FIB levels can be higher in patients with stroke versus non-stroke patients [2]. Due to the connection between elevated FIB levels and the early appearance of atherosclerosis symptoms, the increase in FIB concentration is observed in obese people, smokers, and alcohol abusers, while lower in physically active people[3, 4].

C-reactive protein (CRP) plays a key role in any inflammatory response. CRP works through the interaction of both humoral and cellular effector mechanisms of inflammation [5]. Transcription of the CRP gene occurs mainly in hepatocytes in response to enlarged levels of inflammatory cytokines, particularly interleukin-6 (IL-6) [6]. CRP is widely used for the clinical detection of inflammation due to its high sensitivity in aseptic inflammation [7].

Blood levels of d-dimer (DD) are used to determine the amount of formed and distributed fibrin. In healthy people, the amount of circulating DD is low, although it increases in situations connected with thrombosis [8]. DD levels also are raised in patients with ischemic stroke [9]. 80% of all stroke cases are ischemic stroke[10], in which inflammation may play an important role[11]. This inflammation may result from damage caused by ischemic brain damage and blood flow reperfusion. It leads to the initiation of an inflammatory cascade, including oxidative stress, excitotoxicity, and inflammatory cell infiltration, which further contribute to nerve tissue damage and cell death[12].

Haemorrhagic stroke is less common and accounts for 20% of all strokes [9]. The haematoma compresses the brain and increases intracranial pressure [13]. Secondary damage is the result of inflammation, oedema, disruption of the blood-brain barrier, excessive production of free radicals, glutamate-induced excitotoxicity, and release of haemoglobin and iron from the clot [14].

The aim of the study is to prove a hypothesis that an inflammatory process is involved in the pathogenesis of ischemic and haemorrhagic stroke. The study compares levels of FIB, CRP, and DD among patients admitted to the Department of Neurology at the Medical University in Białystok, due to ischemic or haemorrhagic stroke. We aim was to answer the question whether levels of these parameters differed in the two types of stroke.

MATERIALS AND METHOD

A retrospective study was conducted on a group of 402 patients with ischemic or haemorrhagic stroke. Patients were hospitalized at the Department of Neurology at the Medical University in Białystok from 1 January – 31 December 2016. Patient's demographic and clinical data were obtained from medical records. The diagnosis of ischemic or haemorrhagic stroke was confirmed by head CT. Patients with post-traumatic and subarachnoid haemorrhage and patients with brain tumours were excluded from the study. The study was approved by the Bioethics Committee of the Medical University of Bialystok.

Statistical analysis. Outcomes are presented as numbers with means with standard deviation and confidence intervals. The database was gathered in a Microsoft Excel spreadsheet and analyzed using the statistic program GraphPad Prism 8.0.1. Data were tested using the unpaired t-test. P-value <0.05 was used to indicate statistical significance.

RESULTS

Among the 402 patients hospitalized in the Department of Neurology at the Medical University of Białystok, 91.8% were diagnosed with ischemic stroke, and 8.2% – haemorrhagic stroke. 44.53% of the patients were males and 55.47% were females. Ischemic stroke was diagnosed in 92.83% of females and 90.5% of males, haemorrhagic stroke was diagnosed in 7.17% of females and 9.5% of males. The age of the patients was 23–97 years, the mean age of stroke incidence in all patients was 74.2 years. On average, this was 5 years lower in males (71.2 years) than in females (76.6 years). The mean age at onset also differed depending on the type of stroke, with haemorrhagic stroke (67.7 years) among all patients, which was 6.5 years lower than in ischemic stroke (74.2 years). As many as 84.8% of the patients were over 60 years old. The majority were females (57.48%). On the other hand, in the group under aged 60 (15.2%), there was a slight majority of males (52.63%). In terms of the place of residence, the majority of patients lived in urban areas (55.47%).

Fibrinogen. Fibrinogen (FIB) was tested among 391 patients. The mean FIB concentration among all patients was 405.7 mg/dl, the value ranged between 142 mg/dl – 889 mg/dl. For ischemic stroke (n=360) the mean level of FIB was 409 mg/dl (+/- 110.2 SD) with a minimum level of 142 mg dl and a maximum of 889.0 mg/dl. The average level of FIB in patients with haemorrhagic stroke (n=31) was 367.2 mg/dl (+/- 80.25), ranging from 175.0 mg/dl – 509 mg/dl. Statistical analysis did not show a statistically significant difference between the compared values (p-value=0.0577) (Fig. 1).

