



## BLOOD COAGULATION AND FIBRINOLYSIS PARAMETER CHANGES AFTER VARIOUS TYPES OF BRAIN DAMAGE

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**Summary.** Brain tissue, especially astrocytes, is one of the richest sources of tissue factor (TF) in the human organism. Simultaneously, tissue plasminogen activator (t-PA) has been found in brain blood vessels. Various brain damage induces release of TF and fibrinolysis activators into circulation, and leads to hemostatic disturbances. We have investigated some coagulation and fibrinolysis parameters in 120 patients with various brain damage (30 with isolated head trauma; 30 after brain tumor surgery, 30 after ischemic and 30 after haemorrhagic stroke). Blood samples taken in the first 24 hours after brain damage were determined by the following parameters: prothrombin time (PT), fibrinogen, activated partial thromboplastin time (aPTT), activity of FVII, antithrombin III (ATIII) and alpha-2 antiplasmin (alpha-2 AP), and D-dimer. Significant decreases of PT, FVII, ATIII and increase of D-dimer have been noticed in all groups, most significant after head trauma. Alpha-2 AP has been decreased only after brain tumor surgery. Although described abnormalities did not demanded supportive and/or anticoagulant treatment, their presence in most of investigated patients should be the enough of a reason for routine coagulation investigation in the first 24 hours after brain damage.

**Key words:** Blood coagulation, fibrinolysis, brain damage

### Introduction

The brain is one of the richest sources of tissue factor (TF) in the human organism. It was described that a brain tissue injection caused disseminated intravascular coagulation more than 150 years ago (1). The consequence of this is that the source of TF in laboratory determination of one stage protrombin time is an extract of rabbit brain tissue (2).

Investigations of coagulation and fibrinolysis activity of the brain tissue, in the sixties confirmed high tissue factor activity in brain (3,4) and high fibrinolytic activity in highly vascularized brain tissue, such as choroid plexus and meninges (5,6).

Current investigations point to the localization of TF in the gray matter of the brain (7). The primary source of TF are astrocytes (8,9). Tissue plasminogen activator (t-PA) has been found in cerebral capillaries (10), which confirms fibrinolytic activities of brain tissue.

The presence of high concentration of blood coagulation and fibrinolysis activators in brain tissue can cause pathological intravascular activation of coagulation and fibrinolysis, after brain tissue destruction induced by various etiological factors.

The blood clotting abnormalities have been widely

described after head trauma. Brain contusion induces the destruction of brain tissue, while secondary haematomas compress the brain tissue and cause cerebral ischemia with secondary brain damage. These abnormalities have induced the activation of coagulation and fibrinolysis.

Brain tumor surgery can cause blood coagulation and fibrinolysis disorders. The pathogenesis of these disorders is complex, and includes more factors. On the one hand the neurosurgical intervention by itself causes the destruction of brain tissue and activation of coagulation (11). On the other, tumor compression and infiltration of the brain tissue cause brain tissue destruction and releasing of TF in circulation. In patients with brain tumors an increased concentration of plasminogen activator inhibitor-1 (PAI-1) has been noticed (12,13). This increase is more significant in patients with brain metastasis and high grade gliomas (12). The increase of TF in gliomas which correlates with grade of malignancy has also been described (14).

There is less literature data about coagulation and fibrinolysis abnormalities after stroke.

The blood coagulation disorder is especially complex in ischemic stroke, it being either of atherothrombotic or embolic nature. In both types of

stroke, activation of coagulation is present by itself during the formation of thrombus. Ischemic stroke causes cerebral ischemia and brain tissue damage. This causes release of tissue factors (TF) in circulation and further activation of coagulation. Because of that abnormal coagulation profile is a common phenomenon in ischemic stroke.

