METABOLIČKI OBRT SEROTONINA I DOPAMINA U MOZGU BOLESNIKA SA MOŽDANIM ORGANSKIM PSIHOSINDROMOM

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Moždani organski psihosindrom (MOPS) je u psihijatriji i neuronaukama dijagnostički entitet utemeljen na disfunkciji kognicije, a posledica je organskog oštećenja mozga disperzno multikauzalno. Savremenom imidžing dijagnostikom najčešće je i dokazivano oštećenje mozga kao i gubitak neuronskog kvantuma u MOPS-u. Naše istraživanje je usmereno na utvrđivanje alteracije biogenih amina (serotonina i dopamina) i njihovih metabolita u bolesnika sa MOPS-om. Studija obuhvata bolesnike dijagnostikovane kao MOPS sa kauzalnim oštećenjem mozga infarktnom lezijom (grupa A), bolesnike sa dugovremenom zloupotrebom alkohola (grupa B), kao i kontrolnu grupu (K). Ako je likvor unutrašnja mikrosredina mozga, odnosno neurona, onda nivo i osilacije koncentracije serotonina, dopamina i njihovih metabolita u likvoru moraju kolerirati sa psihometrijski utvrđenim kognitivnim oštećenjem. Ovim istraživanjem je dokazana povezanost neurometaboličkog i neurobiohemijskog disbalansa u likvoru sa disfunkcijom kognicije kod svih ispitanika: u grupi sa oštećenjem mozga ishemijom i u grupi sa oštećenjem mozga alkoholom.

Ključne reči: *serotonin, dopamin, cerebrospinalna tečnost, alkoholizam, ishemija mozga*

UVOD

Moždani organski psihosindrom (MOPS) je sve češće dijagnostičko opredeljenje u psihijatrijskoj praksi zahvaljujući razvoju dijagnostičkih procedura (EEG, CT i MR endokranijuma) i savremenenih biohemijskih metoda. Dijagnostička suština MOPS-a je psihometrijsko utvrđivanje oštećene kognicije i saznanja o spoljašnoj i unutrašnjoj realnosti tih bolesnika. Kognicija i ukupno mentalno čoveka su funkcionalni odnos stalne integrativne delatnosti mozga, osnovnog moždanog kompartmana - neurona, odnosno sveukupnog neuronskog kvantuma (2, 10). Narušenost neuronskog integruma i funkcije mozga, a posebno gubitak mase

neurona smrću u raznim stanjima moždanog oštećenja, ima kao obaveznu posledicu kognitivnu disfunkciju, kako kompleksnu, tako i pojedinačnih saznajnih funkcija. Zbog ishemičnih lezija mozga ili alkoholizma događa se tipična difuzna redukcija neuronskog broja.

Ovakva oštećenja mozga pored neurološkog deficita imaju izražene poremećaje mentalnog sklada u funkcionisanju ukupnog psihičkog (4, 8). Pored citološkog oštećenja moždanog tkiva danas se izučava i govori o neurotransmiterskom i neurometaboličkom oštećenju, kako kod ishemije mozga, tako i kod prekomernog konzumiranja alkohola (8, 9, 7). Biogeni amini serotonin i dopamin bili su prvi za koje je predpostavljeno da participiraju u neuronalnoj leziji. Oni su istovremeno i neurotransmiteri i vazoaktivne supstance sa preciznom ulogom ne samo u cerebralnoj cirkulaciji, već i u metabolizmu mozga (1). U oštećenju neurona bilo ishemijom ili alkoholom, nedostatak energetskih metabolita ne izaziva promene samo u jonskoj homeostazi, već dovodi i do nagomilavanja krajnjih produkata glukoze (laktat, piruvat, CO_2, adenozin), oslobađanja aminokiselinskih transmitera (glutamat, aspartat, GABA) i monoaminergičnih neurotransmitera (dopamin, noradrenalin, serotonin). Verovatno je ovo oslobađanje posledica ekstraceluarnog povećanja koncentracije jona kalijuma, ulaska kalcijumovih jona u ćeliju i ubrzavanja procesa pražnjenja neurotransmiterskih vezikula u trenutku kada su mehanizmi presinaptiškog preuzimanja i metaboličke inaktivacije transmitera inhibirani. Jon kalijuma kao i adenozin, dopamin, noradrenalin i serotonin su svaki za sebe snažni aktivatori membranske adenilat-ciklaze (3, 5, 6).

