CORRELATION BETWEEN URINE BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF) AND GLIAL CELL LINE-DERIVED NEUROTROPHIC FACTOR (GDNF) ON SEVERITY OF OVERACTIVE BLADDER IN WOMEN PARAMEDIS AT H. ADAM MALIK GENERAL HOSPITAL MEDAN

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Abstract: The purpose of this research is to determine the correlation between urine brain-derived neurotrophic factor (BDNF) and Glial cell line-derived neurotrophic factor (GDNF) on severity of overactive bladder (OAB) in women paramedics at H. Adam Malik General Hospital Medan**.** This research was a logistic correlation analysis with cross sectional study design on women paramedics from January 2019 till 37 samples were met using non-probability methods with consecutive sampling technique. Bivariate statistical analyzes were performed using independent T-Test if data was normally distributed or Mann Whitney U test if the data distribution was abnormal. The mean urinary bladder BDNF level in OAB group was 430.11 ± 71.26 ng / mL, higher than in non-OAB group with 230.84 ± 30.29 ng / mL. The mean level of urine GDNF in OAB group is 1318.38 ± 279.53 ng / mL higher than non- OAB group, which is 836.86 ± 119.16 ng / mL. BDNF levels <389.5 are quite high in patients with mild OAB, but overall BDNF levels increase in patients with OAB. GDNF levels tended to decrease in OAB patients with <1321.5 levels most commonly found in patients with mild OAB and overall levels of GDNF tended to decrease in patients with OAB. Based on the calculation, it was found that there was a strong correlation between BDNF and GDNF levels in severity of OAB patients with r value on BDNF and GDNF was 0.879 and 0.751, respectively.

Keywords: overactive bladder¸ Brain-derived Neurotropic Factor, Glial cell line Derived Neurotropic Factor

INTRODUCTION

Overactive bladder has a high prevalence and is estimated to affect around 10.7% of the world's population (around 455 million people). The prevalence increases with increasing age, estimated to increase by around 41% in men and 31% in women aged > 75 years. Based on epidemiological data, there are at least 50-100 million patients with overactive bladder spread throughout the world. In the China, there are about 6% of patients with overactive bladder based on the questionnaire research conducted including around 20,000 patients in 6 regions. The prevalence of overactive bladder is estimated to be around 12-19% in the male and female population. Overactive bladder attacks around 14% of Canadians with the same prevalence between men and women. Increasing age will increase the risk of overactive bladder. The prevalence of overactive bladder reported in Zhu et al's study is around 10-15%. Recent research shows that there is an increased prevalence of overactive bladder in individuals aged 40-50 years. Based on European analysis, only about 24.4% of the population affected by overactive bladder was treated.[1,2,3,4,5]

There are many risk factors that can cause overactive bladder such as age, menopause status, body mass index, comorbid chronic disease, parity, and so on. The main mechanism for this condition is the excessive activity of the bladder detrusor smooth muscle. Clinical manifestations of overactive bladder are collection of symptoms from the lower urinary tract symptoms. Although not life-threatening, but this condition can

cause a decrease in the quality of life of an individual. In addition to having an impact on physical health factors, overactive bladder also has an impact on psychological, social, biological and economic.[6]

To help diagnose and determine the severity of overactive bladder, tools such as overactive bladder Symptoms Score (OABSS) designed by Homma et al and JG Blaives et al were used.[7]

In the case of overactive bladder (OAB), the researchers focused on bladder parameters (presence of detrusor overactivity and bladder wall thickness), serum proteins (reactive C protein), urinary elements (prostaglandins, cytokines and neurotropins) and neurotropic derivatives (Brain-derived Neurotropic Factor / BDNF and Glial cell line Derived Neurotropic Factor / GDNF).[8]

Antunes-Lopes examined the correlation between overactive bladder (OAB) and urinary nerve growth factor (NGF). This group investigated the correlation between Brain derived neurotrophic factor (BDNF) and Glial cell line Derived Neurotropic Factor (GDNF) levels in urine and was reported to increase in the group suffering overactive bladder (OAB). Increased risk of overactive bladder in women and has been proven from previous studies that are characterized by an increase in levels of brain derived neurotrophic factor (BDNF) and Glial cell line Derived Neurotropic Factor (GDNF) in individuals who experience overactive bladder and assess the severity of overactive bladder using overactive bladder Symptoms Score (OABSS).[9]

MATERIAL AND METHODS

This research was a logistic correlation analysis with a cross sectional study design that assessed the correlation between urine Brain-derived neutrophic factor (BDNF) and Glial cell line-derived neurotrophic factor (GDNF) on severity of overactive bladder in women paramedics who experienced it and without overactive bladder in H. Adam Malik General Hospital Medan in January 2019 up to 37 samples were met with non-probability methods and consecutive sampling technique. The sample of this study was women paramedics who met the inclusion criteria, namely women with OAB and without OAB, were willing to take part in the research and had signed a form of willingness; and exclusion criteria namely having bladder infection, diabetes mellitus, obesity, damaged urine samples and research subjects withdrawing from the research.

