Цистеинил леукотриени и хематома-корелативна студија

Долненец-Банева Н[1], Никодијевиќ Д[1], Петровска-Цветковска Д[1], Чапареска Д[2], Банева Е.

[1]Универзитетска клиника за неврологија-Скопје,
[2]Универзитетска Клиника за Токсикологија- Скопје

Абстракт

Вовед: Интрацеребралната хеморагија (ИЦХ) настанува со руптурирање на крвен сад и екстравазација на крвта во околното мозочно ткиво формирајќи хеморагична колекција-хематом и започнувајќи го процесот на продукција на мозочниот перихеморагичен едем (МЕ). Во овој процес се синтезираат повеќе супстанции, како што се простагландините, азотниот оксид, матрикс-металопротеиназите, интерлеукините-6, алфа тумор некротизирачкиот фактор, глутаматот и цистеинил леукотриените (цисЛтс), како потенцијални фактори за продукцијата на МЕ. Цистеинил леукотриените (Ц4, Д4 И Е4) претставуваат нова група на биохемиски супстанции кои и припаѓаат на фамилијата на еикосанондите и се метаболити на арахидонската незаситена масна киселина. Хематомот и едемот се параметри на детериорација и детерминација на клиничката слика и влијаат на понатамошниот тек, прогнозата и крајниот исход на заболувањето. Целта на студијата е мониторирање на вредностите на цисЛТс екскретирани во уринатa и на вредностите на волуменот на хематомот (ВХ); и одредување на нивната меѓусебна поврзаност-зависност.

Материјал и методи: Студијата е проспек-тивна и лонгитудинална, претставува пет дневно (прием/3ден/5ден) мониторирање на вредностите на хематомот и на цисЛТс екскретирани во уринатa кај 62 пациенти (34 мажи, 28 жени) со ИЦХ. Користена е техниката на ензимоимуноанализата (ЕИА) за квантификација на цисЛТс во уринатa и компјутеризирана томографија на мозокот за детекција и визуелизација на ВХ.

Резултати: Вредностите на ЦисЛТс на прием/3ден/5ден: min=268.61/129.15/36.59; max=5787.4/4226.8/3536.7; mean=1842.20 ±1413.2/1181.54±906.2/982.30±774.2SDpg/ml/mg creatinine. ВХ вредностите на прием: min=0.45; max=52; mean=13.05±14.5 SDcm3; на 3ден: min=0.62; max=54.6; mean=13.13±14.7 SDcm3 и на 5 ден: min=0.1; max=54.6; mean=12.99±14.7 SDcm3. Коефициентот на корелација изнесува: на прием p=0.4; на 3 ден p= - 0.04 и на 5 ден p= - 0.08.

Заклучок: По настанувањето на ИЦХ, во тек на целиот 5-дневен период на обсервација, мозочното ткиво е со капацитет за висока синтеза на цисЛТс. Хематомот не покажува промени во вредностите на волуменот. Постои корелациска зависност меѓу хематомот и цисЛтс на приемот-зголемени вредности на хематомот доведуваат до зголемена синтеза на цистеинил леукотриените.

Клучни зборови: интрацеребрална хеморагија, хематом, цистеинил леукотриени, корелација

Cysteinyl leukotrienes and hematoma- correlation study

Dolnenec-Baneva N.[1], Nikodijevic D.[1], Petrovska-Cvetkovska D.[1], Capareska D.[2], Baneva E.

[1] University Clinic of Neurology-Skopje,
[2] University Clinical of toxicology-Skopje,

Abstract

Introduction: In appearing process of intracerebral hemorrhage (ICH) blood vessel rupture causes blood extravasation and the formation of hemorrhagic collection-hematoma is started developing the process of brain edema (BE). Several substances like prostaglandins, nitric oxide, matrix-metalloproteinases, interleukins-6, tumor necrosis factor, glutamate and cysteinyl leukotrienes, which are potential factors for BE production, are synthesized. Cysteinyl leukotreines (C4, D4 and E4) represent a new group of biochemical substances from eicosanoids family, metabolites of arahydonic acyclic unsaturated fatty acid. Hematoma and edema are parameters for deterioration and determination of the clinical picture and influence subsequently to the prognosis and to the final outcome of the disorder. The aim is to monitore the urine excreted cysteinyl leukotrienes and the hematoma volume (HV) values and to determine their relation.