Naše istraživanje je zasnovano na dokazivanju povezanosti oscilacija poremećenog neurobiohemizma mozga i stepena oštećenja kognicije, kod bolesnika sa lediranim mozgom ishemijom ili alkoholom.

CILJ RADA

Istraživački cilj ovog rada je da se kod bolesnika sa verifikovanim MOPS-om, nastalim kao posledica ishemije mozga ili alkoholizmom, u bolničkim uslovima, utvrdi korelacija nivoa dopamina, serotonina i njihovih metabolita u likvoru sa stepenom

oštećenja kognitivnih funkcija.

METODOLOGIJA ISTRAŽIVANJA

Istraživanje je sprovedeno u hospitalnim uslovima Bolnice za cerebrovaskularne bolesti "Sveti Sava", Zavodu za lečenje bolesti zavisnosti i Institutu za biohemiju medicinskog fakulteta u Beogradu. Za postizanje istraživačkih ciljeva sproveli smo metodološku eksploraciju u istraživanim grupama bolesnika. Svi pacijenti, kako u istraživanim tako i u kontrolnoj grupi bili su muškog pola, starosne dobi 55 do 65 godina. Istraživanu grupu A činili su bolesnici sa kliničkom dijagnozom MOPS (30 bolesnika), grupu B (12 bolesnika) alkoholičari, a kontrolnu grupu K bolesnici bez dokazane lezije mozga i bez kognitivnih disfunkcija (10 bolesnika).

U istraživanju su korišćeni sledići istraživački metodi: 1. Metod kliničkog i laboratorijskog pregleda i psihološko-psihometrijskog testiranja; 2. Stastistička obrada dobijenih podataka i rezultata istraživanja.

Za postavljanje dijagnoze MOPS-a primenjivana su neurofiziološka i neuroradiološka ispitivanja (EEG, CT i MR mozga). Dijagnoza alkoholizma je postavljana na osnovu dijagnostičkih kriterijuma iz DSM III-R. Za određivanje nivoa oštećenja kognicije korišćeno je psihološko-psihometrijsko testiranje: modifikovani "Hachinski ishemic score", WB SP forma i Bentonov test vizuelne percepcije. Likvor je lumbalnom punkcijom uziman od pacijenata u količini od 2 ml, neposredno nakon utvrđivanja da ispunjavaju dijagnostičke kriterijume, zamrzavan i jednovremeno analiziran metodom HPCL. Dobijeni rezultati su obrađeni primenom statističke metodologije za ovakva istraživanja.

REZULTATI ISTRAŽIVANJA

Nisu nam iz literature poznate studije u kojima su istraživani obim, stepen ili posebnost oštećenosti kognicije u alkoholičara i bolesnika sa moždanom ishemijom (MOPS) i njihovo koreliranje sa

metabolizmom biogenih amina u mozgu.

Kod bolesnika A grupe (MOPS), B grupe (alkoholočari) i K grupe (kontrola), primenjeno je psihološko testiranje pojedinih kognitivnih funkcija (pažnje, upamćivanja, pisanja i crtanja, odloženog pamćenja) modifikovanim testom "Hachinski ishemic score", WB SP forme i Bentonov test vizuelne percepcije. Dobijene rezultate smo gradirali prema obimu oštećenja kognicije kao teško, srednje i lako, što je prikazano Tabelom 1.

Tabela 1. Distribucija stepena oštećenja kognicije.