After obtaining approval from the ethics commission to conduct research, the researcher divided into two groups, namely the OAB and non OAB paramedics. Anamnesis (patient's age, parity history), physical examination, anthropometric recordings, such as height and weight, were performed. Researchers then looked for OAB sufferers based on the Overactive Bladder Symptom Score. Previously, a Minnesota multiphasic personality inventory (MMPI) test was conducted on these patients. Then an examination of BDNF levels and GDNF levels in the urine. Urine is collected in sterile containers. Samples are stored at 4 ^{o}C for less than 3 hours. Then centrifuged at 3,000 rpm for 20 minutes. Samples were liquefied and processed by enzyme linked immunosorbent assay (ELISA) according to manufacturer's instructions. This system uses a sandwich kit to accurately quantify the detection of urine BDNF and GDNF.

Statistical Analysis

The results of this research are presented in the frequency distribution table. To assess the frequency distribution of the characteristics research subjects based on age, parity and BMI, univariate statistical analysis were carried out. BDNF and GDNF values were then tested for normal distribution with normality tests. To assess the description of urinary BDNF and GDNF levels in women with OAB and without OAB, bivariate statistical analyzes were performed using independent T-Test if data were normally distributed or Mann Whitney U test if the data distribution weren't normally distributed. This study uses a confidence level of 95%.

RESULTS

Characteristics of Research Subjects

Characteristics of research subjects based on age, BMI, and parity can be seen in the table below.

Table 1. Characteristics of research subjects based on age, BMI, and parity

Characteristics	Research Subjects			
	OAB (n=37)	Non OAB (n=37)	Total	p value
Age (years old)				
<52	10 (27%)	4 (10,8%)	9 (12,2%)	1,0*
≥ 52	27 (73%)	33 (89,2%)	65 (87,8%)	
BMI				
Normoweight	8 (21,6%)	15 (40,5%)	23 (31,1%)	0,079**

Overweight	29 (78,4%)	22 (59,5%)	51 (68,9%)	
Parity				
Primipara	0	2 (5,4 %)	2 (2,7 %)	
Secundipara	14 (37,8)	13 (35,1%)	27 (36,4%)	0,093**
Multipara	23 (62,1)	22 (59,4%)	45 (60,8%)	
Total	37 (100%)	37 (100%)	74 (100%)	

Fisher exact test* * Chi-square test*

The table above explains that the characteristics of the research subjects with OAB are generally with age ≥52 years (73%) and the lowest with age <52 years (27%). Likewise, non overactive bladder research subjects generally with age ≥52 years (89.2%) and the lowest with age <52 years (10.8%). Based on Fisher exact statistical tests, there were no significant differences between the ages of the two study groups (p> 0.05).

Based on Body Mass Index (BMI) it can be seen that the subjects of overactive bladder were mostly overweight (78.4%) and others were normoweight (21.6%), while non overactive bladder subjects were also mostly overweight (59.5%) and other normoweight (40.5%) Based on the Chi-square statistical test showed that no significant difference in the BMI of the two study groups (p> 0.05).

Based on parity can be seen from subjects overactive bladder with secundipara as many as 14 people (37.8%) and multipara as many as 23 people (62.1%). In non overactive bladder subjects, primipara was 2 people (5.4%), secundipara 13 people (35.1%) and multiparas were 22 people (59.4%). Based on the chi-square statistical test, there was no significant difference in the parity of the two study groups (p> 0.05)

OAB distribution based on severity of disease

Table 2. OAB distribution based on severity of disease

	Severity of disease			Total
	Mild	**Moderate**	**Severe**	
OAB	20 (51,4%)	12 (32,4%)	5 (13,5%)	37 (100%)

The severity of disease from women with overactive bladder is mostly mild (51.4%) and rarely with severe degrees (13.5%).

Results of BDNF and GDNF Level on Laboratory Examination

The results of laboratory examination of urine GDNF and BDNF levels using the ELISA method are shown in the following table.

