Original Article

Brain Natriuretic Peptide in Patients with Acromegaly: A Comparative Study between those with and without Obstructive Sleep Apnea

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Abstract

Background: Acromegaly is a rare endocrine disorder; it has an incidence of 4 per million annually and a prevalence of 40 per million. It is due to growth hormone-secreting pituitary adenoma. The objective of our study is to evaluate the levels of brain natriuretic peptide (BNP) in patients with acromegaly with and without obstructive sleep apnea (OSA). **Materials and Methods:** One hundred five registered patients with acromegaly in the National Diabetes Center-Mustansiriyah University were enrolled in the study. Out of 105 patients with acromegaly, 81 have OSA while the remaining 24 have no OSA. OSA affects 81.8% of males and 72% of females. All recruited patients have given oral consent to participate in the study which was conducted during the period from January to October 2023. **Results:** Males with OSA had a mean age of 52 years while those without OSA had a mean age of 46 years. Epworth Sleepiness Scale is higher among those with OSA. BNP is found to be higher in females with OSA (905.54 pg/ml) while in males with OSA, it drops down to 878.76 pg/ml. In no OSA group, the BNP level was 355.33 ± 30.1 pg/ml while in those with OSA, it jumped to 890.66 ± 205.63 pg/ml. **Conclusions:** The results showed that BNP was elevated in patients with acromegaly and OSA versus those without OSA, OSA is more common in males particularly when they get older.

Keywords: Acromegaly, brain natriuretic peptide, obstructive sleep apnea

Introduction

Acromegaly is a rare endocrine disorder, due to growth hormone (GH)-secreting pituitary adenoma, 70% of patients harbor a macroadenoma while the remaining 30% have a microadenoma.[1] Its prevalence ranges between 34 and 137 per million with an annual incidence of 4–6 per million, its incidence and prevalence have no sex predilection.[2] Acromegaly is characterized by enlargement of the acral parts (hand, foot, and face) with marked perspiration and increased secretion of sebum, arthralgia affects a good number of patients, and the effect on other hormones may result in symptoms of hypothyroidism and hypogonadism, at the same time, the mass effect within the cranium can cause headache and visual symptoms due to pressure on the optic chiasma.[3] GH augments the hepatic secretion of insulin-like growth factor-1 (IGF-1) which had an impact on gene transcription thus resulting in cardiomyocyte hypertrophy and impaired diastolic ventricular filling the main cause of death in patients with acromegaly is cardiovascular complication.[4]

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Evaluation of the cardiac functions can be done using echocardiography, however, the gold standard diagnostic test is cardiac magnetic resonance imaging (CMRI), brain natriuretic peptide (BNP) is known to be increased in cases of left ventricular hypertrophy.[5] BNP is synthesized as a preprohormone-containing 134 amino acids (a.a), this molecule is cleaved by a convertase enzyme, and the final product is a biologically active BNP molecule composed of 32 a.a. and N-terminal pro-BNP (NT-pro BNP) in equimolar amount is biologically inactive but has longer half-life time than BNP.[6] Patients with acromegaly are prone to chest infection due to the effect of IGF-1 on the bronchial tissues plus the craniofacial

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changes and macroglossia that may alter the airways and induce obstructive sleep apnea (OSA).[7] OSA affects 60% of males and 24% of females, particularly after the age of 60 years.[8] OSA results from cessation of airflow thus resulting in apneic spells and interrupted sleep, snoring can be detected by the sleep partner, and those patients with OSA complain of unsatisfactory sleep, headache, daytime sleepiness, and fatigue.[7]

As far as the main comorbidities in acromegaly are cardiac and respiratory, it sounds logical to study the parameters relevant to the cardiac and respiratory system as STOP-Bang score, BNP, echocardiography, and cardiac MRI.