Coagulation abnormalities on the one hand can be caused by ischemic stroke, while on the other hand can be its consequence. Primary or secondary thrombophilia, such as antithrombin III (ATIII), protein C and S deficiency, resistance on activated protein C or presence of lupus anticoagulants can induce ischemic stroke (15,16). Some authors describe increase of FVIII/VFW and t-PA as risk factor for ischemic stroke (17), while the decrease of tissue factor pathway inhibitor (TFPI) has been noticed in ischemic stroke (18). On the other hand brain damage and release of TF into circulation can cause hypercoagulability.

Literature data about coagulation abnormalities in haemorrhagic stroke is meager.

There have been noticed activation of coagulation, presented in raise of fibrinopeptide A, TAT and D-dimer after subarachnoidal hemorrhage (SAH), which is a consequence of the rupture of saccular aneurysm (19). Serious coagulation abnormalities including disseminated intravascular coagulation could complicate SAH (20).

In some patients with intraventricular hemorrhage the decrease of plasminogen in cerebrospinal fluid has been observed (21).

The above literature data and our previous unpublished experience with abnormalities of coagulation and fibrinolysis after various brain damage resulted in our trying to carry out a prospective study based on this problem.

The aim of the study was to investigate blood coagulation and fibrinolysis parameter changes in first 24 hours after various brain damage (head trauma, brain tumor surgery, ischemic and haemorrhagic stroke).

## Materials and methods

120 patients with various types of brain damage admitted at the Clinic of Neurology and Neurosurgery Clinic, Faculty of Medicine Nis have been included in this prospective study. 30 patients had isolated head

trauma (22 male, 8 female, average age 38 (8-62)); 30 patients have undergone brain tumor surgery (15m., 15f., average age 50 (26-66) (12 with gliomas, 12 with meningiomas and 6 with brain metastases); 30 patients have ischemic (atherotrombotic stroke) (8m., 22f., average age 67 (48-74) and 30 had haemorrhagic stroke (14 m., 16 f., average age 63 (33-74) (20 with intracerebral and 10 with subarachnoidal hemorrhage). 20 healthy volunteers from Blood bank served as a control group.

Blood samples were taken in first 24 hours after brain damage. Blood was centrifuged on 1000G 15 minutes and plasma was separated.

The following parameters were determined: prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen and coagulation activity of FVII. These parameters were determined by standard coagulation methods on coagulometer ACL 2000 (Instrumentation Laboratory) using commercial kits (Instrumentation Laboratory). Concentration of antithrombin III (ATIII) and alpha 2 antiplasmin (alpha-2 AP) were measured by standard colorimetric methods on ACL 2000 using commercial kits (Instrumentation Laboratory). D-dimer was determined by Nycocard D-dimer test (Nycomed).

Blood coagulation and fibrinolysis parameters have been expressed in the following units PT, FVII, ATIII and alpha-2 AP in %, aPTT in s, fibrinogen in g/l and D-dimer in mg/l.

The obtained results have been shown as mean  $\pm$  SD, while statistical significance has been determined by Student's t-test.

## Results

The decrease of PT has been noticed in all estimated groups. Control values of PT were  $95.40 \pm 12.11\%$ . PT after head trauma was  $63.79 \pm 18.45\%$  ( $p < 0.001$ ); after brain tumor surgery was  $77.20 \pm 19.03\%$  ( $p < 0.005$ ); in ischemic stroke it was  $65.64 \pm 17.00\%$  ( $p < 0.001$ ) and in haemorrhagic stroke  $72.42 \pm 28.03\%$  ( $p < 0.01$ ) (Table 1, Figure 1).

