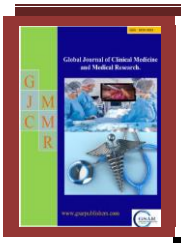

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Hypertension in Acromegaly Patients

By

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Abstract

factor. This condition, which affects approximately 60-90 patients per million, predisposes patients to numerous cardiac complications. It is imperative to add clinical knowledge and experiences regarding this patient group to the literature. We aimed to examine HT, the most common cardiac involvement, in our cohort of acromegaly patients.

Methods: *The data of 121 acromegaly patients were retrospectively analyzed. To confirm the presence of hypertension, repeated diagnoses of hypertension in hospital records, blood pressure values exceeding 140/90 mmHg on at least two consecutive visits, or the use of antihypertensive medication were required.*

Results: *HT was detected in 32 patients(26.44%). When comparing patients with and without hypertension, there were no differences in gender, body mass index, smoking status, family history of HT, duration of acromegaly, chiasm compression, or GH and IGF-1 levels at diagnosis. However, patients with HT were found to be older (p=0.025). Multivariate analysis, including age, gender, estimated duration of acromegaly, and GH and IGF-1 levels at diagnosis, showed that age was the only predictor of HT in acromegaly (OR=1.05; 95% CI, 1.01-1.10; p=0.007).*

Conclusion: *The key findings are: (1) age is a significant predictor of HT in acromegaly,(2) there is no clinically significant relationship between elevated IGF-1 levels and the incidence of HT, and (3) there is no relationship between family history of HT and chiasm compression and the presence of HT at the time of acromegaly diagnosis.*

1. INTRODUCTION.

Acromegaly, characterized by the excessive secretion of growth hormone (GH) from a pituitary adenoma, leads to elevated levels of GH and insulin-like growth factor-1 (IGF-1). While associated with various comorbid conditions and complications, its most striking effects are observed on the cardiovascular (CV) system[1,2]. The most common CV complication in acromegaly is hypertension (HT). Although the prognostic role of HT in acromegaly patients is not fully elucidated[3-7], it is known that uncontrolled HT has a detrimental impact on acromegalic cardiomyopathy[8-10] Numerous studies over the past 15 years have reported the prevalence of HT in the acromegaly population to range from 11% to 54.7% [3,4,6,13-23]. In addition to classical risk factors influencing the prevalence of HT (age, body mass index, genetic predisposition, environmental factors, sedentary lifestyle, excessive salt intake), the duration of acromegaly has also been highlighted as significant[24,25]. Various studies examining the relationship between GH and IGF-1 and the severity of HT have reported conflicting results[6,24,26]. Given that CV diseases are the leading cause of mortality in acromegaly[2,4,11,12], combating CV diseases and risk factors in this patient group is of paramount importance. Therefore, we aimed to investigate HT, the most common CV pathology in acromegaly, in this patient population.

2. Methods

Data from 121 acromegaly patients followed up at the Department of Internal Medicine, Division of Endocrinology, Eskişehir Osmangazi University between 1980 and 2018 were retrospectively analyzed. Patient data were obtained from medical records using the International Classification of Disease (ICD) diagnosis codes. To confirm the presence of hypertension, repeated diagnoses of hypertension in hospital records, blood pressure values exceeding 140/90 mmHg on at

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least two consecutive visits, or the use of antihypertensive medication were required. Our study was conducted in accordance with the World Medical Association Declaration of Helsinki and received ethical approval from the Non-Interventional Clinical Research Ethics Committee of Eskişehir Osmangazi University (decision number 02, dated 18/09/2018).

Statistical Analysis

Descriptive statistics of the evaluation results are presented as number and percentage (n, %) for categorical variables, and mean and standard deviation (SD) for numerical variables. Chi-square test and proportions t-test were applied for categorical variables. Frequency and percentage were displayed. Spearman correlation analysis was used to test the relationships between variables. Statistical analyses were performed using IBM SPSS Statistics 20.0 (SPSS Inc, Chicago, Illinois). A p-value of <0.05 was considered statistically significant.

3. Results

By the year 2018, a total of 121 acromegaly patients had been followed up and documented at the Department of Internal Medicine, Division of Endocrinology, Eskişehir Osmangazi University. Information was obtained by reviewing patient files and the hospital management system.