Materials and Methods

In the National Diabetic Center-Mustansiriyah University, 315 patients with acromegaly are registered and each one has a fully written medical record. During prespecified period of the study, any patient who has attended the center is enrolled to check him carefully, clinically, biochemically, and radiologically but any patient who attended before or after the allocated time of sample collection is not enrolled and patients with other causes of OSA (hypothyroidism, polycystic ovary syndrome, users of alcohol, nasal obstruction, and history of stroke) were excluded thus the patients who enrolled in the study were 105 acromegaly patients. One hundred and five patients with acromegaly who are very compliant are selected to be enrolled in the study, their ages range between 30 and 50 years. Those patients were selected randomly after informed consent was taken. Any recruited patient is familiar with a monthly visit which is prespecified to be examined, investigated, and receive their monthly somatostatin analogous (SST) injection. All the patients fasted for 8–12 h at the time of appointment and the blood samples were taken in the morning before 9 A.M., 10 ml of venous blood was withdrawn and centrifuged at 3000 rpm for 10 min, and the sera were taken to measure GH, IGF-1, and BNP. The other hormonal profiles as thyroid function tests and sex hormones are checked every few months according to the request of the consultant endocrinologist. A physical examination was conducted to measure their vital signs plus a regional examination, followed by a detailed history to stratify the severity of OSA, two scores are utilized to achieve this goal, the Epworth Sleepiness Scale and the STOP-BANG score. Epworth Sleepiness Scale (Ep.s) checks the readiness to sleep on variable occasions, its details are listed below. The Ep.s has 4 scores ranging from 0 to 3 thus o is regarded as normal and such people never doze in abnormal situations while score 3 is the worst thus they doze in normal situations such as sitting in a public place, the scores are gathered to find out the final number and if such gathered number exceeds 10 so this patient is complaining from OSA, as shown in Figure 1. The STOP-Bang questionnaire is a series of 8 questions to be answered by yes or no and its details are listed below, when the STOP-Bang is 0–2 is regarded as normal, 2–5 is a gray zone while a score exceeding 5 is consistent with OSA, as shown in Figure 2. GH, IGF-1, and other hormones are measured using a fully automated device with electrochemiluminescence immune principle (Cobas E411), 1 cc of remaining serum from every patient was stored at −20°C to the time sandwich ELISA assay to measure BNP level, the Statistical Package for the Social Science program (SPSS) version 20 (ELISA kits from mybiosource ,USA , BNP (Catalog #MBS704529)) was used to analyze the data.

Results

The results in Table 1 indicated that out of 105 patients with acromegaly who have been enrolled in this study 55 were males. Forty-five out of the 55 males (81.8%) have OSA, while OSA affects 36 females out of 50 females with acromegaly, thus their percentage is only 72%. OSA percentage difference between males and females is 9.2% in favor of males, however, the difference did not reach statistical significance.

The count of patients with OSA who harbor macroadenoma was 56 and 25 harbor microadenoma and the difference is close to statistical significance $P = 0.059$.

The results in Table 2 indicated that the mean age of patients with OSA is 52 years, however, those without OSA have

Table 1: Sex and pituitary adenoma size in patients with acromegaly with and without obstructive sleep apnea

	Count		*P*
	No OSA	OSA	
Sex			
Female	14	36	0.168
Male	10	45	
Adenoma size (mm)			
Microadenoma ≤10	3	25	0.059
Macroadenoma >10	21	56	

*Significant difference between proportions using Pearson Chi-square test at 0.05 level. OSA: Obstructive sleep apnea

Table 2: Age, body mass index, duration, cumulative dose, growth hormone, insulin-like growth factor-1, Epworth Scale, STOP-Bang score, and brain natriuretic peptide mean±standard deviation in patients with acromegaly with and without obstructive sleep apnea

Parameters	No OSA, mean±SD	OSA, mean±SD	*P*
Age (years)	46±13	52±11	0.016*
BMI (kg/m^2)	30.58±4.48	32.78±5.74	0.089
Duration (years)	7±3	10±7	0.049*
CD (mg)	1274±926	1490±995	0.343
GH (ng/mL)	5.67±6.47	5.08±6.30	0.689
IGF-1 (ng/mL)	487±210	549±231	0.243
Ep.s	5.0±5.1	15.6±8.5	0.001*
Stop	2±1	5±1	0.001*
BNP (pg/mL)	355.33±30.10	890.66±205.63	0.001*

*Significant difference between proportions using independent Student's *t*-test at 0.05 level. BMI: Body mass index, GH: Growth hormone, IGF-1: Insulin-like growth factor-1, EP.s: Epworth Scale, Stop: STOP-Bang score, BNP: Brain natriuretic peptide, SD: Standard deviation, OSA: Obstructive sleep apnea, CD: Cumulative dose a mean age of 46 years, the difference reaches statistical significance ($P = 0.016$).

Patients with a mean body mass index (BMI) of 32.78 kg/m^2 have OSA while their counterparts without OSA were found to have a mean BMI of 30.58 kg/m^2, however, the difference did not reach statistical significance ($P = 0.089$). The mean duration of acromegaly since the time of diagnosis is 10 years in those with OSA and 7 years in those without OSA, the difference is significant ($P = 0.049$).

