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FIRST 5-DAYS FOLLOW-UP AND CORRELATION STUDY BETWEEN URINARY CYSTEINYL LEUKOTRIENES AND EDEMA VALUES IN PRIMARY SPONTANEOUS SUPRATENTORIAL INTRACEREBRAL HEMORRHAGE

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Abstract: **Background:** After intracerebral hemorrhage cysteinyl leukotrienes (C_4, D_4, E_4) are synthetisized in the contact brain parenchyma-extravasated blood and participate in producing of edema formation.The study aim is a 5-days follow up (admittance/3thday/5thday) of urinary cysteinyl leukotrienes, hematoma and edema volume in patients with primary spontaneous supratentorial intracerebral hemorrhage and to determine the relationship: edema/haematoma and edema/leukotrienes.

Methods: An enzymeimmunoassay for leukotrienes measuring in the urine samples from 62 patients with hemorrhage during the first 5 days (admittance/3thday/5thday) and 80 health controls is used. Hematoma and edema volume is visualised and measured by computed-tomography.

Results: Admission values of leukotrienes were significantly higher in the hemorrhagic patients (min = 268.61; max = 5787.36; mean = 1842.20 ± 1413.19 pg/ml/mg creatinine) versus control subjects (min = 297.8; max = 1684.2; mean = 918.6 ± 332) ($p < 0.001$). Significant leukotrienes excretion dynamism (mean: 1842.20 ± 1413.19; 1181.54 ± 906.16; 982.30 ± 774.24 pg/ml/mg creatinine) is found in hemorrhagic patients during 5 day-follow up (admittance/3thday for $p < 0.001$; the 3thday/5thday for $p < 0.05$). The followed hematoma volume (mean: 13.05 ± 14.49; 13.13 ± 14.66; 12.99 ± 14.73 cm^3) for all three periods of examiantion did not show significance ($p > 0.05$). The edema (mean: 12.86 ± 13.52; 22.38 ± 21.10; 28.45 ± 29.41 cm^3) showed very high significance ($p < 0.001$). At admitance and on the 5th day nonsignificant positive correlation ($r = 0.4$; $p > 0.05$) of moderate strength is found between edema and hematoma; and significant positive correlation ($r = 0.6$; $p < 0.05$) of moderate to high strength at the 3thday. Between leukotrienes and edema, the coefficient of correlation $r = – 0.1$ ($p > 0.05$) at admittance, $r = – 0.05$ ($p > 0.05$) on the 3th day (nonexistence of linear correlation, the sign minus presents their tendency for the opposite movement in their values) and $r = 0.2$ ($p > 0.05$) on the 5thday are found (positive linear nonsignificant correlation of slight strength).

Conclusion: Significant urinary leukotrienes excretion (a brain capacity for significant leukotreienes synthesis) and significant edema progression versus constant haematoma are found. The edema size followed the hematoma size of moderate extent. The edema showed an inverse dependence of the leukotrienes (a tendency for opposite movement of their values), the high leukotrienes values at admittance bring to greater edema volume on the third/the fifth day, respectively.

Elevated cysteinyl leukotrienes synthesis and the elevated edema could point to cause-effective relationship between them establishing the leukotrienes as an edema promotive-factor in intracerebral haemorrhage.

Key words: Intracerebral hemorrhage, brain edema, cysteinyl leukotrienes.

INTRODUCTION

Intracerebral hemorrhage (ICH) is an acute cerebrovascular disease, which develops after brain artery rupture and blood extravasation in the surrounding

