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A New Molecule in Aneurysmal Subarachnoid Hemorrhage: Dendroaspis Natriuretic Peptide

Anevrizmal Subaraknoid Hemorajide Yeni Bir Molekül: Dendroaspis Natriüretik Peptid

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ABSTRACT

AIM: Dendroaspis natriuretic peptide (DNP) is the most recently identified member of the natriuretic peptide family. Although DNP has similar structure and function to other members, it is genetically different. The other members are known to cause vasorelaxation but the effects of DNP on vascular structure still remains unclear. In this study, we aimed to find out the role of DNP in the development of vasospasm following aneurysmal SAH (subarachnoid hemorrhage).

MATERIAL and METHODS: DNP levels of 17 patients diagnosed with aneurysmal SAH and 25 volunteers as control were measured. All SAH patients were treated with aneurysm clip. Five ml of venous blood sample was obtained on postoperative 1, 3 and 7th days from each patient. Additionally, DNP levels were determined by obtaining cerebrospinal fluid (CSF) postoperative 1, 3 and 7th days.

RESULTS: Statistically significant difference was observed between cerebrospinal fluid DNP levels on day 1 and day 3 ($P<0.05$).

CONCLUSION: This study suggests that DNP can be anticipated among molecules leading development of vasospasm. The findings of present study are believed to encourage further studies regarding receptors and receptor specific drugs.

KEYWORDS: Dendroaspis natriuretic peptide, Vasospasm, Aneurysmal subaracnoid hemorrhage

ÖZ

AMAÇ: Dendroaspis natriüretik peptid (DNP), natriüretik peptid ailesinin en yeni üyesidir. Yapısal olarak diğer üyelerine benzemesine rağmen genetik olarak farklıdır. Diğer üyelerin vazorelaksasyona neden olduğu bilinmesine rağmen DNP nin insanın vasküler yapısındaki etkisi bilinmemektedir. Bu çalışmada Anevrizmal SAH (subaraknoid hemoraji) sonrası vazospazm gelişiminde DNP nin rolunü araştırdık.

YÖNTEM ve GEREÇLER: Anevrizmal SAH tanısı konan 17 hasta ve 25 gönüllü kontrol grubunda DNP düzeyleri araştırıldı. Tüm SAH hastaları anevrizma klibi ile tedavi edildi. Postoperatif dönemde 5ml venöz kan 1., 3., 7. günlerde alındı. 1., 3., 7. günlerde Beyin Omurilik Sıvısı (BOS) alınarak DNP düzeyleri incelendi.

BULGULAR: Olguların 1.gün BOS'taki DNP düzeyleri 3.gündeki DNP düzeylerinden anlamlı derecede yüksektir ($P<0,05$).

SONUÇ: Bu çalışma, DNP'nin vazospazm gelişmesinde etkenlerden biri olabileceğini düşündürmektedir. Çalışmamızın gelecekte reseptör düzeyinde yapılacak çalışmalar ve bu reseptörlere özgü yeni ilaç çalışmalarını cesaretlendireceğine inanmaktayız.

ANAHTAR SÖZCÜKLER: Dendroaspis natriüretik peptid, Vazospazm, Anevrizmal subaraknoid kanama

INTRODUCTION

Cerebral vasospasm that develops following subarachnoid hemorrhage (SAH) is an important pathological condition primarily affecting morbidity and mortality, and leading to dramatic consequences. Vasospasm occurs clinically in approximately one-third of patients with aneurysmal SAH, peaks in incidence at 3 to 7 days after the hemorrhage, and causes delayed cerebral ischemia (4). Along with vasospasm marked natriuresis and diuresis occur leading in hyponatremia and hypovolemia, which cause further deterioration of cerebral perfusion (5,16). Clarification of the pathogenesis of natriuresis and diuresis in SAH cases might lead identification of novel molecules for treatment aimed reducing the morbidity associated with vasospasm. Therefore, identifying novel peptide molecules causing hypovolemia and natriuresis is of high importance. The first three known members of natriuretic peptide family are atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and C-type natriuretic peptide. This group of structurally similar but genetically distinct peptides play a role in natriuresis, diuresis, arterial vasodilation, inhibition of endothelin release, inhibition of the renin angiotensin-aldosterone axis, and inhibition of vascular smooth muscle cell proliferation (2,3,9,14).