Material and methods: Prospective and longitudinal study of a 5-day monitoring (admission/3thday/5thday) of the urine excreted cysteinyl leukotrienes (cysLTs) and the hematoma volume values of 62 patients (34 men, 28 women) with ICH. Technique of enzyme immunoassay (EIA) has been used for quantification of cysLTs in urine and computer tomography for detection/visualization of HV.

Results: CysLTs values at admission/3thday/5thday were min=268.61/129.15/36.59; max= 5787.4/4226.8/3536.7; mean=1842.20±1413.2/1181.54±906.2/982.30±774.2SDpg/ml/mg creatinine. HV values at admission min=0.45; max=52; mean=13.05±14.5SD cm3; on the 3thday min=0.62, max=54.6, mean=13.13±14.7SD-cm3 and on the 5thday min=0.1, max=54.6, mean=12.99±14.7SD cm3. Coeffitient of correlation: admission r=0.4, 3thday r= - 0.036 and on the 5thday r= - 0.076.

Conclusons: During the whole 5-day observation period after ICH, brain tissue has a capacity for highly synthesis of cysteinyl leukotrienes. Hematoma did not show changes of the volume values. Among the cysteinyl leukotreines and hematoma a correlative relation at admittance is found- increased heamtoma values were followed by increasing synthesized leucotrienes values.

Key words: intracerebral hemorrhage, hematoma, cysteinyl leukotrienes, correlation

Cysteinyl leukotrienes and hematoma- correlation study

Dolnenec-Baneva N.[1], Nikodijevic D.[1], Petrovska-Cvetkovska D.[1], Capareska D.[2], Baneva E.

[1] University Clinic of Neurology-Skopje,
[2] University Clinical of toxicology-Skopje,

Abstract

Introduction: In appearing process of intracerebral hemorrhage (ICH) blood vessel rupture causes blood extravasation and the formation of hemorrhagic collection-hematoma is started developing the process of brain edema (BE). Several substances like prostaglandins, nitric oxide, matrix-metalloproteinases, interleukins-6, alfa tumor necrosis factor, glutamate and cysteinyl leukotrienes, which are potential factors for BE production, are synthesized. Cysteinyl leukotreines (C4, D4 and E4) represent a new group of biochemical substances from eicosanoids family, metabolites of arahydonic acyclic unsaturated fatty acid. Hematoma and edema are parameters for deterioration and determination of the clinical picture and influence subsequently to the prognosis and to the final outcome of the disorder. The aim is to monitore the urine excreted cysteinyl leukotrienes and the hematoma volume (HV) values and to determine their relation.

Material and methods: Prospective and longitudinal study of a 5-day monitoring (admission/3thday/5thday) of the urine excreted cysteinyl leukotrienes (cysLTs) and the hematoma volume values of 62 patients (34 men, 28 women) with ICH. Technique of enzyme immunoassay (EIA) has been used for quantification of cysLTs in urine and computer tomography for detection/visualization of HV.

Results: CysLTs values at admission/3thday/5thday were min=268.61/129.15/36.59; max= 5787.4/4226.8/3536.7; mean=1842.20±1413.2/1181.54±906.2/982.30±774.2SDpg/ml/mg creatinine. HV values at admission min=0.45; max=52; mean=13.05±14.5SD cm3; on the 3thday min=0.62, max=54.6, mean=13.13±14.7SD-cm3 and on the 5thday min=0.1, max=54.6, mean=12.99±14.7SD cm3. Coeffitient of correlation: admission r=0.4, 3thday r= - 0.036 and on the 5thday r= - 0.076.