A slight decrease of fibrinogen has been observed after head trauma ( $3.84 \pm 1.73\text{g/l}$ ) in relation to control values ( $4.18 \pm 0.83\text{g/l}$ ). Slight increase has been observed after brain tumor surgery ( $4.75 \pm 1.71\text{g/l}$ ),

Table 1. Blood coagulation and fibrinolysis parameters after different types of brain damage

	PT (%)	fibrinogen (g/l)	aPTT (s)	D-dimer(mg/l)	ATIII (%)	FVII (%)	alpha-2AP (%)
Control	$95.40 \pm 12.11$	$4.18 \pm 0.83$	$37.22 \pm 2.65$	$0.56 \pm 0.10$	$96.30 \pm 8.86$	$90.10 \pm 9.35$	$94.10 \pm 2.69$
Trauma	$63.79 \pm 18.45^{***}$	$3.84 \pm 1.73$	$36.41 \pm 10.18$	$3.98 \pm 2.76^{***}$	$71.88 \pm 16.99^{***}$	$59.44 \pm 19.80^{***}$	$95.75 \pm 25.60$
Tu surgery	$77.20 \pm 19.03^{**}$	$4.75 \pm .71$	$30.42 \pm 4.90^{***}$	$3.38 \pm 2.59^{**}$	$81.65 \pm 11.86^{***}$	$69.10 \pm 18.48^*$	$82.76 \pm 22.97^*$
Ischemic stroke	$65.64 \pm 17.00^{***}$	$6.11 \pm 1.93^{***}$	$34.86 \pm 8.42$	$1.81 \pm 1.44^{***}$	$81.89 \pm 2.03^{***}$	$72.12 \pm 21.76^*$	$103.56 \pm 26.33$
Haemorrhagic stroke	$72.42 \pm 28.03^*$	$5.61 \pm 2.10^*$	$33.85 \pm 9.00$	$1.20 \pm 0.83^*$	$79.04 \pm 17.46^{***}$	$65.39 \pm 25.94^*$	$88.36 \pm 26.52$

Values are means  $\pm$  SD

\*  $p < 0.05$   
 \*\*  $p < 0.005$   
 \*\*\*  $p < 0.001$

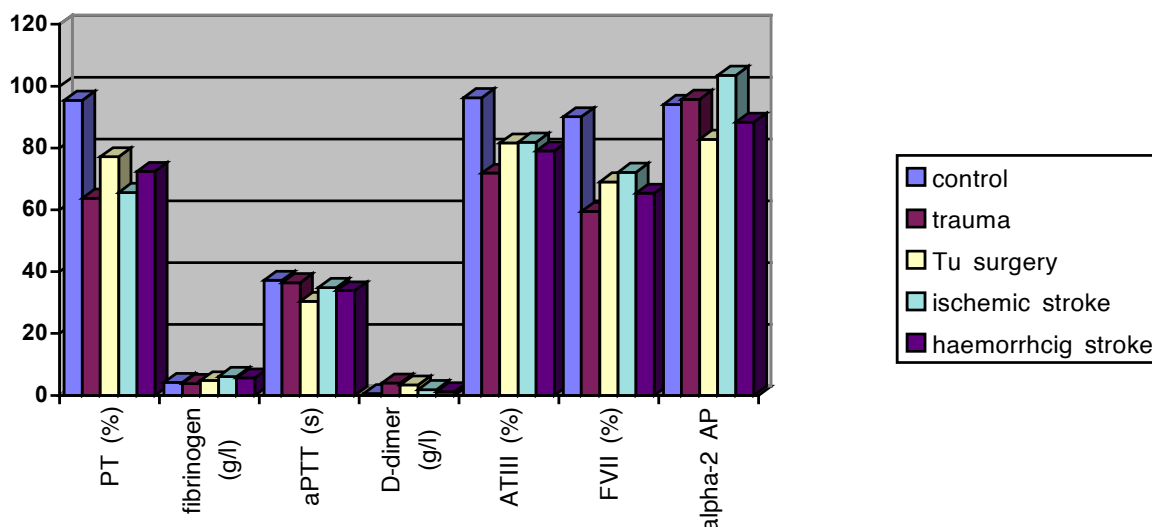


Figure 1. Blood coagulation and fibrinolysis parameters in different types of brain damage

while significant increase has been noticed after ischemic ( $6.11 \pm 1.93$ g/l) ( $P < 0.001$ ) and haemorrhagic stroke ( $5.61 \pm 2.10$  g/l) ( $p < 0.05$ ) (Table 1, Figure 1).

aPTT has been in the level of control values, except after brain tumor surgery, where it was shortened ( $30.42 \pm 4.90$ s) in relation to control values ( $37.22 \pm 2.65$ s) ( $p < 0.001$ ) (Table 1, Figure 1).