The cumulative dose of octreotide (C.D.) mean ± standard deviation (SD) was 1490 ± 995 mg in patients with OSA and in patients without OSA was 1274 ± 926 mg, the difference did not reach statistical significance.

GH mean ± SD in patients without OSA was 5.67 ± 6.47 ng/ml and 5.08 ± 6.3 ng/ml in patients with OSA and the difference did not reach statistical significance.

IGF-1 mean ± SD in patients without OSA was (487 ± 210) ng/ml and (549 ± 231) ng/ml in patients with OSA and the difference did not reach statistical significance.

Epworth scale (Ep.s) is 15.6 in those with OSA and 5 in those without OSA, the difference is highly significant statistically ($P = 0.001$), as shown in Figure 3.

STOP-Bang score is almost more than double in those with OSA (5 vs. 2) and the difference is highly significant from the statistical point of view ($P = 0.001$), as shown in Figure 4.

BNP in patients with OSA has a mean of 890.66 pg/ml while the mean drops to 355.33 pg/ml in those without OSA the difference is highly significant ($P = 0.001$), as shown in Figure 5.

The results in Table 3 indicated that females with OSA and without OSA have higher mean body mass indices compared to males (34.08 vs. 32.55 kg/m^2, respectively) while males without OSA have a BMI of 27.83 kg/m^2 and those with OSA have a BMI of 31.71 kg/m^2, the difference in BMI is found to be statistically significant, when females and males without OSA are compared with each other, the difference in BMI is highly significant in favor of females ($P = 0.008$), however, in the presence of OSA, the difference in BMI between males and females did not reach statistical significance ($P = 0.065$).

The disease duration and cumulative dose of octreotide (C.D.) show no significant difference if males and females were compared with each other irrespective of having or not having OSA. Sex has no impact on the value of both GH and IGF-1 where the difference did not reach statistical significance between males and females in both groups (with and without OSA).

Epworth scale and STOP-Bang have been found to be higher in males than females in patients with OSA and the difference is highly significant ($P = 0.001, 0.03$, respectively). Sex has its impact on BNP levels thus females have higher levels

Epworth Sleepiness Scale				
Scale 0= No chance of dozing 1= Slight chance of dozing 2= Moderate chance of dozing 3=High chance of dozing				
How often do you doze?				
Sitting and reading	**0**	**1**	**2**	**3**
Watching television	**0**	**1**	**2**	**3**
Sitting in a public inactive place	**0**	**1**	**2**	**3**
Riding in a car for one hour without a break (as a passenger)	**0**	**1**	**2**	**3**
Lying down in the afternoon when circumstance permit	**0**	**1**	**2**	**3**
Sitting and talking to someone	**0**	**1**	**2**	**3**
Sitting quietly after lunch , without alcohol	**0**	**1**	**2**	**3**
Stopped in traffic for a few minutes	**0**	**1**	**2**	**3**
Total				

Figure 1: Epworth sleepiness scale[9]

STOP BANG screening tool for obstructive sleep apnea	
S	Snoring ? yes or no
T	Tiredness ? yes or no
O	Observed apnea ? yes or no
P	High blood pressure ? yes or no
B	Body mass index >35 kg/m^2 ? yes or no
A	Age >50 years ? yes or no
N	Neck circumference >40 cm ? yes or no
G	Male gender ? yes or no
Scoring : 0-3	Low risk

Figure 2: STOP-BANG questionnaire[10]

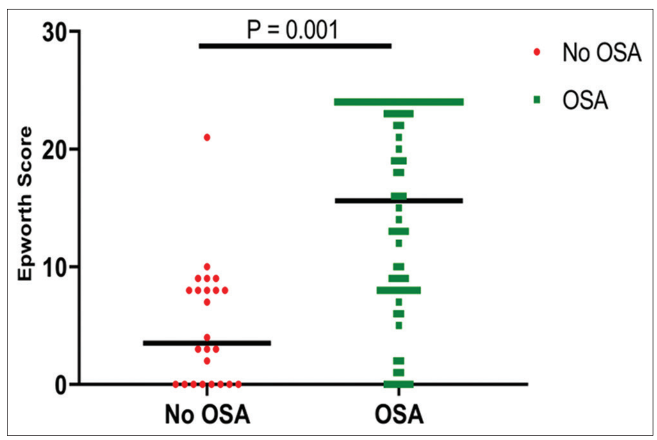

Figure 3: Epworth sleepiness scale distribution of patients with acromegaly with and without obstructive sleep apnea. OSA: Obstructive sleep apnea

compared to males (905.54 vs. 878.76) pg/ml but this sex difference of BNP in patients with acromegaly did not reach statistical significance irrespective of having or not having OSA ($P = 0.564, 0.12$, respectively).