Conclusons: During the whole 5-day observation period after ICH, brain tissue has a capacity for highly synthesis of cysteinyl leukotrienes. Hematoma did not show changes of the volume values. Among the cysteinyl leukotreines and hematoma a correlative relation at admittance is found- increased heamtoma values were followed by increasing synthesized leucotrienes values.

Key words: intracerebral hemorrhage, hematoma, cysteinyl leukotrienes, correlation

Introduction

In appearing process of intracerebral hemorrhage blood vessel rupture causes blood extravasation and the formation of hemorrhagic collection-hematoma is started developing the process of brain edema (BE) and neuronal lesions in the surrounding parenchyma. Fluid begins to collect in the surrounding hematoma tissue and the swelling usually persists for about 5 days. BE is an essential ICH characteristic which distracts and compresses the brain parenchyma. 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 supra-tentorial ICH and at the same time it is a cause of a patient's death. Early edema surrounding the hematoma arises from the release and accumulation of osmotic active serum proteins from blood clot. In the disruption of the blood-brain barrier, the vasogenic/cytotoxic edema, the sodium pump damage and the death of neurons subsequently appear. These processes generate several substances like prostaglandins, nitric oxide, matrix-metalloproteinases, interleukins-6, alfa tumor necrosis factor, glutamate and cysteinyl leukotrienes which are potential factors for BE production. 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, stay an enigma for the time being. [1,2,3,4,5,6,7,8,9]

In the brain parenchyma cysteinyl leukotrienes (cysLTs) act vasoconstictedly, increase the permeability of the cell-brain barrier and participate in the local ischemia [4,10]. Cysteinil leukotreines (C4, D4 and E4) represent a new group of biochemical substances from eicosanoids family, metabolites of arahydonic acyclic unsaturated fatty acid, which are synthetized in a lipoxygenase way. [3,4,10]

Protagonists of the hemorrhagic cascade, hematoma, cysteinyl 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 is to determine the extracted cysLTs values in urine and the hematoma volume values in the first 5 days in ICH (on the day of admission, on the third and on th fifth day) and to determine their mutual relation

Material and methods

This study is prospective and longitudinal conducted in hospital conditions. The investiga tion is a 5-day monitoring (admission, the thir and the fifth day) of the excreted cysteinyl leukot rienes values in urine and the hematoma volum values of 62 patients (34 men and 28 women) wit acute spontaneous primary supratentorial ICH aged from 39 to 80 years (mean=62.9±7.1SD). In clusion of examinees in this study was accordin to previously determined criteria for inclusion i the study: ICH without ventricular or subarach noidal penetration, without advanced alteratio of consiciousness, precise evidence for the disea se onset (appearance of initial neuropsychic sig or symptom), arrival in the hospital in the firs 24 hours since the occurrence of the sign/sym prom and absence of somatic disorders in whic occurs the increase of production/excretion o cystLTs (pulmonary, renal, immunologic, coagu lopathies). Control group consisted of 80 (con ditionally) healthy examinees at the age of 1 to 75 years (mean=37.6±12.3SD). Technique o enzymeimmunoassay (EIA) has been used afte standardized protocol and with standardized re agents for quantification of cysLTs in urine samp le for both groups. CysLTs values were expresse in pg/mg creatinine. [11]

Detection, visualization and dimensionin of the values of hematoma volume were reali zed with computerized axial tomography of th brain. For mathematical estimation of the vol ume, special spheroid and ellipsoid formula wa used V=AxBxC/2 (A-the longest diameter, B-th crosswise diameter, C-the thickness of the visual ized hematoma). HV values were approximativ and expressed in cm^3. Statistcal analysis of dat was made by coeffitient of correlation.

Results

The cysLTs results of the control group ex aminees range were within the rank of 297.8 pg mg creatinine for minimal to 1684.2 pg/ml/m creatinine for maximal value, the mean value wa 918.6±332SD pg/ml/mg creatinine.