brain parenchyma. It is considered that ICH is the most serious risk for mortality, disability and severe morbidity compared to all other stroke types (1). A cascade of several mechanisms has been formed in the contact of brain tissue-extravasated blood and many substances (prostaglandins, nitric oxide) are released from destructed brain tissue and blood components which participate in formation of the brain perifocal edema (BE) (2, 3, 4). Which is the exact mechanism of BE formation, which substances participate, how many and how they participate, for the time being remain enigma, which leaves a space for perifocal edema to be comprehended as a multifactorial one (5). BE essentially participates in further alteration of the clinical manifestation, in prognosis and outcome of the disease increasing the parenchymal vascular lesion which, initially, has been formed by the action of extravasated blood (6). Among the all substances participants for BE, cysteinyl leukotreines (C_4, D_4 and E_4) (cystLT) also appear which are highly active substances in generation of the BE (6, 7, 8, 9). Cystenyl leukotrienes are a new group of biological and chemical substances derived from the family of eicosanoids, the metabolites of the arachidonic acyclic unsaturated fatty acid, which are synthesized in lipoxygenase pathway (10, 11). Due to their feature to act in vasoconstrictor way, to take part in local ischemia and to increase the blood-brain barrier permeability, they are included in the group of an important edema-promoting factor (6, 10).

THE AIM OF THE STUDY

The aims of the study are:

1. To determine the values of the excreted cystLT in the urine within the first 5 days followed ICH (on the admittance day, the third and the fifth day) when maximal production of BE is expected; to determine the values of the hematoma volume (HV) and the volume of the brain perifocal edema within the observation period of 5 days (on the admittance day, the third and the fifth day).

2. To determine the relationship between hematoma volume and the edema volume values; and to determine the relationship between the cysLT and the edema volume values within the observation period of 5 days (on the admittance day, the third and the fifth day).

PATIENTS AND METHODS

This investigation represents a prospective longitudinal study of the 5-day screening (admittance, the third and the fifth day) of the cysLT excreted in urine, of the volume values, hematoma and of the brain perifocal edema in 62 patients (34 men; 28 women) with acute primary spontaneous supratentorial ICH (lobar and basal ganglia localization) at the age of 39 to 80 years (mean = 62.9 ± 7.1), being included according to determined inclusion criteria: ICH with no ventricular and/or subarachnoidal penetration, without advanced alteration of consciousness (sopor, coma), with a precise data of the beginning of the disease, arrival at the hospital in the first hours since the occurence of the inital sign/symptom, absence of some somatic diseases/conditions (pulmonary, renal, immunologic, coagulopathies, intubation, assissted respiratry ventilation), anticoagulant medications being not used premorbidly, absence of arteriovenous malformations and aneurysm.

Quantification of cystLT in the urine sample of the experimental examinees and the control group has been made in two steps: extraction of cysLT by magnetic separation with mini columns and cysLT purification by enzyme-immuno-analysis after standard protocol and by standardized reagents (12). The cystLT values are expressed as pg/ml/mg creatinine.

Detection, visualization and dimension of the HV and BE in ICH patients were realized by brain computerized axial tomography (specific formula for spherical and ellipsoid shape V = AxBxC/2 for mathematical calculation of the volumes was used) (13). HV and BE values were approximate and are expressed in cm^3.

The control group consisted of 80 (conditionally) healthy examinees at the age from 18 to 75 years (41 men; 39 women) (all procedures for cysLT determination in urine of the control group were performed after identical methodology and protocol as with the ICH examinees).

Statistical program STATISTICA for Windows was used for elaboration of data obtained. Numerical values were analyzed by determination of the mean, minimal and maximal values of the parameters. Wilcoxson matched pairs test and Friedman ANOVA test were used for testing the significance of differences among some parameters. Coefficient of correlation was used for determination of the relationship of some parameters. Values of $p < 0.05$ are considered for significant and values of $p < 0.01$ for high significant.

RESULTS AND DISCUSSION

A control group of 80 (conditionally) healthy examinees at the age of 18 to 75 years (mean = 37.6 ± 12.3) (41 men; 39 women) for insight of the pathological cysLT values in ICH patients was included. The results of cysLT for the control group ranged from 297.8 pg/ml/mg creatinine for minimal up to 1684.2 pg/ml/mg creatinine for maximal values, the mean value was 918.6 ± 332 pg/ml/mg creatinine (Table 1).