Discussion

In this study, OSA is less common in females with acromegaly than males, which is in harmony with other studies that demonstrated that this is probably due to their airway mechanics plus the protective role of estradiol and progesterone. In addition, the increased prevalence of OSA in males is probably related to insulin resistance that may culminate in beta cell dysfunction, the story may be worsened by the marked increase in visceral fat, while in females, the bulk of stored fat was in the subcutaneous tissue in agreement with other studies conducted by Martins and Conde and Zhou *et al*.,[11,12] respectively. Other study revealed that at all ages, OSA is more common in men than women, but the prevalence increases throughout life in both sexes.[13]

This study revealed that having OSA is found to increase with age, it can be explained by fat deposition and changes in pharyngeal muscles plus a reduction in lean mass thus the chance of OSA may reach 25%–40% in the elderly that is in line with a study conducted by Silva *et al*. in population-based study.[14] Franklin *et al*. sought to determine the prevalence of OSA in women in the general population and found that up to 50% of women between the ages of 20 and 70 had OSA.[15] Schiza and Bouloukaki mentioned that the difference in prevalence between men and women narrows in older individuals (> age 50) due to the increased prevalence of OSA in women after menopause.[16]

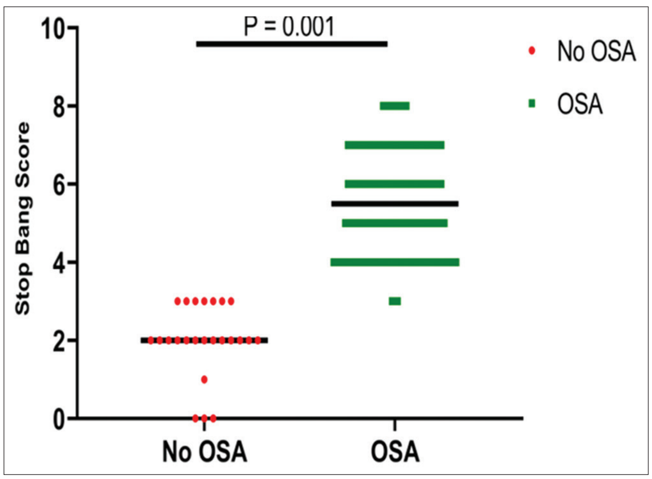

Figure 4: STOP-BANG score distribution of patients with acromegaly with and without obstructive sleep apnea. OSA: Obstructive sleep apnea

The results of this study showed that having macroadenoma increases the chance of having OSA as well as a prolonged duration of acromegaly. Obesity has an impact on having OSA due to its anatomical/mechanical effect and its effect on metabolic dysfunction which is in agreement with a study by Bonsignore *et al*.[17]

Our study revealed that GH and IGF-1 levels have no impact on having OSA, the physiological basis of the action of GH and IGF-1 on OSA is still not clear. From another view, both GH and IGF-1 may play a role in augmenting central sleep apnea by acting on the respiratory centers and they may have a direct effect on the airways thus causing bronchoconstriction or worsening of prognathism and macroglossia, the explanation is supported by other researchers.[18] Other study conducted by Galerneau *et al*. demonstrated that low IGF-1 levels could be considered a biomarker of OSA severity toward cardiometabolic health, being specifically related to OSA and associated with an increased cardiometabolic risk.[19]

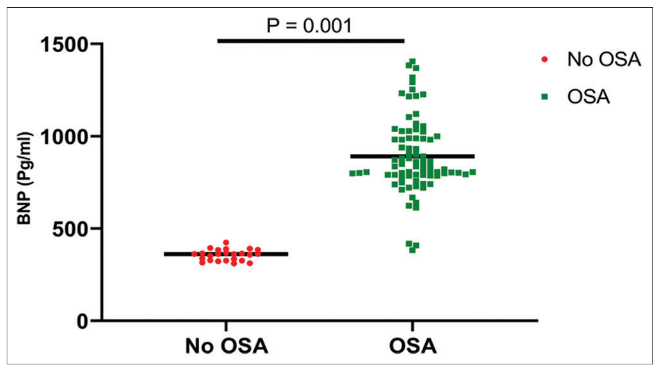

Figure 5: Brain natriuretic peptide distribution of patients with acromegaly with and without obstructive sleep apnea. BNP: Brain natriuretic peptide, OSA: Obstructive sleep apnea