Dendroaspis natriuretic peptide (DNP) that was isolated from the venom of the Green Mamba snake (Dendroaspis augusticeps) is the most newly identified member of natriuretic

peptide family (12). The physiology DNP and its relationship with central nervous system diseases have not been studied adequately, and solely the study by Khurana et al. (7) has pioneered us. Therefore, it is crucial to investigate the relationship between this newly discovered peptide and cerebral vasospasm and pathogenesis of aneurysmal subarachnoid hemorrhage patients.

Dendroaspis natriuretic peptide is thought to be the most potent for the natriuretic and diuretic effect. Thus, in this study we aimed to find out the relationship between DNP and the development of cerebral vasospasm by determining the serum and CSF (cerebro spinal fluid) levels of DNP in samples obtained from patients with aneurysmal SAH and healthy volunteers.

MATERIAL and METHODS

This study was conducted under permission of Goztepe Training and Research Hospital ethics committee (Decision #: 32/E, 20/10/2006).

The subjects of the present study constituted by 17 SAH patients applied to the neurosurgery clinic of the Göztepe Training and Research Hospital and 25 healthy volunteers as control. Laboratory investigations were performed in Elisa Laboratory of Göztepe Training and Research Hospital. Transcranial Doppler Ultrasound (TCD USD) was performed to each patient for measurement of cerebral blood flow velocity using Toshiba powervision 6000. SAH patients who deny to participate in the study and those have not an appropriate TCD due to technical problems were excluded from the study. Demographic data of all cases were recorded during the application. Hypertension was observed in four patients, hypertension + diabetes in one and electrolyte imbalance in 1 patient (Table I). Aneurysmal SAH patients were managed according to established clinical protocols for SAH, after providing intensive care unit conditions. None of the patients was treated with colloids, and fluid intake was limited to 0.9% NaCl. For SAH patients, five ml of venous blood sample was collected from each patient on postoperative day 1, 3, and 7; then the collected samples centrifuged at 2500 rpm for 10 minutes and kept at -80°C until analysis.

Following the same steps of process for blood samples, collected CSF samples were kept at -80°C until analysis. Measured serum and CSF DNP levels were recorded. For the control cases, only serum DNP levels were measured and recorded (Table II).

TCD USD was performed to each patient on post-incident day 1, 3 and 7. Electrolyte levels and fluid balance of the patients were followed on a daily basis. Measurements of flow velocity of both middle cerebral artery (MCA) were taken from the 1st cm of bifurcation to the distal by TCD and highest value measured was recorded. MCA flow velocity of 120 cm/sec and higher were considered as vasospasm (Table III). Cases of control group were selected among healthy volunteers, not on medication, with no current or history of any disease. The age, sex, and serum DNP levels of control cases were recorded (Table IV).

Statistical Analysis

The obtained data was analyzed using SPSS (Statistical Package for Social Sciences) for Windows 10.0 software

Table I: Demographic and Clinical Data of Aneurysmal SAH Patients

Patient no.	Age	Sex	Comorbidity	Antihypertensive Medication	Abnormal Electrolyte at Admission	Smoker
1	57	F	Hypertension, diabetes mellitus	Candesarten	No	No
2	70	F	None	None	No	No
3	58	M	None	None	No	Yes
4	66	F	None	None	No	No
5	65	M	None	None	Yes	Yes
6	43	F	None	None	No	No
7	58	F	None	None	No	No
8	50	M	None	None	No	No
9	16	M	None	None	No	No
10	47	M	Hypertension	None	No	Yes
11	45	F	Hypertension	None	No	Yes
12	57	M	None	None	No	Yes
13	29	M	None	None	No	Yes
14	47	M	Hypertension	None	No	No
15	40	F	None	None	No	No
16	49	M	Hypertension	None	No	Yes
17	60	M	None	None	No	Yes