OŠTEĆENJE KOGNICIJE	GRUPE					
	A		B		K	
	n	%	n	%	n	%
Teško (ispod 10 poena)	22	73,0	3	25,0	-	-
Srednje teško (10 - 20 poena)	8	27,0	7	58,o	-	-
Lako (21 - 24 poena)	-	-	2	17,0	-	-
Bez oštećenja (25 - 30 poena)	-	-	-	-	10	100
UKUPNO	30	100	12	100	10	100

$p < 0,001$

Gradacija oštećenja kognicije je izvršena na osnovu rezultata ostvarenih na testovima: teško oštećenje kognicije imaju bolesnici koji nisu ostvarili 10 poena na testovima. Srednje teško oštećenje imaju bolesnici čiji je zbir poena bio od 10 do 20. Lako oštećenje kognicije postoji kod pacijenata sa ostvarenih 21 do 24 poena. Bez oštećenja kognicije su oni sa skorom od 25 do maksimalnih 30 poena.

Iz Tabele 1. uočava se da teško oštećenje kognicije imaju 22 bolesnika ili 73% iz ispitivane grupe A (bolesnici sa ishemijom mozga) i samo 3 bolesnika ili 25% iz ispitivane grupe B (alkoholičari); nema utvrđenog teškog oštećenja kognitivnih funkcija među bolesnicima kontrolne grupe K. Srednje teško oštećenje kognicije utvrđeno je kod 8 (27%) bolesnika ispitivane grupe B, u kontrolnoj grupi K nema bolesnika sa srednje teškim oštećenjem kognitivnih funkcija. Lak stepen oštećenja kognitivnih funkcija nema nijedan bolesnik iz ispitivane grupe A niti iz kontrolne grupe K, a

dva bolesnika ili 17% iz ispitivane grupe B imaju lako oštećenu kogniciju. Odsustvo oštećenja kognitivnih funkcija su pokazali svih 10 (100%) bolesnika kontrolne grupe K i nijedan bolesnik iz ispitivanih grupa A i B.

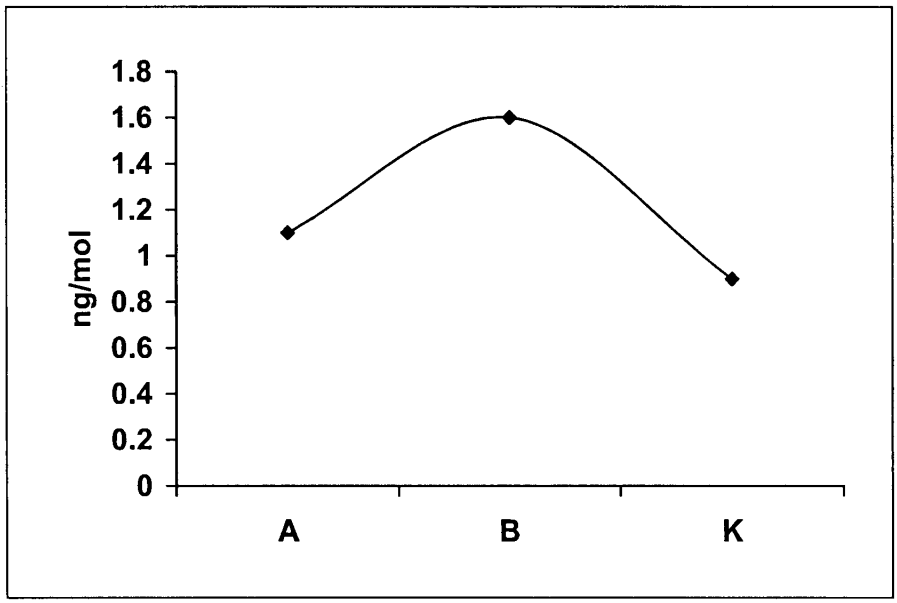
Tabela 2. prikazuje nivo serotonina i njegovih metabolita u likvoru bolesnika iz ispitivanih grupa (A i B) i kontrolne grupe (K).

Tabela 2. Nivo serotonina i njegovih metabolita u likvoru bolesnika.