Admission values of urinary cysLT were significantly higher in the hemorrhagic patients (min = 268.61;

max = 5787.36; mean = 1842.20 ± 1413.19 pg/ml/mg creatinine) versus control subjects (min = 297.8; max = 1684.2; mean = 918.6 ± 332 pg/ml/mg creatinine) for $p < 0.001$ and significant deviation of the mean cysLT values was registered in the examinees from the experimental group (1842.20 ± 1413.19; 1181.54 ± 906.16; 982.30 ± 774.248 pg/ml/mg creatinine) compared to the control examinees (918.6 ± 332 pg/ml/mg creatinine) for the whole observation period: admittance, third day, fifth day (Table 2), which indicates the increased cysLT excretion in urine, i.e. of the increased cysLT synthesis in the brain parenchyma in the newly formed conditions after the ICH occurrence. Winking et al. found that the urinary cys-LT excretion at the end of the measurements was significantly lower in the operatively treated group (N = 12) than in the patients with conservative therapy (N = 5) (6).

In follow-up of the cysLT excretion in urine the Wilcoxon matched pairs test showed statistical significance in all the investigated relations ($p < 0.01$), due to reduction of the excreted leukotrienes in urine from admittance to the fifth day (Table 3). The period admittance/the third day for $p < 0.001$ showed the highest degree of significance, which comes out from the high excretion of the cysLT in the first 3 days. Then, they continue to excrete, but not with such a tempo (the third/the fifth day, $p < 0.05$). Winking et al. noted nonsignificant differences of the cysLT values lowering for the whole period of five days, which has been due most probably to their small sample of patients, on separate localization (only in basal ganglia) and the homogenous dimensions of hematoma (30–50 ccm), opposite to the big sample (N = 62), the heterogenous localization of hematoma (lobar and basal ganlia) and the heterogenous of hematoma volumes sizes (0.45–52 ccm) in our examinees (6).

Table 1. *Cysteinyl leukotrienes values in the control group*

Cysteinyl leukotrienes-control group (N = 80) (pg/ml/mg creatinine)		
min	**max**	**mean ± SD**
297.8	1684.2	918.6 ± 332

Table 2. *Cysteinyl leukotriene values from the experimental group distributed according to the period of examination*

Period of examination	Cysteinyl leukotrienes-experimental group (N = 62) (pg/ml/mg creatinine)		
	min	**max**	**mean ± SD**
Admittance	268.61	5787.36	1842.20 ± 1413.19
3th day	129.15	4226.78	1181.54 ± 906.16
5th day	36.59	3536.69	982.30 ± 774.24

Table 3. *Differences of the cysteinyl leukotrienes values regarding the period of examination*

CysLT/period of examination	Wilcoxon matched pairs test		
	Z	**p-level**	**Sig/N. Sig**
Admittance/3th day	3.663	0.00025	Sig
3th day/5th day	4.28	0.0357	Sig
Admittance/5th day	2.099	0.00002	Sig

Table 4. *Hematoma volume values distributed regarding the period of examination*

Period of examination	HEMATOMA VOLUME (cm^3)		
	min	**max**	**mean ± SD**
Admittance	0.45	52.0	13.05 ± 14.49
3th day	0.62	54.6	13.13 ± 14.66
5th day	0.1	54.6	12.99 ± 14.73

Table 5. *Differences of the hematoma volume regarding the period of examination*

HEMATOMA VOLUME	Wilcoxon matched pairs test		
	Z	**p-level**	**Sig/N. Sig**
Admittance/3th day	1.01	0.311	N. Sig
3th day/5th day	0.322	0. 746	N. Sig
Admittance/5th day	0.578	0.562	N. Sig

Determining the HV values (Table 4) within the period of admittance (min = 0.45 cm^3; max = 52.0 cm^3; mean = 13.05 ± 14.49 cm^3), the third day (min = 0.62 cm^3; max = 54.6 cm^3; mean = 13.13 ± 14,66 cm^3) and the fifth day (min = 0.1 cm^3; max = 54.0 cm^3; mean = 12.99 ± 14.73 cm^3) we noticed that the mean values as well as the other two HV parameters were with a tendency of stability (hematoma did not change its dimensions) or were with inital signs for a slight reduction. The tested differences of the hematoma volume values followed for all three periods (admittance/3th day/5th day) of examiantion did not show significance for $p > 0.05$, which indicated for stability of the hematoma volumes. The started resorption in agreement with the pathological principles could not essentially influence to the hematoma volume dimensions for this short period of 5 days. The nonsignificant differences in the size of the hematoma pointed to the absence of additional bleeding (Table 5) (6).