Table II: Blood and CSF DNP Levels

Patient no.	Blood DNP Levels (ng/ml)			CSF DNP Levels (ng/ml)			Vasospasm	Hyponatremia	Fluid Balance
	Day 1	Day 3	Day 7	Day 1	Day 3	Day 7			
1	1	2	2.1	1.1	1.8	0.7	Day 4	130	neg.
2	0.5	0.6	0.6	0.8	1.9	0.7	Not observed	No	
3	0.7	1.9	0.8	1.1	1.9	1.9	Not observed	No	
4	1.1	1	1.1	1.4	1.1	1.9	Day 4	No	
5	1.9	1	1.8	0.8	1.9	0.7	Day 5	No	
6	1.6	0.7	0.6	0.7	1	0.9	Day 9	No	neg.
7	0.5	0.6	0.6	1.7	1.8	0.9	Not observed	No	
8	0.8	0.7	0.6	9.2	7.1	6.9	Day 3	128	neg.
9	0.8	0.5	0.3	8.3	25.2	30	Day 7	130	
10	0.7	0.4	0.8	1.2	1.7	5.8	Day 9	No	
11	0.7	0.4	0.7	4.8	6.3	7.6	Day 6	No	
12	0.7	6.5	0.5	0.5	5.1	0.6	Day 5	125	
13	0.5	0.6	0.6	0.8	3.8	4	Not observed	No	
14	0.7	0.8	3.1	0.8	6.2	4	Day 5	No	
15	0.5	0.5	0.6	9.9	7.7	5	Day 7	130	neg.
16	0.8	0.3	0.3	0.9	3	0.9	Day 4	No	
17	0.7	0.8	0.6	1.1	7.7	1.3	Day 4	No	

Table III: Transcranial Doppler Measurements of SAH Patients (cm/sec)

Patient no.	Day 1	Day 2	Day 3
1	100	130	96
2	86	92	81
3	78	94	84
4	102	142	131
5	97	135	106
6	87	90	138
7	82	76	78
8	118	146	137
9	94	118	145
10	101	131	138
11	98	126	133
12	110	128	122
13	78	86	91
14	117	120	138
15	92	107	129
16	116	146	138
17	108	128	131

program. Beside descriptive statistical methods (mean, standard deviation, frequency), Student's t test was used for inter-group comparisons of quantitative parameters showing normal distribution, and Mann-Whitney U test was used for inter-group comparisons of parameters that are not normally distributed. Wilcoxon signed rank test was used for intra-group comparisons of not normally distributed parameters. The chi-square test was used to compare qualitative data. Probability values of less than 0.05 ($p<0.05$) were considered statistically significant.

RESULTS

The study group of 42 cases consisted of 20 (47.6%) females and 22 (52.4%) males. The participants divided into two groups as "case/SAH patients (n=17)" and "control (n=25)". The ages of participants were ranged from 16 to 85 year with a mean age of 44.83±17.66 years. All SAH patients were treated with aneurysm clip ligation, and none of them was treated with coil embolization. Among SAH patients 13 (76.5%) showed vasospasm. The occurrence time of vasospasm ranged between 1 day and 7 days, with a mean of 2.85 ± 1.91 days. There was no statistically significant relationship between mean age and sex distribution of participants from case and control groups ($p> 0.05$) (Table V).

Levels of Blood DNP (Aneurysmal SAH Patients and Controls)

There was no statistically significant difference between serum DNP levels of SAH patients and control group measured on days 1, 3, and 7 ($p>0.05$) (Table VI).

For the case group subjects; no statistically significant change was observed between blood DNP levels of day 1 compared with those of day 3 ($p>0.05$).

There was no statistically significant change between SAH patients' blood DNP levels of day 1 and day 7 ($p>0.05$).

Table IV: Age, Gender and DNP Levels of Control Cases

Control Case no.	Age	Gender	DNP level
1	42	M	0.7
2	25	F	0.9
3	21	M	0.4
4	42	F	0.7
5	24	F	0.8
6	23	M	0.9
7	35	F	0.6
8	20	F	0.7
9	30	F	0.7
10	24	F	0.4
11	41	M	0.6
12	28	M	0.8
13	55	M	0.7
14	85	F	0.5
15	43	M	0.6
16	70	M	0.6
17	71	F	2.0
18	65	F	0.6
19	32	M	0.8
20	45	M	0.3
21	45	F	0.6
22	75	F	0.5
23	18	F	0.6
24	23	M	0.7
25	44	M	0.7

Similarly, no statistically significant change was observed between SAH patients' blood DNP levels of day 3 compared with day 7 (p>0.05).

Levels of CSF DNP (Aneurysmal SAH Patients)

A statistically significant increase of levels of CSF DNP was observed on day 3 compared with day 1 (p<0.05); However, no statistically significant change was observed between levels of CSF DNP on day 1 compared with day 7 (p> 0.05). Similarly, there was no statistically significant change between levels of CSF DNP on day 3 compared with day 7 (p>0.05) (Table VII).

Association between Blood DNP Levels and Cerebral Vasospasm

Blood DNP levels, measured on day 1 in aneurysmal SAH patients experienced vasospasm was significantly higher than those blood DNP levels of cases not experienced vasospasm (p<0.05).