The gender distribution of the patients was determined to be 56 (46.3%) females and 65 (53.7%) males (p=0.467). It was found that 20 (16.7%) of the cases had microadenomas, 52 (43.3%) had macroadenomas, and 48 (40%) had invasive macroadenomas. Among the macroadenomas, 4 (3.3%) were identified as giant adenomas. At diagnosis, a significant positive correlation was found between adenoma size and GH and IGF-1 levels (r=0.332, p=0.003, and r=0.360, p<0.001, respectively). Chiasm compression was observed in 52 patients, and a relationship was found between adenoma size and chiasm compression (p<0.001).

HT was detected in 32 patients (26.44%). When comparing patients with and without hypertension, there were no differences in gender, body mass index, smoking status, family history of HT, duration of acromegaly, chiasm compression, or GH and IGF-1 levels at diagnosis. However, patients with HT were found to be older (p=0.025) (Table 1).

Multivariate analysis, including age, gender, estimated duration of acromegaly, and GH and IGF-1 levels at diagnosis, showed that only age was a predictor of HT in acromegaly (OR=1.05; 95% CI, 1.01-1.10; p=0.007) (Table 2). Among the patients with HT, 4 were on a combination of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACE/ARB), calcium channel blocker (CCB), and thiazide. Nine patients were on a combination of ACE/ARB and thiazide, 18 patients on CCB, and 1 patient on beta-blocker therapy. No cases of resistant HT, characterized by repeated high blood pressure values at follow-up visits, were encountered among the patients with HT.

4. Discussion

In our study, we aimed to retrospectively demonstrate the cause, clinical course, and response to treatment of HT in acromegaly patients. Our results indicated that HT in the acromegaly patient group does not differ in cause, clinical course, and treatment response from HT cases in the general population. The key findings of this study are: (1) age is a significant predictor of HT in acromegaly patients, (2) there is no clinically significant relationship between elevated IGF-1 levels and the incidence of HT, and (3) there is no relationship between family history of HT and chiasm compression and the presence of HT at the time of acromegaly diagnosis.

The prevalence of HT in the acromegaly population has been reported at various rates in different studies[3,4,6,13-23]. In our study, this rate was found to be 26.44%, which is close to the average of previous studies (Table 3). We believe that the variability in prevalence among studies is due to differences in HT diagnostic methods, lifestyle, and dietary habits of the population.

Although many studies have shown that HT is more common in acromegaly than in the general population, its pathogenesis is not fully elucidated. However, various hypotheses have been investigated. The primary etiologic causes accepted in studies are volume overload due to GH/IGF1 excess, increased peripheral vascular resistance and sleep apnea[27]. While volume overload due to atrial natriuretic peptide (ANP) inhibition by high IGF-1 levels is considered one of the main causes of HT pathogenesis, some studies have reported that high IGF-1 levels are not associated with HT and even that its deficiency might lead to HT [28,29]. In our study, when comparing patients with HT to those with normal blood pressure, we found that the HT group was significantly older. This finding aligns with the observation that HT becomes more common with increasing age in individuals without acromegaly. Although values such as family history of HT and IGF-1 levels were numerically higher in the HT group, they did not reach clinical significance. Multivariate analysis in our study showed that only age was a predictor of HT in acromegaly (OR=1.05; 95% CI, 1.01-1.10; p=0.007). We found that elevated IGF-1 levels did not predict HT. Costenaro et al. [30] demonstrated that uncontrolled HT was more frequent in patients with uncontrolled IGF-1 levels compared to the control group. Sardella et al. [31] found that age and body mass index correlated with HT in the acromegaly patient population, while IGF-1 did not. Data on the correlation of family history of HT and gender with the incidence of HT are also conflicting. The common finding across studies is that age is the most significant predictor of HT [24].

There is no definitive information regarding the choice of antihypertensive agents in treating HT in the acromegaly patient group. However, from a pathogenetic perspective, selecting vasodilatory agents that are more effective on peripheral vascular resistance may be more beneficial. While RAAS blockade is often the first choice, studies have not shown increased RAAS activation in patients without HT [32].

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In our study, 22 patients were using CCBs. A review of the literature did not reveal information on the prevalence of resistant HT in the acromegaly population. As previously mentioned, resistant HT was not observed in our cases.