D-dimer has been increased in all types of brain damage. D-dimer after head trauma was  $3.98 \pm 2.76$ mg/l ( $p < 0.001$ ), after brain tumor surgery it was  $3.38 \pm 2.59$ mg/l ( $p < 0.005$ ), after ischemic stroke it was  $1.81 \pm 1.44$ mg/l ( $p < 0.01$ ) and in haemorrhagic stroke it was  $1.20 \pm 0.83$ mg/l ( $p < 0.05$ ). Control values of D-dimer was  $0.56 \pm 0.10$ mg/l (Table 1, Figure 1).

FVII and ATIII have been significantly lower in all estimated groups. Control values of FVII was  $90.10 \pm 9.35\%$  and ATIII  $96.30 \pm 8.86\%$ . Values of FVII after head trauma was  $59.44 \pm 19.80\%$  ( $p < 0.001$ ), while ATIII was  $71.88 \pm 16.99\%$  ( $p < 0.001$ ). After brain tumor surgery FVII was  $69.10 \pm 18.48\%$  ( $p < 0.05$ ), while ATIII was  $81.65 \pm 11.86\%$  ( $p < 0.001$ ). Values of FVII were  $72.12 \pm 21.76\%$  ( $p < 0.05$ ) in ischemic and  $65.39 \pm 25.94\%$  ( $p < 0.05$ ) in haemorrhagic stroke, while values of ATIII were  $81.89 \pm 12.03\%$  ( $p < 0.001$ ) in ischemic and  $79.04 \pm 17.46\%$  ( $p < 0.001$ ) in haemorrhagic stroke (Table 1, Figure 1).

Alpha-2 AP after head trauma is in the level of control values ( $95.75 \pm 25.60\%$ ) to ( $94.10 \pm 2.69$ ). A slight increase of alpha-2 AP has been noticed after ischemic stroke ( $103.56 \pm 26.33\%$ ), while a slight decrease has been observed after haemorrhagic stroke ( $88.36 \pm 26.52\%$ ). Alpha-2 AP has significantly decreased after brain tumor surgery ( $82.76 \pm 22.97\%$ ) ( $p < 0.05$ ) (Table 1, Figure 1).

A significant positive correlation between level of ATIII and alpha-2AP has been noticed in estimated group, except in head trauma  $r^2 = 0.569$  ( $p < 0.01$ ),  $0.520$

( $p < 0.05$ ) and  $0.387$  ( $p < 0.05$ ) respectively after brain tumor surgery, ischemic and haemorrhagic stroke.

## Discussion

The human brain is a significant source of TF and activators of fibrinolysis. TF concentration is high in the gray matter, especially astrocytes (7-9), while t-PA concentration is high in brain microvasculature (10). Brain damage causes releasing of TF and t-PA in circulation and intravascular activation of coagulation and fibrinolysis. According to the primary role of TF in blood coagulation (22) laboratorically recognizable changes of blood coagulation and fibrinolysis parameters are the logical consequence of brain damage.

Head trauma can cause brain contusion and direct destruction of brain tissue. Traumatically acute subdural and epidural haematomas are the consequence of the brain blood vessels destruction and induce compression of the brain with consequential focal ischemia and brain damage. Decrease of PT, fibrinogen and activity of clotting factors, and shortening of aPTT have been noticed after head trauma (23-26). The raises of fibrin degradation products (FDP) or D-dimer are common phenomenon after head trauma and correlated with course and prognosis (26-29). Decrease of antithrombin III (ATIII) and alpha 2 antiplasmin (alpha-2 AP), as well as increase of sensitive thrombotic markers fibrinopeptid A, thrombin - antithrombin III (TAT) and prothrombin F1+2 have been noticed in head trauma (30,31).