CysLTs values in examinees with ICH within the 5-day follow-up (admission/3thday/5thday were: minimal 268.61/129.15/36.59 pg/ml/m

atinine; maximal 5787.4/4226.8/3536.7 pg/
/mg creatinine and mean 1842.20±1413.2/11
54±906.2/982.30±774.2SD pg/ml/mg creat-
ıe (*Table 1*). Highly differences of the cysLTs
ues from the examinees with ICH were found
the observed period admission/3thday/5th-
.

The results obtained from the hematome vol-
e values were: at admission min=0.45cm3,
x=52cm3 and mean=13.05±14.5SDcm3; on
third day: min=0.62cm3, max=54.6cm3
l mean=13.13±14.7SDcm3 and on the
h day min=0.1cm3, max=54.6cm3 and
an=12.99±14.7SDcm3 (*Table 2*). No differenc-
of the hematome volume values were found
all three periods of examination. Hematoma
ume values were constant.

Figure 1, 2 and 3 show the correlative rela-
ıs between leukotrienes and hematoma val-
; in all three periods of examination: admis-
n r=0.4, on the third day r= - 0.04 and on the
h day r= - 0.08.

amination riod	Cysteinyl leukotrienes experimental group values (pg/ml/mg creatinine)		
	minimal	maximal	mean±SD
dmittance	268,61	5787,36	1842,20±1413,19
' day	129,15	4226,78	1181,54±906,16
' day	36,59	3536,69	982,30±774,24

ıle 1. Cysteinyl leukotrienes experimental group values: period of examination

amination riod	Hematoma volume values (cm^3)		
	minimal	maximal	mean±SD
dmittance	0,45	52	13,05±14,49
' day	0,62	54,6	13,13±14,66
' day	0,1	54,6	12,99±14,73