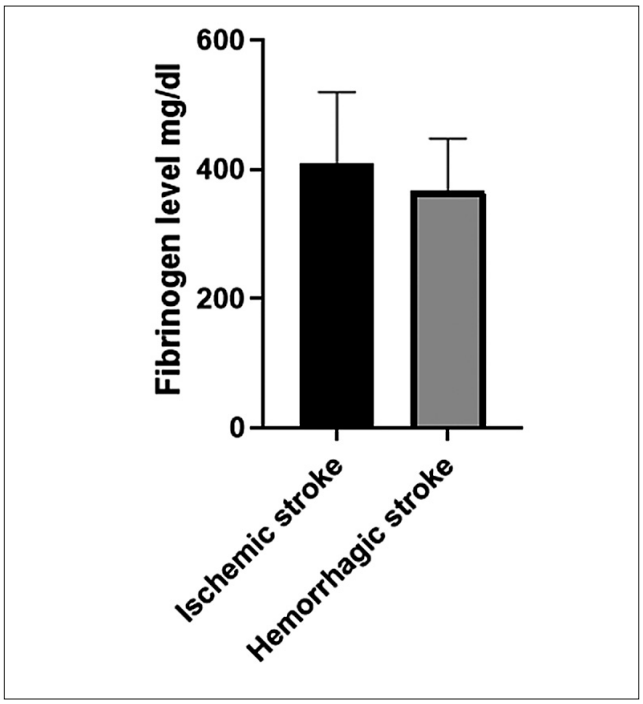

Figure 1. Difference between fibrinogen value in ischemic and haemorrhagic stroke

Some tested patients had confirmed comorbidities: 24.5% diabetes, 79% hypertension, 54.7% dyslipidaemia, 25.8% atrial fibrillation, 20% ischemic heart disease, 7.9% had past myocardial infarction and 8% present at the time or a previous malignant neoplastic disease.

D-dimer. D-dimer (DD) level was tested among 326 participants. The mean DD level in the group of all patients was 3.97 µg/L, the value ranged between 0.27 µg/L – 525.7 µg/L. The mean DD level was 3.93 µg/L among patients with ischemic stroke and in patients with haemorrhagic stroke 4.36 µg/L. There was no statistical difference between the tested groups.

Some tested patients had confirmed comorbidities 25.4% diabetes, 79.4% hypertension, 55.5% dyslipidaemia, 26.3% atrial fibrillation, 20% ischemic heart disease, 8.8% had past myocardial infarction and 8.2% present at the time or previous malignant neoplastic disease.

CRP. C-reactive protein (CRP) was tested among 393 participants. The mean CRP in all patients was 21.37 mg/l, the value ranged between 0.2mg/l – 306.8 mg/l. The mean CRP was 22.27 mg/l among patients with ischemic stroke and in patients with haemorrhagic stroke – 10.82mg/l. There was no statistical difference between the study groups at the p--value =0.101

Some tested patients had confirmed comorbidities 24.6% diabetes, 78.8% hypertension, 55% dyslipidemia, 25.6% atrial fibrillation, 20% ischemic heart disease, 8% had past myocardial infarction and 7.8% present at the time or past malignant neoplastic disease. The correlation between the total mean of FIB, CRP, and DD level was tested among all patients (Tab. 1).

The correlation between FIB, CRP, and DD level in the group of patients with ischemic stroke was tested among all patients. Results are presented in Table 2.

The correlation between FIB, CRP, and DD level in the group of patients with haemorrhagic stroke was tested among all patients (Tab. 3).

Table 1. Correlation between fibrinogen (FIB), C-reactive protein (CRP) and blood levels of d-dimer (DD) among all patients

	FIB	CRP	DD
FIB	1	0.580	0.242
CRP	0.580	1	0.494
DD	0.242	0.494	1

Table 2. Correlation between fibrinogen (FIB), C-reactive protein (CRP) and Blood levels of d-dimer (DD) in patient with ischemic stroke

	FIB	DD	CRP
FIB	1	0.265	0.598
DD	0.265	1	0.517
CRP	0.598	0.517	1

Table 3. Correlation between fibrinogen (FIB), C-reactive protein (CRP) and Blood levels of d-dimer (DD) in patients with haemorrhagic stroke

	FIB	DD	CRP
FIB	1	-0.214	0.222
DD	-0.214	1	0.090
CRP	0.222	0.090	1

A positive moderate correlation was found between CRP and FIB. This correlation in the group of patients with ischemic stroke was high (0,59) compared to the group of patients with haemorrhagic stroke (0,22). Furthermore, in the group of patients with ischemic stroke a correlation was found between DD and CRP (0.517), this correlation was not found in the group of patients with haemorrhagic stroke (0.09). The rest of the observed correlations did not show a significant difference between the two types of stroke.

DISCUSSION

In the current study, no difference was observed between levels of FIB, DD, and CRP in patients with ischemic and haemorrhagic stroke. In patients with ischemic stroke but not in patients with haemorrhagic stroke, 2 positive correlations were found: between CRP and FIB, and between CRP and DD.