Brain tumors compress and infiltrate brain tissue and cause brain damage. On the other hand the surgical removal of tumors, or a part of tumors, causes destruction of the brain and tumor tissue. This induces release of TF and fibrinolysis activators and can cause the activation of coagulation and fibrinolysis after brain

tumor surgery. Higher thrombotic activity laboratorically manifested in shortened aPTT (32) and clinically presented in expanded tendency to deep vein thrombosis (33). The occurrence of thrombosis correlates with the prolongation of PT increase of plasminogen and the decrease of fibrinogen.

There have been described a few cases of disseminated intravascular coagulation after brain tumor surgery (34,35), which confirms the seriousness of this problem. On the other hand, serious hyperfibrinolysis has been noticed in one patient after brain tumor surgery. There has been the activation of coagulation before surgery, manifested through the increase of TF and prothrombin F1+2. Activation of fibrinolysis has been developed during the surgery (increase of t-PA and total degradation products (TDP)), and it was a major component of a serious coagulopathy in this case (36).

Intravascular activation of coagulation is a necessary condition for the development of atherothrombotic stroke. On the other hand developed ischemic stroke induces cerebral ischemia and brain infarction which cause brain tissue damage. Although it is very hard to make a distinction between what is the cause and what is the consequence of coagulation activation in ischemic stroke, in the last few years there have been some papers on coagulation abnormalities after ischemic stroke. Hipercoagulability, hiperaggregation of platelets, depression of fibrinolysis and hiperviscosity of blood have been present after ischemic stroke (37). There have been observed the increase of fibrinogen, D-dimer, thrombin - antithrombin III (TAT) and plasmin - alpha 2 antiplasmin (PAP) complexes, and the decrease of ATIII and alpha-2 AP and protein C in these patients (38-40). Increase of plasminogen activator inhibitor (PAI-1) has been noticed in atherothrombotic ischemic stroke too (41).

Haemorrhagic stroke induces compression of brain tissue in SAH, or compression and destruction in ICH. Both phenomena induce brain tissue damage and destruction of blood vessels. At the same time local coagulation and fibrinolysis activity is present in haematoma (42).

Destruction of neurons, glial cells and blood vessels cause the release of TF and t-PA into circulation and activation of coagulation and fibrinolysis. Laboratorically recognizable coagulation and fibrinolysis abnormalities are a logical consequence of this activation.

We have observed the decrease of PT, FVII and ATIII, as well as the increase of D-dimer in first 24 hours after various brain damage. Decreases of PT and blood clotting factors activity have already been described (23,43,44). Decrease of prothrombin complex and FVII is a consequence of consumption of coagulation factors after coagulation activation induced by release of tissue factor and forming stable fibrin. Lower values of ATIII have also been noticed in head trauma (30,45). Decrease of ATIII could be the consequence of its consumption in forming of TAT

complex (11,19,46). ATIII is an important mechanism for prevention of DIC development, and we think that the fact that most of our patients did not acquire DIC should be the consequence of the adequate response of ATIII to the coagulation activation and the forming of thrombin.

Increased thrombotic activity with consequential secondary fibrinolysis, which has been shown through the raise of FDP and/or D-dimer has been widely described in literature after various brain damage (19,28,30,36,44,45,47,48). We consider this mechanism, that is the adequate secondary fibrinolytic response to the thrombotic stimulus, which is expressed through the increase of D-dimer, with normal values of alpha-2 AP, is yet another reason for which in most of our patients there was no development of DIC.

Increase of fibrinogen in stroke could be a consequence of the acute phase reaction.