ıle 2. Hematoma values: period of examination

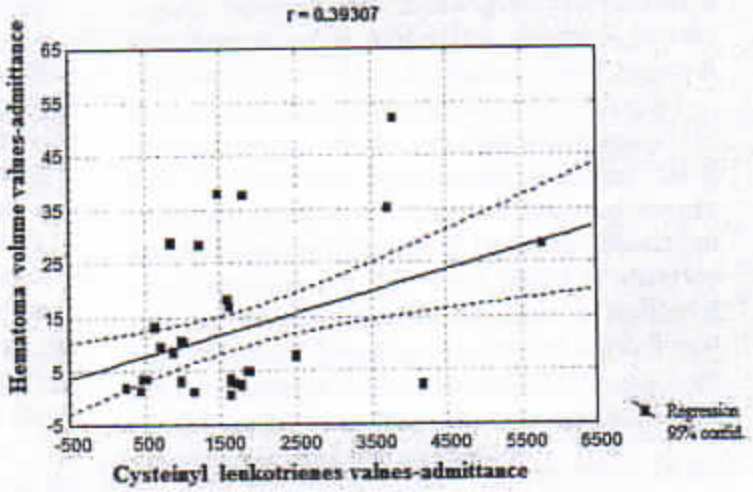

Figure 1. Correlation: Cysteinyl leukotrienes/hematoma volume – admittance

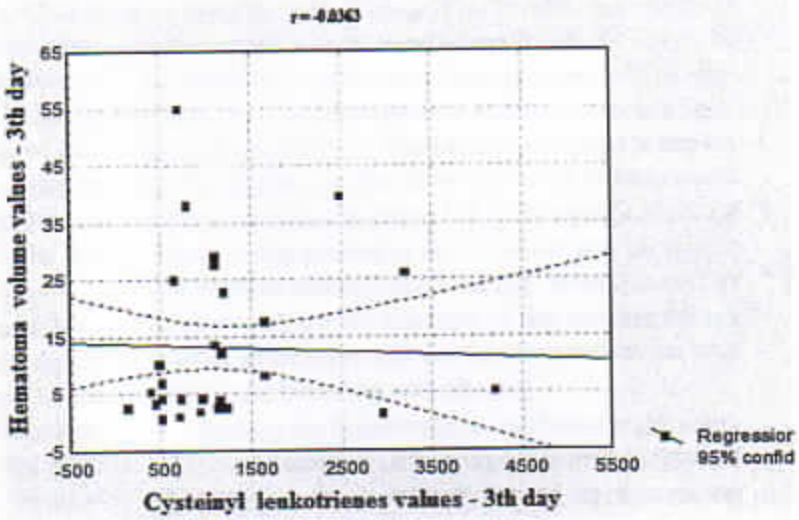

Figure 2. Correlation: Cysteinyl leukotrienes/hematoma volume –3th day

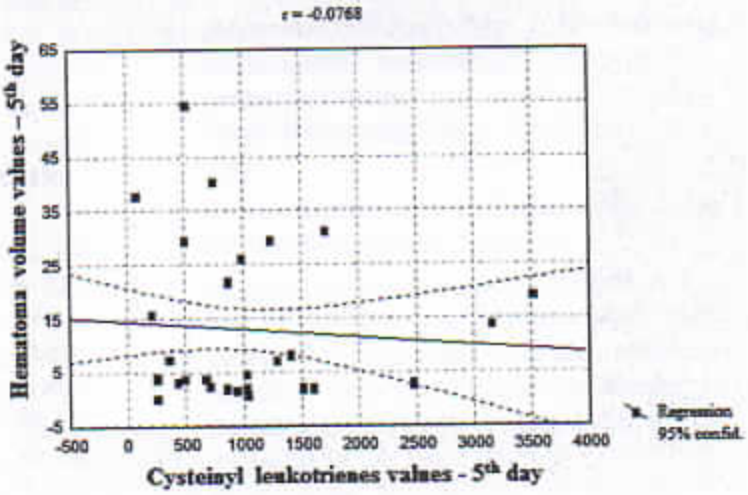

Figure 3. Correlation: Cysteinyl leukotrienes/hematoma volume –5th day

Discussion

High mean cisLTs values in urine in all examnees of the experimental group (1842.20±1413 2/1181.54±906.2/982.30±774.2) was found for he whole period of observation admission/3th-lay/5thday versus the mean values of the con-rol group examinees (918.6±332) (Table 1). It ointed to increased cysLTs excretion in urine in ine with their increased synthesis in the brain issue (newly developed conditions) after the CH occurrence. The period admission/third day howed the highest dynamics of excreted cisLTs which came out from the excretion of the high ysLTs values in the first three days. So, cysLTs ontinued to excrete, but not with such dynam-cs.Winking et al, who first started to research on his field, did not note differences of the cysLTs or the whole 5-day follow-up. It has been due, nost probably, to the small sample of examinees n their group, to specific location (only in basal anglia) and to homogenous dimensions of he-natoma (30-50cm3), versus the great sample n=62), heterogenous localization of hematoma nd heterogenous hematoma volumes in our ex-minees (0.45-52cm3). [3,4]

The results obtained from the values of the ematoma volume (mean, minimal and maximal) howed a feature of steadiness, which meant that he hematoma did not change its dimensions or ts volumenous values were with initial signs for mall reduction or initial resorbtion in hemor-hagic collection (Table 2). In favour to hemato-na volumes steadiness for all three periods of xamination (admission/3thday/5thday) spoke hat the differences of the hematoma volume alues were minimal. Pathophysiological code of nitial resorbtion could not influence significant-y on the dimensions of hematoma volume for his short 5-day period. For absence of additional leeding spoke the minimal differences of the he-natoma dimensions (Table 2). [4,12,13]