Starting from the day of admittance up to the fifth day, significant increase of BE volume is followed, observed through the mean values (12.86 ± 13.52 cm^3; 22.38 ± 21.10 cm^3; 28.45 ± 29.41 cm^3), through the minimal (0 cm^3; 2.13 cm^3; 3.61 cm^3) and through the maximal values (40.17 cm^3; 79.03 cm^3; 132.09 cm^3) (Table 6).

Table 6. *Values of the edema volume distributed according to the period of verification*

Period of verification	EDEMA VOLUME (cm^3)		
	min	max	mean ± SD
Admittance	0	40.17	12.86 ± 13.52
3th day	2.13	79.03	22.38 ± 21.10
5th day	3.61	132.09	28.45 ± 29.41

Table 7. *Differences of the edema volume values in relation to the period of examination*

EDEMA VOLUME	Wilcoxon matched pairs test		
	Z	p-level	Sig/N. Sig
Admittance/3th day	5.857	0.00000	Sig
3th day/5th day	4.254	0.00002	Sig
Admittance/5th day	5.563	0.00000	Sig

Table 8. *Leukotrienes/Hematoma volume/Edema volume-differences of the values regarding the period of examination*

Admittance/ 5th day/3th day	Friedman ANOVA test		
	Chi. Sqr	p-level	Sig/N. Sig
Leukotrienes	24.419	0.00001	Sig
Hematoma volume	2.188	0.334	N. Sig
Edema volume	69.77	0.00000	Sig

The differences of the BE volume values tested for the observation period (admittance/3th day/5th day) showed very high significance for $p < 0.001$, which came from the great edema increase (Table 7). This can be explained by its pathophysiological features being characterized with the inital slightest value at admittance, but as it started its formation intensely, it reached the maximum on the 3–5th day. Gradual reduction was expected from the fifth day. Similar results also showed Gebel et al. (3, 14, 15, 16).

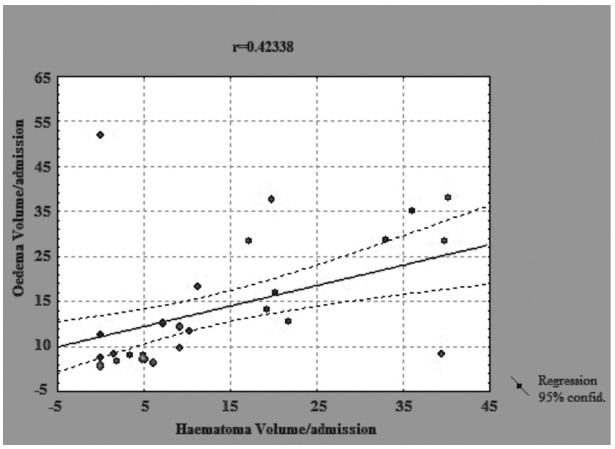

Figure 1. *Correlation: Edema volume/Hematoma volume-admittance*

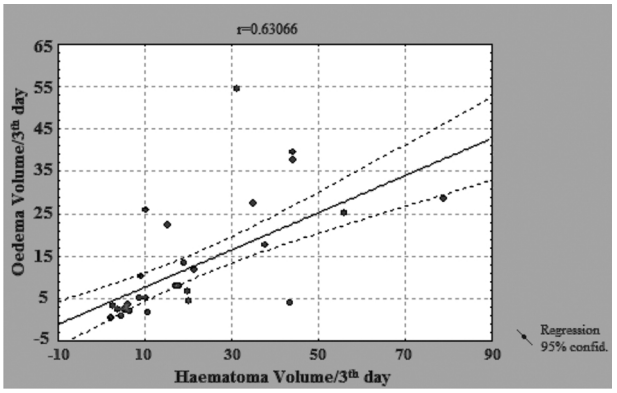

Figure 2. *Correlation: Edema volume/Hematoma volume-3th day*

By Friedman ANOVA test the differences of the hematoma volume, edema volume (EV) and cysteinyl leukotrienes values were tested at the same time in relation of admittance/3th day/5th day. The results obtained were with very high significance for the differences of the edema ($p < 0.001$) and leukotrienes values ($p < 0.001$), but were without significance in hematoma ($p > 0.01$) (the results from Friedman ANOVA test are comparable with the results obtained by Wilcoxon matched pairs test in each of them separately) (Table 8).