	GRUPE			p
SEROTONIN	A	B	K	A : B
5-HT (pmol/ml)	69,3 ± 4,9*(30)	69,9 ± 5,1*(12)	48,9 ± 4,8*(10)	>0,05
5-HIAA (pmol/ml)	74,0 ± 7,2*(30)	96,8 ± 4,2*(12)	45,1 ± 9,3*(10)	>0,05
5-HIAA/5-HT (5-HTT)	1,1(30)	1,6(12)	0,9 (10)	<0,05

Sadržaj 5-HT serotonina u likvoru bolesnika ispitivanih grupa A i B (MOPS i alkoholizam) je značajno povišenog nivoa u odnosu na sadržaj 5-HT u likvoru bolesnika kontrolne grupe K. Potvrđena je visoka značajnost statističke razlike 5-HT u bolesnika ispitivanih grupa A i B u odnosu na grupu K. ($p<0,05$). Sadržaj metabolita serotonina 5-HIAA u likvoru bolesnika ispitivanih grupa A i B značajno je povišen u odnosu na kontrolnu grupu. Nivo metabolita u likvoru ispitivane grupe A (MOPS) značajno je viši u odnosu na nivo u likvoru bolesnika ispitivane grupe B (alkoholičari). Potvrđena je i visoka statistička značajnost razlike nivoa 5-HIAA u likvoru bolesnika ispitivanih grupa A i B u odnosu na kontrolnu grupu, dok je između ispitivanih grupa $p<0,05$.

Grafikon 1.: Metabolički obrt serotonina (5-HIAA/5-HT).



Metabolički obrt serotonina je povišen u likvoru bolesnika ispitivanih grupa A i B u odnosu na kontrolnu grupu, a posebno u likvoru bolesnika ispitivane grupe B (alkoholičari) sa potvrđenom statistički značajnom razlikom ($p<0,05$).

Metabolizam dopamina kao i sadržaj metabolita ovog monoamina DOPAC i HVA u likvoru bolesnika ispitivanih grupa A i B i kontrolne grupe K prikazan je na Tabeli 3.

Tabela 3. Nivo dopamina i njegovih metabolita u likvoru bolesnika.

DOPAMIN	GRUPE			p
	A	B	K	A:B
DOPAC(pmol/ml)	93,3 ± 5,8*(30)	98,0 ± 10,3*(12)	49,0 ± 5,0(10)	>0,05
HVA (pmol/ml)	267,0 ± 21,0*(30)	278,1 ± 11,4*(12)	141,0 ± 21,0(10)	>0,05
DOPAC + HVA	361,2 ± 15,4*(30)	376,1 ± 12,8*(12)	190,0 ± 14,3(10)	<0,05

Statistički je potvrđena značajna razlika nivoa sadržaja

dopamina i njegovih metabolita u likvoru bolesnika ispitivanih grupa A i B u odnosu na kontrolnu grupu. Nema statistički značajnih razlika nivoa ispitivanih metabolita u likvoru među ispitivanim grupa A i B. Metabolički obrt dopamina je povišen u likvoru bolesnika ispitivanih grupa A i B u odnosu na kontrolnu grupu K, ali bez potvrđene statističke značajnosti razlika ($p<0,05$).

ZAKLJUČAK

Oštećenje mentalnog sklada kognicije u bolesnika sa MOPS-om (zbog moždane ishemije ili alkoholizma), odraz je metaboličkih neuronskih disfunkcionalnosti, ali i redukcije neuronskog kvantuma. Naš zaključak je, samo rezultatima potvrđena istraživačka hipoteza, da stepen kognitivnih oštećenja MOPS-a prati i poremećaj metaboličkog obrta serotonina i dopamina u mozgu tih bolesnika.

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METABOLIC BRAIN CIRCULATION OF SEROTONINE AND DOPAMINE IN PATIENTS WITH BRAIN ORGANIC PSYCHOSYNDROME.