Figure 1 shows that at the admittance urine xcreted cysteinyl leukotriene values follow he-natoma values. Coeffitient of correlation r=0.4 t admittance showed connection among these wo values, namely the analysis showed that the ncreased heamtoma values were followed by ncreased leucotrienes values. Winking et al, in heir 17 ICH examinees study found more high-r correaltion (r=0.84). We think it has been due, nost probably, to the small sample of examinees n their group, to specific location (only in bas-l ganglia) and to homogenous dimensions of ematona (30-50cm3), versus the great sample (n=62), heterogenous localization of hematoma and heterogenous hematoma volumes in our examinees (0.45-52cm3). Figure 2 and Figure 3 show coeffitient of correlation on the 3th day r= - 0.04 and on the 5th day r= - 0.08 which speak of a lack of connection, because, the declining values of the excreted leukotrienes in urine are bigger and the process is faster, in terms of absorption of a hematoma for this short piriod of observation (initial resorbtion did not have an influence and additional bleeding was absent-almost constant hematoma volume values). Both values do not follow the same dynamic of decline, thus they even tend to opposite correlation.

Conclusion

Rupture of the blood vessel wall causes blood extravasation and local cumulation in form of hemorrhagic collection (hematoma) which distracts and compresses the brain parenchyma. In such conditions, the brain tissue has a capacity for highly synthesis of cysteinyl leukotrienes which excretion in urine is highly significant for a whole 5-day period of observation, but mostly in the period: admission/third day. Hematoma didnt show significant changes of the volume values (initial resorbtion did not have an influence, and additional bleeding was absent).

Among the leukotreines and hematoma a correlative relation at admittance is found-increased heamtoma values were followed by increasing synthesized leukotrienes values.

References

[1] Skidmore CT, Andrefsky J. Spontaneous intracerebral hemorrhage: epidemiology, pathophysiology, and medical management. Neurosurg Clin N Am 2002;13:281-288

[2] Krieger D. Intracerbral Hemorrhage. Acute Stroke Management 1997; 3-6.

[3] Winking M, Deinsberger W, Jodicke A, Boker DK. Leukotriene synthesis after intracerebral hemorrhage: a further indicator for their pathophysiologic significance in the CNS. Zentralbl Neurochir 1998; 59(2): 113-120.

[4] Winking M, Deinsberger W, Joedicke A, Boeker DK. Cysteinyl – Leukotriene Levels in Intracerebral Haemorrhage: An Edema-Promoting Factor? Cerebrovasc Dis 1998; 8:318-326.

[5] Bhasin RR, Xi G, Hua Y, Keep RF, Hoff JT. Experimental intracerebral hemorrhage:Effect of lysed erythrocytes on brain edema and blood-brain barrier permeability. Acta Neurochir 2002; (Suppl. 81):249-51.

[6] Brott T, Broderick J, Barsan W, Kothari R, Tomsick T, Spilker J, Huster G. Hyper-acute clot retraction in spontaneous intracerebral hemorrhage. Stroke 1992; 23:141.

[7] Brott TG, Broderick JP, Kothari RU,Barsan W, Tomsick T, Sauerbeck L, Spilker J, Duldner J, Khoury J. Early hemorrhage growth in patients with intracerebral hemorrhage. Stroke 1997;28:1-5.

[8] Suzuky J, Ebina T. Sequential changes in tissue surrounding ICH. In:Pia HW, Longmaid C,Zierski J, eds. Spontaneous Intracerebral Hematomas. Berlin, Germany; Springer,1980:121-128.

[9] Yang G-Y, Betz AL, Chenevert TL, Brunberg JA, Hoff JT. Experimental intracerebral hemorrhage: relationship between brain edema, blood flow, andblood-brain-barrier permeability in rats. J Neurosurg 1994;81:93-102.

[10] Piper Pj, Samhoun M. Leukotrienes. British medical Bulletin 1987;43 (2):285-296.

[11] Lindgren JA,Hammarstrom S, Goetzel Ej.A sensitive and specific radioimmunoassay for leukotriene C4. FEBS Lett 1983;7;152:83-88.

[12] Caplan LR. Clinical features of spontaneous intracerebral hemorrhage. In:Kauffman HH,editor. Intracerebral hematomas. New York: Raven,1992:31-47

[13] Huang FP. XiG, Keep RF, et al. Brain edema after experimental intracerebral hemorrhage; Role of haemoglobin degradation products. J neurosurg 2002; 96:287-293.