However, no statistically significant difference was observed between blood DNP levels of SAH patients experienced vasospasm and those not experienced vasospasm, for day 3 and 7 (p>0.05) (Table VIII).

Association between CSF DNP Levels and Cerebral Vasospasm

No statistically significant difference was observed between CSF DNP levels of SAH patients experienced vasospasm and those CSF DNP levels of cases not experienced vasospasm, for day 1, 3, and 7 (p>0.05) (Table IX). However, CSF DNP levels measured on day 3 was higher compared to remaining measurements (Table IX).

DISCUSSION

Dendroaspis natriuretic peptide (DNP) is a newly discovered, potent, endogenous vasodilating peptide of 38 amino acids

Table V: Assessment of Cases in Respect of Demographic Data

		SAH Patients (Mean±SD)	Controls (Mean±SD)	Test; p
Age		50,41±13,68	41,04±19,27	***t:1,728 p:0,092***
		n (%)	**n (%)**	
Gender	**Female**	7 (41.2%)	13 (52.0%)	χ^2***:0,475 p:0,491***
	Male	10 (58.8%)	12 (48.0%)	

t: *Student t test,* ***χ^2:*** *Ki-square test.*

Table VI: Assessment of Blood DNP Levels

Blood DNP Levels (ng/ml)	SAH Patients		Controls		Test ; p
	Mean±SD	Median	Mean±SD	Median	
Day 1	0.83±0.38	0.7	0.70±0.31	0.7	***Z:-1.412 p:0.158***
Day 3	1.13±1.46	0.7	0,70±0.31	0.7	***Z:-0.493 p:0.622***
Day 7	0.92±0.74	0.6	0.70±0.31	0.7	***Z:-0.171 p:0.865***
Day 1- Day 3 *p#*	***p:0.875***				
Day 1- Day 7 *p#*	***p:0.817***				
Day 3- Day 7 *p#*	***p:0.860***				

Z: *Mann Whitney U test,* ***#*** *Wilcoxon signed rank test was used.*

containing a 17–amino acid disulfide ring structure with a 15-residue C terminal extension (12).

Studies concerning physiological functions of DNP have particularly focused on cardiovascular, renal, and gastrointestinal tract related issues. However, little is known regarding its effects on the central nervous system (1,8,13). Furthermore, mechanism responsible for vasodilatation, as an effect of DNP, has not been fully elucidated. However, this effect was attributed to be through cGMP and secondary messengers, and antagonist effect to the endothelin-1 (ET-1). There are a number of studies dealing with the effects of natriuretic peptides' (ANP, BNP, CNP) in patients with aneurysmal SAH. A study by Wijdicks et al. (15) revealed higher ANP levels in 14 patients with SAH compared to the control group. ANP levels reached peak value following natriuresis and negative sodium balance in 8 patients (15). The Juul et al. (6) study did not show statistically significant differences between levels of ANP-like immune reactivity of 11 patients with SAH and healthy control cases. Thus, they concluded that there was no correlation between ANP levels and SAH. McGirt et al. (10) investigated serum BNP and sodium levels of 40 SAH patients; and they reported that a 3-fold increase in BNP levels was associated with hyponatremia.

Table VII: Assessment of CSF DNP Levels

CSF DNP Levels (ng/ml)	SAH patients	
	Mean±SD	Median
Day 1	2,65±3,25	1,1
Day 3	5,01±5,74	3
Day 7	4,34±7,02	1,9
Day 1- Day 3 *p#*	***p:0,015****	
Day 1- Day 7 *p#*	***p:0,205***	
Day 3- Day 7 *p#*	***p:0,205***	

 # Wilcoxon signed rank test was used.
** p<0.05 considered significant.*

Blood DNP Levels in Control Group and Aneurysmal SAH Patients

In the present study, no statistically significant difference was observed between serum DNP levels measured in aneurysmal SAH patients and in control cases on days 1, 3, and 7 following the ictus (p>0.05). The Median levels of blood DNP for control group were detected to be 0.7, 0.7, 0.7ng/ml on days 1, 3, 7 respectively, while those were 0.7, 0.7, 0.6ng/ml in SAH patients, respectively. Similarly, no statistically significant difference was reported between serum DNP levels of aneurysmal SAH patients and of control cases, in a study by Khurana et al. (7) (p>0.05).

