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INTRACEREBRAL HEMATOMA, PERIHEMORRHAGIC EDEMA AND URINARY EXCRETED CYSTEINYL LEUKOTRIENES CORRELATION STUDY

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Abstract

Introduction. Several mechanisms in formation of perihemorrhagic edema are activated after contact of brain tissue-extravasated blood in intracerebral hemorrhage. Cysteinyl leukotrienes (cysLT) (C4, D4, E4) are included in this process as significant edema factors and they determine the neurological deficit and outcome. The study aim was a 5-day follow-up (admission/3 day/5 day) of urinary cysLT, hematoma volume, edema volume values and their correlation in patients after spontaneous, primary supratentorial intracerebral hemorrhage.
Methods. An enzyme immunoassay was used for urinary cysLT measured in 62 patients and 80 healthy controls. Hematoma and edema volumes were visualized and measured by computed tomography and mathematically calculated with a special spheroid shape formula (V=AxBxC/2).
Results. CysLT of hemorrhagic patients (1842.20±1413.2, 1181.54±906.2, 982.30±774.2pg/ml/mg creatinine) were significantly excreted ($p<0.01$). Brain edema (12.86±13.5, 22.38±21.1, 28.45±29.4cm³) was significantly increased ($p<0.01$). Hematoma volume values (13.05±14.5, 13.13±14.7, 12.99±14.7cm³) were not significant ($p>0.05$). A high correlation (multiple regression) between cysLT, hematoma and edema was found on the 3rd day (R=0.6) and a moderate correlation at admission (R=0.3) and on the 5th day (R=0.3).
Conclusion. In our 5-day follow-up study a significant cysLT brain synthesis and significant brain edema progression versus constant hematoma volume values in hemorrhagic patients was found. A high correlation between cysLT, hematoma and edema volume was found on the 3rd day, a moderate correlation on admission and on the 5th day, which means that high cysLT and hematoma values were associated with high/moderate edema values.

Key words: intracerebral hemorrhage, perihemorrhagic edema, cysteinyl leukotrienes

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Introduction

Blood vessel rupture causes blood extravasation and local accumulation in a form of hemorrhagic collection (hematoma) which distracts and compresses the brain parenchyma. Generally, there are two types of intracerebral hemorrhage (ICH): primary and secondary. Primary ICH constitutes about 80-85% of all ICH [1]. In 60% it originates from rupture of a blood vessel (lipohyalinosis change) when arterial hypertension exists-hypertensive type of the primary ICH, while in 20% it is due to amyloid angiopathy with no present arterial hypertension-non-hypertensive type of primary ICH [2]. Secondary ICH constitutes about 15-20% and has been most frequently connected to a rupture of vascular malformation (other participants are anticoagulant/thrombolytic medications, aneurysms and neoplasms). Of all, ICH supratentorial hemorrhage with 80% takes the highest percent (in 80% per hematoma type).
Since the first hour of bleeding, a brain perihemorrhagic (perifocal) edema (BE) has been made, which reaches a maximal size within 3 to 5 days since the onset of ICH. BE is an essential ICH characteristic which increases the parenchymal vascular lesion, previously produced by action of the extravasated blood. Working compressively on the adjacent brain structures, BE increases the intracranial pressure and additionally aggravates the focal neurologic deficit. Subsequent BE growth increases the intracranial pressure and it is the most frequent reason for trans-tentorial herniation in supratentorial ICH, and at the same time it is a cause of a patient's death. Usually, after blood vessel rupture, the blood extravasation stops and perifocal BE reaches its maximal dimensions between the third and the fifth day since the ICH onset, but if the bleeding continues BE will persist for longer period. When the regression process of the intracerebral hematoma begins, the BE starts to decrease.
In contact of brain tissue with extravasated blood in ICH several substances (potential factors for BE) generate from destructed brain tissue and from the blood components, which start the mechanisms for occurrence of brain perihemorrhagic edema. In that context, prostaglandins, nitric oxide, metaloproteinase, glutamate, and in recent time the leukotrienes are separated [3,4]. Each of

these substances, in its manner and volume, participates in BE formation. However, the possibility is not excluded for their direct or indirect mutual supplementation, attachment or favoring. What is the exact mechanism for formation of perifocal edema, which substances participate in, and how many participants are there, stay an enigma for the time being. It is supposed that several mechanisms are involved in the process of genesis of perifocal edema, which leaves a space to be understood as a multifactorial one [5-9].

When the biological actions of cysteinyl leukotrienes (cysLT) in the brain parenchyma were discovered to have vasoconstictive effect, to increase the permeability of the cell-brain barrier and to participate in the local ischemia, the scientists included them in the group of significantly edema-promoted factor [4,10]. Cysteinil leukotreines (C4, D4 and E4) represent a new group of biochemical and chemical substances from eicosanoids family, metabolites of arahydronic acyclic unsaturated fatty acid, which are synthetized in a lipoxygenase way [10].