Table 3. Mean BDNF levels in OAB and Non OAB

Research Subjects	N	BDNF levels (ng/mL)				P value
		Mean	Std. Deviation	Minimum	Maximum	
OAB	37	430,11	71,26	323	609	0,001**
Non OAB	37	230,84	30,29	170	288	

***Mann-Whitney test*

The table above shows that the mean urine BDNF levels of overactive bladder group was 430.11 ± 71.26 ng / mL higher than the mean BDNF level of non overactive bladder group with 230.84 ± 30.29 ng / mL. Statistically using Mann-Whitney test showed a significant difference in BDNF levels between the overactive bladder group and non overactive bladder (p <0.05).

Table 4. Mean GDNF levels in OAB and Non OAB

Research Subjects	n	GDNF levels (ng/mL)				P value
		Mean	Std. Deviation	Minimum	Maximum	
OAB	37	1318,38	279,53	1030	2110	0,001*
Non OAB	37	836,86	119,16	533	1012	

** t-Test*

The table above shows that the average urine GDNF level of the Overactive Bladder group was 1318.38 ± 279.53 ng / mL higher than the average GDNF level of the non Overactive Bladder group, which is 836.86 ± 119.16 ng / mL. Statistically the t-test showed significant differences in the levels of GDNF between the overactive bladder and non overactive bladder group (p <0.05).

Table 5. Distribution of BDNF levels due to OAB based on the severity of disease

		OAB Severity					
		Mild	**Moderate**	**Severe**	**Total**	**P**	**R**
BDNF	≥389.5	8	9	5	22	0.001	0.879
	<389.5	12	3	0	15		
Total		20	12	5	37		

The table above shows that the mean urine BDNF level in the overactive bladder group were 8, 9, 5 for mild, moderate and severe degrees with BDNF levels> 389.5 while in the group with BDNF levels <389.5 there were 12,3 and 0 for mild, moderate and severe degrees. This shows that the BDNF level <389.5 is quite high in patients with mild OAB, but overall BDNF levels are increased in patients with OAB.

Table 6. Distribution of GDNF levels due to OAB based on the severity of disease

		OAB Severity					
		Mild	**Moderate**	**Severe**	**Total**	**P**	**R**
GDNF	≥1321.5	1	4	5	10	0.001	0.751
	<1321.5	19	8	0	27		
Total		20	12	5	37		

The table above shows that the mean level of urine GDNF in the overactive bladder group was 1.4.5 for mild, moderate and severe degrees with GDNF levels ≥ 1321.5 while in groups with GDNF levels <1321.5 there were 19, 8 and 0 for mild, moderate and severe degrees. This shows that GDNF levels tend to decrease in OAB patients with <1321.5 levels most commonly found in patients with mild OAB and overall levels of GDNF tend to decrease in patients with OAB. Based on the calculation, it was found that there was a strong correlation between BDNF and GDNF levels in OAB patients where the r value on BDNF and GDNF was 0.879 and 0.751, respectively.

DISCUSSIONS

Age

Overactive bladder is a clinical condition where there is urinary urgency, usually in conjunction with frequency and nocturia with or without urinary incontinence urgency in the absence of urinary tract infections or other pathological conditions. Overactive bladder is different from urinary incontinence because urinary incontinence is one component in overactive bladder. Urinary incontinence affects about 1/3 of patients who experience overactive bladder. Increasing age will increase the risk of overactive bladder associated with degenerative processes. The prevalence of overactive bladder reported in Zhu et al's study is around 10-15%. Recent research shows that there is an increased prevalence of overactive bladder in individuals aged 40-50 years. Menopausal women have a higher risk of overactive bladder than women who have not yet menopause, which makes menopausal symptoms an independent risk factor for the occurrence of overactive bladder.[2,10,11]

There are many risk factors that can cause overactive bladder such as age, menopause status, body mass index, comorbid chronic disease, parity, and so on. The main mechanism for this condition is excessive activity of the bladder detrusor smooth muscle which can be triggered by neurological factors or at the biomolecular stage. Clinical manifestations that arise in overactive bladder are a collection of symptoms from the lower urinary tract symptoms which, although not a life-threatening condition, can cause a decrease in the quality of life of an individual. In addition to having an impact on physical health factors, overactive bladder also has an impact on psychological, social, biological and economic.[6]

Body mass index

In a study conducted by Stewart et al. They found that the prevalence of overactive bladder with urgency incontinence increased in patients who had a body mass index ≥30 (obesity) as much as 2.2 times higher than patients who had a body mass index <24. There is a hypothesis which states that weight can increase intraabdominal pressure which causes pressure in the bladder and intravenous pressure, this will cause excessive activity of the bladder.[12,13]