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Brain organic psychosyndrome (BOPS) in psychiatry and neuroscience represents an entity based on cognition dysfunction, arisen as a result of multicausal brain damage dispersion. Contemporary imaging diagnostic mostly proves the alteration of biogenic amins (serotonine and dopamine) and their metabolotes in patients with BOPS. Two groups of patients are treated and compared to the control group of patients with BOPS diagnosis and causal brain damage by infarction lesions (group A) and long-time alcohol abuse patients (group B). In liquour of internal brain microenvironment and neurones levels and osillations of concentration of serotonine, dopamine and their metabolites often correlates with cognitive damages which are defined by psychometric methods. This research also goes to prove the connections of neurometabolic disbalance in liquor with dysfunction of cognition and in patients with ischemic brain damage, as well as neurone quantum loss in MOPS. Besides,our research aims at proving alternation of biogenic amines (serotonine) in group with ishemic brain damage and in group with alcohol related brain damage.

Key words: *serotonine, dopamine, cerebrospinal fluid, alcoholism, brain ischemia*

INTRODUCTION

BOPS is becoming, on an increasing scale, the diagnostic determination in psychiatric practice thanks to the development of diagnostic methods (EEG, CT, MRI) and contemporary laboratory and biochemical possibilities. The BOPS diagnostic essence is the psychometric defining of damaged cognition, knowledge about external and internal reality of these patients.

Cognition and overall mental condition of the human being is the functional relation of the permanent activity of his integrative

brain, more precisely of the basic brain compartment - neurons resp. overall neurone quantum (2, 10).

Dysfunction of brain - neurone integrum and particularly loss of neuron mass, under various conditions of the brain damage, obligatory results in dysfunction of cognitive complex and some cognitive functions. Due to ischaemic lesions of the brain or alcoholism, a typical diffuse reduction of neuron numbers occurs.

With the neurological deficit in such brain damage more important and more distinct is disorder of the mental harmony in functioning of the overall psychical (4, 8). Besides cytological damage of the brain tissue we are studing and speaking nowadays about the neurotransmitter and neurometabolic damage, both in the brain ischemia and in excessive consuming of alcohol (8, 9, 7).

Biogenic amines, serotonine and dopamine especially, where the firstonce for which it was assumed to participate in neuronal lesion because they are at the same time both neurotransmitters and vasoactive substances with the precise role not only in cerebral circulation but also in the brain metabolism (1).

In every neurone damage, by ischemia or alcohol, deficiency of energetic metabolites shall cause changes not only in ionic homeostasis but shall lead to accumulation of glucosae and products of glucose degradation (lactate, piruvate, CO_2, adenosine) and to releasing of aminoacidic transmitters (glutamate, aspartate, GABA) and monoaminergic neurotransmiters (dopamine, noradrenaline, serotonine). This release is probably due to extracellular increase in concentration of K+, input of Ca++ into the cell and acceleration of the discharge rate of neurotransmitter vesicles at the moment when the mechanisms of presynaptic overtaking and metabolic inactivation if transmitters inhibited. ion K and adenosine, dopamine, noradrenaline and serotonine are powerful activators of the membrane adenilat-cyclase (3, 5, 6).

Our research is founded on proving the correlation between oscillations of the disturbed neurobiochemism c.s.f. and the degree of cognition damage in patients with damaged brain by ischemia or alcohol.

PURPOSE OF THE STUDY

The research is aimed at defining, in the liquor of the patients with verified BOPS occurred due to brain ischemia or alcoholism, in the hospital conditions, the correlation of the levels of dopamine, serotonine and their metabolites, with the degree of damage of cognitive functions.

RESEARCH METHODOLOGY

The research is conducted in the hospital conditions - Hospital for cerebrovascular diseases "Sveti Sava", Institute for Healing addiction Diseases, and the Institute for Biochemistry of the Begrade Medical Faculty, and for achieving the research goals we have conducted the methodological exploration in the tested groups of patients. All the patients, both in tested and in the control groups, were of male sex, approximately 55 to 65 years old, at which the tested group A consisted of the patients with clinical diagnosis BOPS (30 patients), group B formed of 12 patients with diagnosis alcoholism, and the control group K - the patients without confirmed brain lesion and without cognitive dysfunctions (10 patients).