After the blood vessel rupture, brutal and dramatic clinical picture of ICH occurs. With the initial extravasation the hematoma slowly grows, allowing the symptoms to reach their maximal intensity within the period of 10-30 minutes (mostly for 3 hours) [11]. The occurred BE significantly participates in subsequent alteration of the clinical picture [4].

Protagonists of the hemorrhagic cascade, hematoma, leukotrienes and edema, are parameters for deterioration and determination of the clinical picture and influence subsequently the prognosis and final outcome of the disorder.

The aim of this investigation was to determine the extracted cysLT values in urine, the hematoma volume and the parenchymal edema in the first 5 days of ICH (on the day of admission, on the third and on the fifth day) and to determine their mutual relation.

Material and methods

This is a prospective and longitudinal study, conducted in hospital conditions. The investigation was a 5-day monitoring (admission, the third and the fifth day) of the excreted cysteinyl leukotrienes values in urine, of the hematoma volume values, and of the BE values of 62 patients (34 men and 28 women) with acute spontaneous primary supratentorial ICH, aged from 39 to 80 years (mean=62.9±7.1SD). Inclusion of examinees in this study was according to previously determined criteria: ICH without ventricular or subarachnoidal penetration, without advanced alteration of consiciousness, precise evidence for the disease onset (appearance of initial neuropsychic sign or symptom), arrival at the Clinic of Neurology in the first 24 hours since the occurrence of the sign/symprom and absence of somatic disorders when the increase of production/excretion of cystTL (pulmonary, renal, immunologic, coagulopathies) occurs. Control group consisted of 80 (conditionally) healthy examinees at the age of 18 to 75 years (mean=37.6±12.3SD). Technique of enzyme immunoassay (EIA) was used after standardized protocol and with standardized reagents for quantification of cysTL in urine sample [12]. CysTL values were expressed in pg/mg creatinine. Detection, visualization and dimensioning of the values of hematoma volume (HV) and the BE volume were realized with computerized axial tomography of the brain. For mathematical estimation of the volume, special spheroid and ellipsoid formula was used V=AxBxC/2 (A-the longest diameter, B-the crosswise diameter, C-the thickness of the visualized hematoma). HV values and the BE volume were approximative and expressed in cm^3.

Statistcal analysis of data was made by Wilcoxon matched pairs test, Mann-Whitney U test and multiple regression.

Results

The cysTL results of the control group ranged from 297.8 pg/mg creatinine for minimal to 1684.2 pg/ml/mg creatinine for maximal value, the mean value was 918.6 ±332SD pg/ml/mg creatinine.

Minimal cysTL values in examinees with intracerebral hemorrhage within the 5-day follow-up (admission/3day/5day) were 268.61/129.15/36.59pg/ml/mg creatinine, maximal 5787.4/4226.8/3536.7pg/ml/mg creatinine, and mean 842.20±1413.2/1181.54±906.2/982.30±774.2pg/ml/mg creatinine (Table 1). Tested differences of the cysTL values of the examinees with ICH for the observed period (admission, 3 day/5 day) were highly significant (Table 1).

Table 1. CysLT values in the experimental group: period of examination

Time of follow-up	CysLT – experimental group (pg/ml/mg creatinine) mean±SD	min – max	p - value	
admission	1842.20±1413.2	268.61-5787.4	admission/3 day	p<0.01 (0.0002)
3 day	1181.54±906.2	129.15-4226.8	3 day/5 day	p<0.05 (0.036)
5 day	982.30±774.2	36.59-3536.7	admission/5 day	p<0.01 (0.00002)

p (Wilcoxon matched test), CysLT – Cysteinyl leukotriens

The results obtained from the hematoma volume values at admission were min=0.45cm^3; max=52cm^3; mean=13.05±14.5SD; on the third day min=0.62cm^3; max=54.6cm^3; mean=13.13±14.7SD, and on the fifth day min=0.1cm^3; max=54.6cm^3; mean=12.99±14.7SD (Table 2). Tested differences of the hematoma volume values were non-significant in all three periods of examination (p>0.05) (constant values of the volume) (Table 2).

Table 2. Hematoma volume values: period of examination

Time of follow-up	Hematoma volume (cm^3) mean±SD	min - max	p - value	
admission	13.05±14.5	0.45-52	admission/3 day	p<0.05
3 day	13.13±14.7	0.62-54.6	3 day/5 day	p<0.05
5 day	12.99±14.7	0.1-54.6	admission/5 day	p<0.05

p (Wilcoxon matched test)

The brain edema volume values in the 5-day-period were 0/40.17/12.86±13.5cm^3 at admission; 2.13/79.03/22.38 ±21.1cm^3 on the third day; and 3.61/132.09/28.45± 29.4cm^3 (Table 3). Significant increase of the brain edema volume was registered (by minimal, maximal, mean values) since the admission to the fifth day. Tested differences of the BE volume values for the observed period admission/third day/fifth day showed a very high significance (p<0.01) which was a result of edema increase (Table 3).