Alpha-2 AP has been decreased after brain tumor surgery only. It could be explicated by hiperfibrinolysis after surgery (36). Slight, but not significant increase of alpha-2 AP in ischemic stroke has not correlated with literature data about decrease of alpha-2 AP in ischemic CVI (48). Our explanation is that alpha-2 AP raises as acute phase protein.

A significant correlation between level of ATIII and alpha-2 AP after brain tumor surgery and both type of stroke could show a simultaneous activation of coagulation and secondary fibrinolysis in the first 24 hours after brain damage.

Clinical presentations of coagulation and fibrinolysis abnormalities have not demanded supportive and/or anticoagulant treatment.

## Conclusion

Blood coagulation and fibrinolysis parameter changes have been observed in the first 24 hours after various types of brain damage.

These changes include the decrease of PT, FVII, ATIII, and increase of D-dimer and they have been the most significant after head trauma.

Alpha-2 AP has decreased after brain tumor surgery probably as a consequence of hiperfibrinolysis.

An increase of fibrinogen in both ischemic and haemorrhagic stroke has been probably caused by the acute phase reaction.

A statistically significant positive correlation between level of ATIII and alpha-2 AP has shown on simultaneous presence of coagulation and fibrinolysis activation.

The activation of coagulation is present in almost all of the patients, however, clinically recognizable symptoms of DIC have been noticed only in a small number of patients, the reason for which should probably be found in the adequate response of the inhibitory mechanisms (antitrombin III) and secondary fibrinolysis to the thrombotic stimulus.

Although systemic, clinically manifested hemostatic abnormalities, which have demanded supportive and/or anticoagulant treatment have not been present in our patients, our opinion is that routine estimation of coagulation and fibrinolysis profile could be very useful in patients with various types of brain damage in the first 24 hours.

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## PROMENE PARAMETARA KOAGULACIJE I FIBRINOLIZE NAKON RAZLIČITIH TIPOVA OŠTEĆENJA MOZGA

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Kratak sadržaj: *Dobro je poznato da je moždano tkivo jedno od tkiva najbogatijih tkivnim faktorom (TF) u ljudskom organizmu. TF se nalazi u sivoj masi, naročito u astrocitima. Sa druge strane tkivni aktivator plazminogena (t-PA) je otkriven u krvnim sudovima mozga. Oštećenje mozga uzrokovano različitim etiološkim faktorima, dovodi do oslobađanja TF-a i aktivatora fibrinolize u cirkulaciju uzrokujući tako hemostatske poremećaje. Mi smo ispitivali neke koagulacione i fibrinolitičke parametre kod 120 pacijenata sa različitim tipovima oštećenja mozga (30 sa izolovanom traumom glave, 30 nakon operacije tumora mozga, 30 nakon ishemijskog i 30 nakon hemoragijskog cerebrovaskularnog inzulta (CVI)). Krv je uzimana u prva 24 sata nakon oštećenja mozga i određivani su sledeći parametri: protrombinsko vreme (PT), fibrinogen, aktivisano parcijalno tromboplastinsko vreme (aPTT), aktivnost FVII, antitrombina III (ATIII), alfa-2 antiplazmina (alfa-2AP) i D-dimer. Značajno smanjenje PT-a, FVII i ATIII, kao i porast D-dimera je zapažen u svim grupama. Ove promene su najizrazitije nakon traume glave. Alfa-2AP je snižen samo nakon operacije tumora mozga. Iako hemostatske abnormalnosti nakon različitih tipova oštećenja mozga nisu zahtevale suportivni i/ili antikoagulantni tretman, mišljenja smo da je prisustvo ovih abnormalnosti dovoljno dobar razlog za rutinsko koagulaciono ispitivanje u prva 24 sata nakon oštećenja mozga.*

Ključne reči: *Koagulacija krvi, fibrinoliza, oštećenje mozga*

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