The following research methods were applied: 1. Method of clinical and laboratory examination and psychological-psychometrical testing, 2. Statistical processing of data - results.

Diagnosis of BOPS was determinated by EEG, CT and MRI endocranial findings. For setting alcoholism diagnostic criteria DSM III-R were used, while for determining the level of cognition damage psychological-psychometric testing were performed (modified "Hachinski ishemic score", WB SP form I, Benton test of visual perception). Liquor used to be taken from patients by lumbal punction in the quantity of 2 ml, directly after establishing that they satisfy the diagnostic criteria, frozen and analysed at the same time, at the Institute for Biochemistry, Belgrade Medical faculty, by HPCL method.

The results obtained are processed by application of the statistical methodology for such researches.

RESEARCH RESULTS

We are not acquainted with the studies from literature in which the scope, degree, or damage of cognition in alcoholics and patients with brain ischemia (BOPS) are explored and correlation with byogenic amins metabolism in brain which was the reason for scheduling our research.

In the patient of A group (with BOPS), B group (alcoholics) and K group (without confirmed brain lesion) by application of the psychological testing of individual cognitive functions (attention, memorizing, writing and drawing, postponed memory) and that by modified "Hachinski ishemic score", WB SP forms and Benton test of visual perception, the results obtained were graded in the form of the level of cognition damage such as: haevy, medium, light and with no damage which is shown in the Table 1.

Table 1. Distribution of the level of cognition damage.

COGNITION DAMAGE	GROUPS					
	A		B		K	
	n	%	n	%	n	%
Haevy (below 10 points)	22	73,0	3	25,0	-	-
Medium (10 - 20 points)	8	27,0	7	58,o	-	-
Light (21 - 24 points)	-	-	2	17,0	-	-
No damage (25 - 30 points)	-	-	-	-	10	100
TOTAL	30	100	12	100	10	100

$p < 0,001$

Grading of cognition damage is made on the bases of the tests conducted: heavy cognitive damage have those patients which have not realised 10 points on tests. Medium heavy damage have those patients whose the sum of points was from 10 to 20 points; light damage of cognition with obtained 21 - 24 points and with no

cognition damage was those patients who obtained 25 to maximal 30 points.

It is obvious that heavy damage of cognition have 22 patients (73%) from the tested group A and only 3 patients (25%) from the tested group B; there was no heavy damages of cognitive functions among the patients of control group K. Medium heavy cognition damage was defined in 8 (27%) patients of the tested group B, in the control group K there were no patients with heavy damage of cognitive functions.

Light level of damage of cognitive functions was no found in any patient from the examined group A and the control group K, while 2 patients (17%) of the tested group B had lightly damaged cognition. Without confirmed damage were all 10 (100%) patients from control group K and no one patient from the tested groups A and B. Metabolism and level of serotonine in the liquor of the tested groups A, B and K are shown in Table 2.

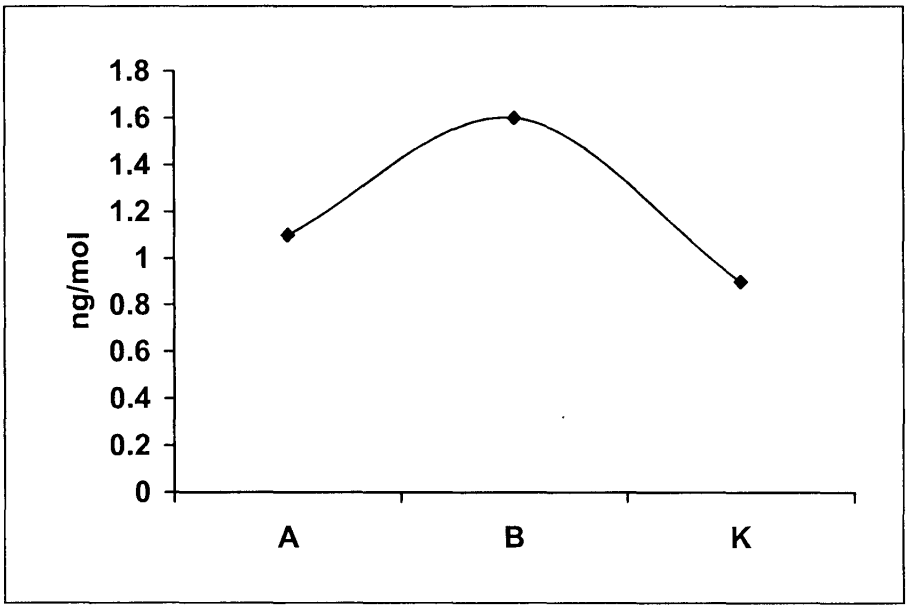
Table 2. Level of serotonine and its metabolits in the liquor of patients from A, B and K groups.