A study published in 2015 evaluated the role of CRP, FIB, and DD among patients with different subtypes of ischemic stroke. It was found that CRP and DD could be useful in recognizing subtypes of acute ischemic stroke. DD had a higher diagnostic value when compared to CRP[15]. Another study published in the same year evaluated the role of DD, FIB, and CRP as plasma biomarkers in acute ischemic stroke. It proved that these biomarkers might be helpful in detecting the etiology of acute cerebral vascular stroke[16]. A study released in 2016 evaluated CRP, FIB, and DD in patients with progressive cerebral infarction. The results showed that the changes observed in these biochemical markers might contribute to identifying patients with progressive cerebral infarction[17].

This study aimed to compare the levels of FIB, DD, and CRP between patients with ischemic and haemorrhagic stroke. The results did not show a statistical difference between those two groups. The mean value of FIB in patients with ischemic and haemorrhagic stroke was higher than the

normal value, and higher among patients with ischemic than with haemorrhagic stroke. The mean level of DD in both groups of patients (with ischemic and haemorrhagic stroke) was similar to the normal laboratory value. The mean CRP value was higher than the normal CRP level. Patients with ischemic stroke had a higher value of CRP than patients with haemorrhagic stroke.

Several studies proved a correlation between the value of FIB among patients and ischemic stroke [18–21]. It proves the correlation between a high level of FIB and ischemic stroke, which was found in the current study. However, the Edinburgh Stroke Study showed the opposite and did not find a relationship between FIB and recurrent stroke [22].

A study published in 2006 found a positive association between FIB and intraparenchymal haemorrhage [23]. In the current study, patients with haemorrhagic stroke had a higher value of FIB than the normal level. Interestingly, one study in 2005 declared that FIB is only a risk predictor for ischemic stroke, but not for haemorrhagic stroke [24].

Recently published studies proved that DD level was increased in patients with ischemic stroke [25, 26], whereas another study that compared the level of FIB and DD among patients with ischemic and haemorrhagic stroke proved that these parameters were increased in these 2 types of stroke [27]. The current study did not find increased mean DD levels in patients with ischemic and haemorrhagic stroke.

It is a well-known fact that both ischemic and hemorrhagic stroke can cause inflammatory responses due to brain tissue injury that occurs in both types of stroke [14][28]. Recently published studies found that CRP level is elevated in patients with ischemic stroke [29] and haemorrhagic stroke [30, 31], which shows that inflammatory response occurs in these 2 types of stroke, which was also found in the current study. This might be explained by the general rise in CRP in the observed group of patients with risk factors for stroke: heart disease [32], atrial fibrillation, and heart failure [33]. One study did not find elevated levels of CRP to be a predictor of stroke [34]. Similar to the current study, a study conducted in 2005, did not find a correlation between ischemic and haemorrhagic stroke and coagulation biomarkers. The patient group was significantly fewer and the majority of admitted patients suffered from transient ischemic attacks [35].

The probable explanation for the findings of the current study is the inflammatory background of atherothrombosis of cerebral vessels. However, it is still important to remember that the pathology of stroke and neuroinflammation is still unknown [36]. Brain tissue injury causes acute phase response in which FIB plays a crucial role [37]. That may explain the higher likelihood of elevated FIB levels among patients with ischemic stroke, where tissue damage plays a key role [38].

A positive correlation between DD and CRP was indicated in patients with ischemic stroke. This could be explained by the fact, that a high DD level is the indicator of hypercoagulability, which often leads to ischemic stroke due to subclinical formation of a fibrin thrombus [39]. The high likelihood of an increased level of CRP might be explained by the fact that the molecular processes of inflammation and thrombosis are closely related to each other [40]. The current study did not find a correlation between the same parameters in patients with haemorrhagic stroke.

CONCLUSIONS

This study has shown that an inflammatory process is involved in the pathogenesis of ischemic and haemorrhagic stroke, but high levels of indicators could also be associated with comorbidities. Increased CRP correlates with higher levels of fibrinogen and DD in ischemic stroke, but not in haemorrhagic stroke.

Limitations. Some limitations of the current study need to be underlined. The first significant limitation is the relatively small number of patients included in the study. Future studies should consist of a larger group of patients with ischemic and haemorrhagic stroke.

Secondly, the study included a small group of patients with haemorrhagic stroke. To be able to measure significant biochemical parameters to differentiate the pathogenesis of these 2 types of stroke, future studies must contain more patients with the haemorrhagic type of stroke. There is also a need to conduct nationwide or even international studies in order to be able to measure regional differences of biochemical parameters between patients with different ethnicity. The short period of time during which the study was conducted was an additional limitation.

The third limitation was the large proportion of patients with comorbidities that could have influenced the results of laboratory tests. The most common was hypertension, together with other confirmed diseases, such as diabetes, dyslipidaemia, atrial fibrillation, ischemic heart disease, past myocardial infarction, and present at the time or past malignant neoplastic disease.

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