Association between Blood DNP Levels and Cerebral Vasospasm

Study by Khurana et al. (7) revealed that blood DNP levels measured on day 1 in aneurysmal SAH patients experienced vasospasm was significantly higher than blood DNP levels of those cases not experienced vasospasm (p<0.05). This was compatible with the findings obtained from the present study.

CSF DNP Levels in Control Group and Aneurysmal SAH Patients

In the present study, a statistically significant increase of levels of CSF DNP was observed on day 3 compared with day 1 (p<0.05); However, no statistically significant change was observed between levels of CSF DNP on day 1 compared with day 7 (p> 0.05). Additionally, there was no statistically significant change between levels of CSF DNP on day 3

Table VIII: Association between Blood DNP Levels and Cerebral Vasospasm

Blood DNP Levels (ng/ml)	Cerebral Vasospasm				Test; p
	Observed (n=13)		Not observed (n=4)		
	Mean±SD	Median	Mean±SD	Median	
Day 1	0,92±0,40	0,8	0,55±0,10	0,5	***Z:-2,453 p:0,014****
Day 3	1,20±1,65	0,7	0,92±0,65	0,6	***Z:0,000 p:1,000***
Day 7	1,01±0,83	0,6	0,65±0,10	0,6	***Z:-0,294 p:0,769***

***Z:** Mann Whitney U test.*
** p<0.05 considered significant.*

Table IX: Association between CSF DNP Levels and Cerebral Vasospasm

CSF DNP Levels (ng/ml)	Cerebral Vasospasm				Test; p
	Observed (n=13)		Not Observed (n=4)		
	Mean±SD	Median	Mean±SD	Median	
Day 1	3,13±3,60	1,1	1,10±0,42	0,9	***Z:-0,571 p:0,568***
Day 3	5,83±6,37	5,1	2,35±0,97	1,9	***Z:-0,852 p:0,394***
Day 7	5,10±7,91	1,9	1,87±1,51	1,4	***Z:-0,684 p:0,494***

***Z:** Mann Whitney U test.*

compared with day 7 (p>0.05). Median levels of CSF DNP in SAH patients experienced vasospasm were 1.1 ng/ml, 5.1 ng/ml and 1.9 mg/ml on days 1, 3 and 7, respectively. On the other hand, CSF DNP levels of cases not experienced vasospasm were 0.9 ng/ml, 1.9 ng/ml and 1.4 ng/ml on days 1, 3 and 7, respectively. The increase of levels of CSF DNP between day 1 and 3 is indicative of early period increase patients experienced vasospasm and might show its contribution of negative fluid balance, and hyponatremia. This finding was compatible with Khurana et al.'s (7) study.

The effect of various parameters such as age, gender, use of angiotensin-converting-enzyme inhibitors, and endocrine system and renal diseases on serum concentrations of natriuretic peptides is among the most controversial issues. However, to our knowledge none of these parameters has specific effect on DNP. A study by Redfield et al. (11) indicated higher DNP levels in women than men. On the contrary, compared with the control group blood DNP levels did not show significant difference on days 1, 3 and 7, in the present study. On the other hand, a significant difference was observed between day 3 CSF DNP levels of patients experienced vasospasm and those did not experienced vasospasm. Regarding the DNP levels in aneurysmal SAH patients, CSF DNP level is thought to be more specific than blood DNP levels. However, the present findings are not sufficient for further comments since CSF sample could not be obtained from control cases and CSF DNP levels of control cases are not known. Although many of the functions of the natriuretic peptide ffamily have been clarified, why their regulation is perturbed in SAH is not known. Because natriuretic factors modulate the response to volüme loading under normal circumstances, it seems paradoxical that enhanced natriuretic peptide secretion favoring a hypovolemic state emerges at a time when vasospasm is profound

CONCLUSION

This study is the second to find out the role of DNP in aneurysmal SAH patients but the first to examine the CSF DNP levels in aneurysmal SAH patients. Furthermore, the present study is the largest ever, regarding the title, with its case number. However, further studies with larger patients and control case number are needed to provide more accurate findings. Further studies to examine ANP, BNP, C-type NP and DNP together will contribute elucidating the etiopathogenesis of vasospasm caused by the multiple factors. Presenting significantly higher blood DNP levels on day 1 in patients experienced vasospasm and significant increase of CSF DNP levels on day 3 compared with day 1, this study suggests that DNP can be anticipated among molecules leading development of vasospasm. The findings of present study are believed to encourage further studies concerning related receptors and receptor specific drugs.

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