	GROUPS			p
SEROTONINE	A	B	K	A : B
5-HT (pmol/ml)	69,3 ± 4,9*(30)	69,9 ± 5,1*(12)	48,9 ± 4,8*(10)	>0,05
5-HIAA (pmol/ml)	74,0 ± 7,2*(30)	96,8 ± 4,2*(12)	45,1 ± 9,3*(10)	>0,05
5-HIAA/5-HT (5-HTT)	1,1(30)	1,6(12)	0,9 (10)	<0,05

The content of 5-HT serotonine in the liquor of the patients from the tested groups A and B (BOPS and alcoholism) is of significantly increased level in relation to the content of 5-HT in liquor patients of the control group K. High significance of the statistical diference of 5-HT in the patients of the tested groups A and B in relation to the group K shows $p<0,05$. The content of the serotonine metabolite 5-HIAA in the liquor of patient of the tested groups A and B and the control group K is considerably raised in the liquor of the tested groups A and B. However, the level of metabolite is in the liquor tested group A (BOPS) is considerably higher in relation to the level in liquor patient of the tested group B

(alcoholics). There has been also confirmed a high statistically tested significance of the level difference 5-HIAA in the liquor of patients of the tested groups A and B in relation to K group, but between the tested groups for $p<0,05$.

Graph 1. Serotonine metabolic turn (5-HIAA / 5-HT).



Serotonine metabolic turn is increased in liquor patients from the tested groups A and B in relation to group K, and particularly in liquor patients of the tested group B with confirmed high significance at the statistical difference for $p<0,05$. Metabolism of dopamine as well as the content of metabolites of this monoamine DOPAC and HVA in the liquor of the patients from the tested groups A and B and the control group K is shown in Table 3.

Table 3. Level of dopamine and its metabolites in liquor of patients from A, B and K groups.

DOPAMINE	GROUPS			p
	A	B	K	A:B
DOPAC (pmol/ml)	93,3 ± 5,8*(30)	98,0 ± 10,3*(12)	49,0 ± 5,0(10)	>0,05
HVA (pmol/ml)	267,0 ± 21,0*(30)	278,1 ± 11,4*(12)	141,0 ± 21,0(10)	>0,05
DOPAC + HVA	361,2 ± 15,4*(30)	376,1 ± 12,8*(12)	190,0 ± 14,3(10)	<0,05

The significance of difference in the level of contents of dopamine and its metabolites in the liquor of patients from the tested groups A and B in relation to the control group is statistically confirmed. There is no statistical significance of the difference in the liquor between the tested groups A and B. Metabolic turn of dopamine is considerably increased in liquor of patients from the tested groups A and B in relation to the control group K with the confirmed statistical significance of differences for $p<00,5$. Table 3.

CONCLUSIONS

Damage of the mental cognition harmony in patients with BOPS (due to brain ischemia or alcoholism) is the reflection of metabolic neurodisfunctions as well as of reduction in neuron quantum. Our conclusion is only that the research hypothesis confirmed only by the results is that the degree of BOPS cognitive damages is also followed by the disorders of serotonine and dopamine in the brains of those patients.

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