Table 3: Age, body mass index, duration, cumulative dose, growth hormone, insulin-like growth factor-1, Epworth Scale, STOP-Bang score, and brain natriuretic peptide in patients with acromegaly according to their sex with and without obstructive sleep apnea

Parameters	No OSA		*P*	OSA		*P*
	Female, mean±SD	Male, mean±SD		Female, mean±SD	Male, mean±SD	
Age (years)	46±13	46±14	0.968	53±13	52±10	0.717
BMI (kg/m^2)	32.55±4.25	27.83±3.28	0.008*	34.08±6.74	31.71±4.57	0.065
Duration (years)	7±3	7±4	0.923	11±6	10±8	0.489
CD (mg/mL)	1191±687	1388±1218	0.618	1447±914	1525±1065	0.726
GH (ng/mL)	7.02±7.24	3.78±4.94	0.234	5.82±6.92	4.48±5.77	0.346
IGF-1 (ng/mL)	520±194	441±234	0.380	505±210	584±243	0.130
Ep.s	4.1±3.6	6.3±6.7	0.302	12.6±6.4	19.3±9.0	0.001*
Stop	2±1	2±0	0.386	5±1	6±1	0.03*
BNP (pg/mL)	363.45±29.46	343.98±28.56	0.120	905.54±247.32	878.76±167.03	0.564

*Significant difference between proportions using independent Student's *t*-test at 0.05 level. BMI: Body mass index, GH: Growth hormone, IGF-1: Insulin-like growth factor-1, EP.s: Epworth Scale, Stop: STOP-Bang score, BNP: Brain natriuretic peptide, SD: Standard deviation, OSA: Obstructive sleep apnea, CD: Cumulative dose

The study results showed that patients with OSA have higher BNP, thus this molecule may be useful in discriminating cardiac from pulmonary dyspnea. Such discrimination requires other investigations such as cardiac MRI which are a bit expensive and not easily affordable. The diagnosis of dyspnea in the emergency department is regarded as a challenge for health-care providers, the discrimination of cardiac and pulmonary dyspnea may be achieved by measuring BNP. These results are supported by other studies which indicate that when the after load rises it results in stretching of the left ventricle thus resulting in augmented secretion of atrial natriuretic peptide (ANP) from the atria and BNP from ventricles. Those two molecules result in vasodilation, diuresis, and natriuresis, and finally, in blood pressure reduction.[20] A high BNP level is found to be a predictor of poor cardiovascular (CV) outcomes such as fatal and nonfatal myocardial infractions in patients with acromegaly. In addition, hypophysectomy was found to be very useful in improving the CV outcome in comparison with those patients treated by medical therapy or radiotherapy or both modalities of treatment.[21] The poor CV outcome of patients with acromegaly versus nonacromegaly counterparts can be attributed to excess epicardial fat, high adiponectin, and BNP.[22] The level of BNP varies with sex, being higher among females, the cause of such elevation is not known yet, but it has been hypothesized that the cause of such increment is attributed to female sex hormones, BNP is low among males, and such decrement was attributed to the action of testosterone which lower BNP and increase neprilysin.[23] Estrogen is known to increase BNP gene expression and this may explain the higher level of BNP in females. Other researchers have found that estrogen can augment the level of neprilysin, BNP, and ANP have been found to be increased by hormone replacement therapy, and free testosterone was found to increase lean body mass thus indirectly decreasing BNP.[24] BNP emerges not just as a marker of heart failure but as a crucial biomarker reflecting the cardiac consequences of hormonal excess in acromegaly.[25] A 3-month prospective study investigating short-term cardiac effects of treatment in acromegalic patients. Cardiac function was evaluated by the gold standard method CMRI and circulating levels of B-type natriuretic peptides (BNP and NT-proBNP) found that increased levels of BNP and NT-proBNP suggesting an initial decrease in cardiac function.[26]

Conclusions

- The STOP-Bang score is twice as high in patients with acromegaly and OSA than in those without OSA
- Epworth Sleepiness Scale is high among OSA patient's versus those without OSA, however, this has been preplanned on enrollment
- Males were found to be more prone to OSA
- The risk of developing OSA increases with age, longer duration of acromegaly, and increased BMI
- Having macroadenoma was found to increase the chance of OSA
- BNP levels were found to be high among patients with acromegaly which is accompanied by OSA.

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Conflicts of interest

There are no conflicts of interest.

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