Parity

From the research of Nadeem et al, 2017, it was found that as many as 160 people (42.1%) were multiparas. From Cheung et al., 2011, the most parity was multiparous with 86 people (44.3%). There was a significant relationship between parity and urgency type incontinence with odds ratio 1.983 for parity <3 and odds ratio 2.00 for parity 3-5. Parity increasement more than 2 shows a significant relationship with an OAB incidence with prevalence 72%. An explanation for this is thought to be due to changes in neuropathy that increases sensitivity of the bladder detrusor muscle during the filling process while pregnant. It was also reported that women who gave birth normally had a more accurate relationship to the incidence of OAB. Repeated labor will cause damage to the integrity of the pelvic supporting organs, and weaken the strain. This is also related to giving birth to a baby macrosomia.[14,15]

OAB Severity

From the results of Tomaszewski's research in 2014, it was found that 11% to 73% of women experienced symptoms of Lower Urinary Tract Symptoms (LUTS). Among subjects who experienced OAB, urgency, incontinence, frequency and nocturia were reported to occur in 24%, 37%, and 37%, respectively. However, only 33% of women with OAB reported symptoms of frequency and 31% with nocturia. According to Jones et al, 2016, the most common OAB symptoms were nocturia with 73.2%, then urinary incontinence with 28.5%.[3]

Mean levels of BDNF and GDNF in OAB and Non OAB

In the Alkis et al. study, the mean BDNF was 838 ± 310.8 compared with the control group at 340.2 ± 199.0, according to this study where there was an increasement in BDNF levels in OAB patients. In a study by Antunes-Lopes et al., BDNF was increased in OAB patients with an mean levels of 628.1 ± 590.5 compared to the control group with 110.4 ± 159.5. This shows low BDNF levels in non-OAB patients without seeing the time of urine collection. From Wang et al's study, the mean BDNF levels in OAB patients was significantly higher than the control group, which was 20.609 ± 23,932 vs. 1,779 ± 0.729. There is evidence that BDNF plays an important role in the inflammatory process including inflammation of the bladder. Increased neurothropin stimulates afferent fibers so that plasticity changes from afferent fibers can increase acetylcholine and decrease nitric oxide so that detrusor overactivity can occur.[12,16,17]

In the study of Antunes-Lopes et al, there was an increasement in GDNF levels in OAB patients with an mean levels of 1220.5 ± 513.5. From the research of Ochodnicky P et al., mean GDNF levels in OAB patients was significantly higher than the control group, which was 1.220 ± 513.5 vs. 958.1 ± 826.2. Based on this we can see that it is possible that GDNF has an important role in the occurrence of overactive bladder where GDNF is found to increase in the urine as a sign of proliferation of nerves in the bladder destrusor muscle.[18,19]

Mean BDNF and GDNF levels due to severity of OAB

From the results of the research it was found that the mean urine BDNF level in the overactive bladder group were 8, 9, 5 for mild, moderate and severe degrees with BDNF levels> 389.5 while in the group with BDNF levels <389.5 there were 12,3 and 0 for mild, moderate and severe degrees. This shows that the BDNF level <389.5 is quite high in patients with mild OAB, but overall BDNF levels are increased in patients with OAB.

From this research it shows that mean level of urine GDNF in the overactive bladder group was 1.4.5 for mild, moderate and severe degrees with GDNF levels> 1321.5 while in groups with GDNF levels <1321.5 there were 19, 8 and 0 for mild, moderate and severe degrees. This shows that GDNF levels tend to decrease in OAB patients with <1321.5 levels most commonly found in patients with mild OAB and overall levels of GDNF tend to decrease in patients with OAB. Based on the calculation, it was found that there was a strong correlation between BDNF and GDNF levels in OAB patients where the r value on BDNF and GDNF was 0.879 and 0.751,respectively.

CONCLUSION

Based on the results of this research there was no difference of urine BDNF (Brain Derived Neurotrophic Factor) and GDNF (Glial Cell Line Derived Neurotrophic Factor) mean levels in women who had OAB and who did not experience OAB. Besides that, there was a relationship between BDNF and GDNF mean levels on the severity of OAB.

ACKNOWLEDGEMENT

The researcher thanked the supervisor of the obstetrics and gynecology department for his guidance and contribution in this research. In addition, the researcher also thanked all parties from the staff to the research samples involved in conducting this research.

CONFLICT OF INTEREST

The researcher ensures that there is no conflict of interest in this research

ETHICAL CLEARANCE

For research permission, research approval was obtained from the research subject and the Ethics Committee of the Faculty of Medicine, University of North Sumatra who would conduct an assessment of the feasibility of the research proposal.

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