Table 3. Edema volume values: period of examination

Time of follow-up	Edema volume (cm^3) mean±SD	min – max	p - value	
admission	12.86±13.5	0-40.17	admission/3 day	p<0.01
3 day	22.38±21.1	2,13-79.03	3 day/5 day	p<0.01 (0.00002)
5 day	28.45±29.4	3,61-132.09	admission/5 day	p<0.01

p (Wilcoxon matched test)

Correlation analysis between leucotrienes, hematoma and edema in all three periods of examination: admission (R=0.3), moderate correlation on the fifth day (R=0.3), and high on the third day (R=0.6).

Discussion

Significant decline of the mean cysLT values in urine in all examinees of the experimental group (1842.20± 1413.2/1181.54±906.2/982.30±774.2) was found for the whole period of observation: admission/3day/5 day, versus the values of the control group examinees (918.6± 332) (Table 1). It pointed to increased cysLT excretion in urine in line with their increased synthesis in the brain tissue after the ICH occurrence. The differences tested of the cysLT values of the examinees with ICH in the observed period were highly significant (p<0.01), which proved the increased cysTL synthesis in brain parenhyma in the newly developed conditions after ICH occurence [4]. The dynamics of cysLT excretion in urine showed to be statistically significant for all investigated relations, which was due to the increased leucotrienes excretion in urine from admission to the fifth day (Table 1). The period admission/third day showed the highest degree of significance (p<0.01) that was a result of the excretion of high cysLT values in the first three days. Thus, cysTL continued to excrete, but not with such dynamics (third day/fifth day, p<0.05). Winking *et al*. who first started the research in this field, noted non-significant differences of the cysLT for the whole 5-day follow-up. This was most probably due to the small sample of examinees in their group, to specific location (only in basal ganglia) and to homogenous dimensions of hematona (30-50 cm^3), versus the great sample (n=62), heterogenous localization of hematoma and heterogenous hematoma volumes in our examinees (0.45-52 cm^3) [4].

The results obtained for hematoma volume values (mean, minimal and maximal) showed a feature of steadiness, which meant that the hematoma did not change its dimensions or its volumenous values were with initial signs for small reduction or initial resorption in hemorrhagic collection (Table 2). In favor to hematoma volume steadiness for all three periods of examination (admission/3 day/5 day) spoke the differences tested of the hematoma volume values which were non-significant (p>0.05). Pathophysiological code of initial resorption could not influence significantly on the dimensions of hematoma volume for this short 5-day-period. For absence of additional bleeding spoke the non-significant differences of the hematioma dimensions (Table 2) [4].

The edema volume, monitored through minimal, maximal and mean values, showed a significant increase starting from admission to the fifth day (Table 3). Their tested differences showed a very high significance (p<0.01) which pointed to edema increase in the whole follow-up period: admission/3 day/5 day, but most pronounced within the third day/fifth day (Table 3). According to the pathophysiological features, edema showed the least value at admission-the period of the beginning of its formation, but then intensly started its formation and reached its maximum from the third to the fifth day. After the fifth day its gradual decrease was expected to start. Gebgel *et al.* showed similar results in their investigations [3,14].

Multiple regression test showed a correlation among these three values; the increased leucotrienes and hamtoma values were followed by increased edema values, but of the moderate degree at admission (R=0.3) and on the fifth day (R=0.3), and of a higher degree on the

third day (R=0.6). Such relation was due to the inversion relation between leukotrienes/hematoma values on one side, (at admission high values of both sizes, and on the fifth day decreased cysLT value due to excretion and preserved and/or slightly decreased hematoma values-initial resorption) and the edema values on the other side (at admission the least, and on the third/the fifth day with very high values) [4].

Conclusion

Rupture of the blood vessel wall causes blood extravasation and local accumulation in a form of hemorrhagic collection (hematoma) which distracts and compresses the brain parenchyma. In such conditions, the brain tissue has a capacity for significant synthesis of cysteinyl leukotrienes which excretion in urine was highly significant in the whole 5-day-period of observation, but mostly in the period admission/third day. Hematoma showed significant changes of the volume values (initial resorption did not have an influence, and additional bleeding was absent). Peri-hemorrhagic brain edema was produced and enlarged with very high significance in the observed period, especially in the period the third day/the fifth day.
A correlation appeared among the leukotreines, hematoma and edema of moderate to high degree which speaks about their mutual connection and establishes their cause and effect relation.

Conflict of interest statement. None declared.

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