Figures 1, 2 and 3 presents the results from this investigation related to the volume values between the hematoma (as independently changeable value) and the edema (as dependent changeable) at admittance, the third day and the fifth day. At admittance positive nonsignificant correlation of a moderate strength ($r = 0.4$; $p > 0.05$) was found between these two values, the time period was short (the first 24 hours) necessary for edema formation in order to correspond the hematoma size (Figure 1).

The literature data speaks that the edema has been maximally expressed on the third and/or the fifth day, which has been due from the multifactorial mechanism of the action (among which also from the hematoma volume values), which mechanisms come out from the moment of hematoma appearance, so from here moderate to high significant positive correlation ($r = 0.6$, $p < 0.05$) is found among them on the third day (Figure 2) (1, 4, 15, 16, 17, 18). Greater edema values correspond to higher hematoma values, respectively.

Coefficient of linear correlation ($r = 0.4$, $p > 0.05$) on the fifth day, which corresponds to moderate nonsignificant assotiation among them, speaks for data that the edema size after the third day or on the fifth day moderately follows the hematoma size. The process of regression (resorption) of hematoma starts from the third day and according to the results obtained, the edema moderately follows the corresponding newly-occurred conditions (Figure 3).

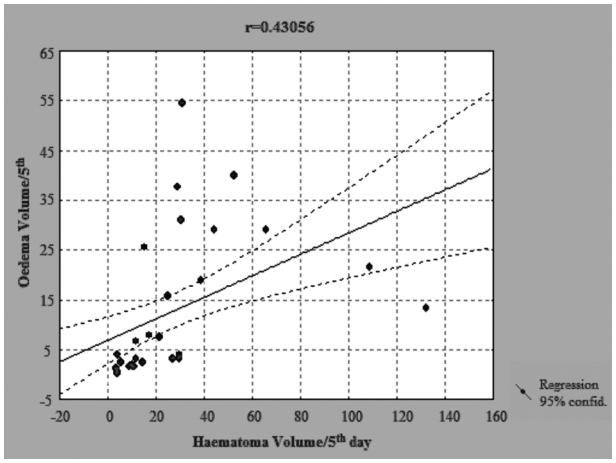

Figure 3. *Correlation: Edema volume/Hematoma volume-5th day*

Figures 4, 5 and 6 register the dependence of the follow-up of the leukotreines, as independent changeable variable and the edema, as dependent changeable, in all three periods of examination. Coefficient of correlation r = – 0.1 (p > 0.05) at admittance and r = – 0.05 (p > 0.05) on the third day, result from the nonexistence of linear correlation between them, but the sign minus presents their tendency for the opposite movement in their values (Figure 4 and 5). On the fifth day, leukotrienes and the edema start entering into the positive linear nonsignificant correlation of slight strength (r = 0.2; p > 0.05). This relation comes from the pathophysiological features of these two values. More precisely, the leukotrienes are maximally synthesized at admittance (due to the contact brain tissue-extravasated blood) and start to excrete in the urine with some dynamics, up to the fifth day. Their values are quantitatively sufficient at admittance, but also in the other terms of observation (beside the excretion dynamics), to start the mechanism of edema formation, which maximal presentation occurs on the third day. From here an inverse position of both values come out, to higher leukotrienes values correspond the lower edema values. From the fifth day