Given that cardiac complications are highly prevalent in acromegaly patients[33,34], careful physical examination, blood pressure measurement, echocardiography, and ECG should be meticulously conducted and interpreted in this patient group. Since HT is the most common cardiac complication, we believe that in addition to in-hospital and office blood pressure measurements, home blood pressure measurement, and if necessary, 24-hour ambulatory blood pressure monitoring should be implemented. It is well-known that a significant portion of the general HT population has uncontrolled blood pressure despite treatment. We believe that the achieved blood pressure control in our HT cases is due to close follow-up and high medication adherence related to the primary disease.

5. Conclusion

The most important limitations of our study are the retrospective nature of data collection and the small number of HT cases. Given that our center includes acromegaly patients from surrounding cities, we consider this number to be the maximum we can reach. There is a need for multicenter prospective clinical studies to investigate the presence, clinical course, and treatment response of HT in the acromegaly patient group in more detail and with a larger number of cases.

TABLE 1. Comparison between hypertensive and normotensive patients.

	Hypertensive	*Normotensive*	*P value*
No. of subjects	32	89	
Woman/man	16/16	40/49	
Age	56±4.2	40±7.8	0.025
BMI, kg/m^2	25.48±2.17	25.01±2,37	NS
Family history for HT (%)	28.1	26.9	NS
Smoking, n/%	18.7	19.1	NS
Estimated disease duration (years)	6.09±4.41	6.09±5.33	NS
Chiasm compression(%)	%37	%43	NS
Serum GH levels (µg/l) (at diagnosis)	21.9±17.4	20.61±21.07	NS
Serum IGF-1 levels (µg/l) (at diagnosis)	969.2±962.4	851.7±690.3	NS

Abbreviations; BMI-body mass index, HT- hypertension, GH-growth hormone, IGF-1- insulin-like growth factor.

TABLE 2. Probable predictors of hypertension in acromegaly.

	OR	*95% CI*	*P value*
Age	1.05	1.01-1.10	0.007
Male sex	1.41	0.5-3.97	NS
Estimated disease duration	0.98	0.88-1.09	NS
Serum GH at diagnosis	1.0	0.98-1.03	NS
Serum IGF-1 at diagnosis	1.0	1.0-1.01	NS

Abbreviations; GH- growth hormone, IGF-1- insulin-like growth factor.

TABLE 3. Prevalance of hypertension in acromegaly in literature.

References	*No. cases*	*Prevalance (%)*	*Measurement*
Nabarro et al. (1987)[17]	256	30.5	Clinical
Rodrigues et al. (1989)[25]	34	26	Clinical
Kraatz et al. (1990)[24]	158	31.6	Clinical
Molitch (1992)[26]	639	23	Clinical
Ezzat et al. (1994)[23]	500	51	Clinical
Ohtsuka et al. (1995)[22]	64	37.5	Clinical
Lopez-Velasco et al. (1997)[15]	39	33.3	Clinical
Minniti et al. (1998)[21]	40	42.5	Clinical
Minniti et al. (1998)[21]	40	17.5*	ABPM
Terzolo et al. (1999)[29]	16	31.2*	ABPM
Colao et al. (2000)[16]	130	35.4	Clinical
Fukuda et al. (2001)[20]	65	38	Clinical
Jaffrain-Rea et al. (2001)[18]	68	51.5	Clinical
Jaffrain-Rea et al. (2001)[18]	68	47**	ABPM
Otsuki et al. (2001)[28]	21	21	Clinical
Pietrobelli et al. (2001)[19]	25	56	Clinical
Pietrobelli et al. (2001)[19]	25	40*	ABPM
Weiss et al. (2000)[27]	55	38.2	Clinical

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Colao et al. (2005)	200	46	Clinical
Isgandarov et al. (this study)	121	26.4	Clinical

ABPM, 24-h ambulatory blood pressure monitoring.

*Evaluated on the basis of mean 24-h blood pressure (BP) exceeding 136/84 mmHg.

**Evaluated on the basis of diurnal hypertension: systolic BP > 135 mmHg and/or diastolic BP > 85 mmHg.

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Authors' contribution: K.I: Conceptualization, writing, original draft, review, and editing; D.KI: original draft, review and editing.

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