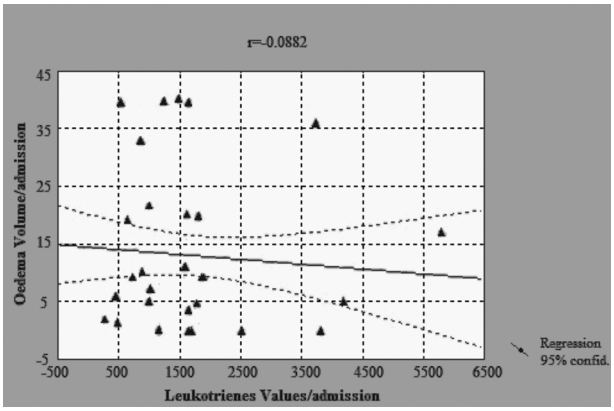

Figure 4. *Correlation: Edema volume/Cysteinyl leukotrienes-admittance*

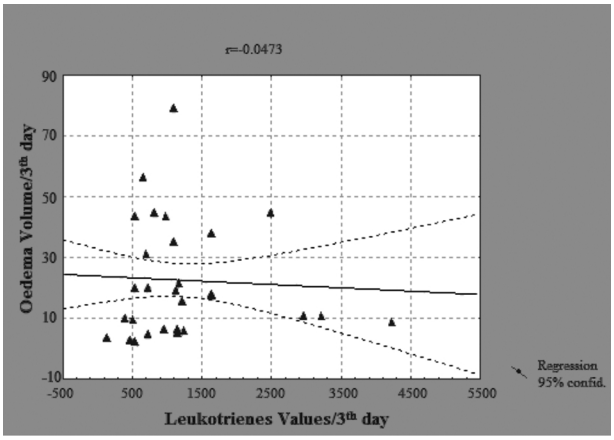

Figure 5. *Correlation: Edema volume/Cysteinyl leukotrienes-3th day*

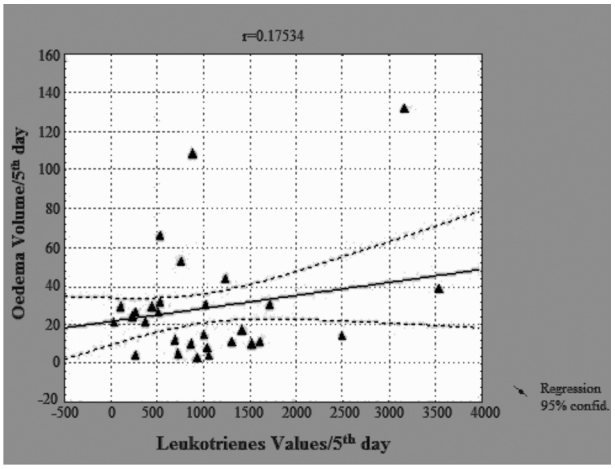

Figure 6. *Correlation: Edema volume/Cysteinyl leukotrienes-5th day*

already, the leukotreiens and the edema start to follow each other slightly, after the fifth day they start to fall, respectively (Figure 6).

CONCLUSION

After the ICH occurrence, the brain tissue has a capacity for significant synthesis of cysteinyl leukotreienes. The dynamics of cysLT excretion in urine for the whole 5-day observation period is highly significant, but mostly in the period admittance/the third day. The 5-day hematoma screening did not show significance in the change of its volume values (the started resorption does not significantly influence and additional bleeding is absent). Perifocal BE elevates with high significance in the observational 5-day period. There is a moderate nonsignificant correlation between the size of the hematoma volume and the size of the brain edema volume at the admittance and the fifth day; and moderate to high nonsignificant correlation on the third day (the size of the edema volume follows the size of the hematoma volume of moderate extent). The edema

volume showed an inverse dependence of the cysteinyl leukotrienes values (a tendency for opposite movement of their values), the high leukotrienes values at admittance bring to greater oedema volume on the third/the fifth day period, respectively.

Elevated cysLT synthesis and the elevated values of the brain edema could point to cause- effective relationship between them establishing the leukotrienes as an edema-promoting factor in intracerebral haemorrhage.

Abbreviations

BE — brain edema
cysLT — cysteinyl leukotrienes
HV — hematoma volume
ICH — intracerebral hemorrhage

Sažetak

5-DNEVNA STUDIJA MONITORINGA I KORELACIJE IZMEĐU MOŽDANOG EDEMA I CISTEINIL LEUKOTRIJENA EKSTRAHOVANIH IZ URINA KOD PRIMARNE SPONTANE SUPRATENTORIJALNE INTRACEREBRALNE HEMORAGIJE

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Uvod: Posle nastanka intracerebralne hemoragije, u kontaktu ekstravazirane krvi sa moždanim parenhimom sintetizuju se cisteinil leukotrijeni (C_4, D_4, E_4) koji participiraju u formiranju moždanog perifokalnog edema. Cilj studije je određivanje vrednosti volumena hematoma, perifokalnog edema i leukotrijena ekstrahovanih iz urina i određivanje korelacije kod edema/hematoma i edema/leukotrijena u toku prvih 5 dana intracerebralne hemoragije (prijem/3dan/5dan).

Metod: Enzimoimunoanalizom odredili smo vrednosti cisteinil leukotrijena iz urina kod 62 pacijenta sa primarnom spontanom supratentorijalnom intracerebralnom hemoragijom u toku prvih 5 dana (prijem/ /3dan/5dan) i kod 80 zdravih kontrolnih ispitanika. Vizuelizaciju i dimenzioniranje volumena hematoma i edema vršili smo kompjuterizovanom aksijalnom tomografijom mozga.

Rezultati: Vrednosti leukotrijena na prijemu bili su signifikantno veći kod hemoragičnih pacijenata (min = 268,61; max = 5787,36; mean = 1842,20 ± 1413,19 pg/ml/mg creatinin) nego kod kontrolnih ispitanika (min = 297,8; max = 1684,2; mean = 918,6 ± 332) ($p < 0,001$). Signifikantan dinamizam ekskrecije cisteinil leukotrijena u urinu (mean: 1842,20 ± 1413,19; 1181,54 ± 906,16; 982,30 ± 774,24 pg/ml/mg creatinin) je registrovan kod hemoragičnih pacijenata u toku celokupnog observiranog perioda (prijem/3. dan za $p < 0,001$; 3.dan/ /5.dan za $p < 0,05$). Evaluirane vrednosti hematoma nisu pokazale signifikantnost u toku tri praćena perioda (mean: 13,05 ± 14,49; 13,13 ± 14,66; 12,99 ± 14,73 cm^3) ($p > 0,05$). Vrednosti volumena perifokalnog edama pokazali su veoma visoku značajnost (mean: 12,86 ± 13,52; 22,38 ± 21,10; 28,45 ± 29,41cm3) za $p < 0,001$. Na prijemu i u petom danu dobijena je nesignifikantna pozitivna korelacija umerene jačine ($r = 0,4$; $p > 0,05$) između edema i hematoma, a trećeg dana signifikantna pozitivna korelacija umerene do visoke jačine ($r = 0,6$; $p < 0,05$). Između leukotrijena i edema dobijen je koeficijenat korelacije $r = – 0,1$ ($p > 0,05$) na prijemu, $r = – 0,05$ ($p > 0,05$) trećeg dana (ne postoji linearna korelacija, predznak minus prezentuje tendenciju za suprotno kretanje njihovih vrednosti) i $r = 0,2$ ($p > 0,05$) petog dana (pozitivna linearna nesignifikantna korelacija sa slabe jačine).

Zaključak: Dobijena je signifikantna ekskrecija leukotrijena ekstrahovanih iz urina (signifikantna sinteza leukotrijena u moždanom parenhimu) i signifikantna progresija edema nasuprot konstatne vrednosti volumena hematoma. Vrednosti volumena edema prate vrednosti volumena hematoma od umerenog stepena. Edem je pokazao inverznu zavisnost od leukotrijena (tendencija za suprotno kretanje njihovih vrednosti), tako, visoke vrednosti leukotrijena na prijemu dovode do većeg volumen edema u trećem/petom danu.

Povećana sinteza cisteinil leukotrijena i povećane vrednosti edema mogu ukazivati na uzročno-posledične relacije izmedju nih, što može etablirati leukotrijene kao edem promotivne faktore kod intracerebralne hemoragije.

Ključne reči: Intracerebralna hemoragija, moždani edem, cisteinil leukotrijeni.

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