CLINICAL STUDY

THE EFFECT OF ACROMEGALY ON OLFACTORY FUNCTIONS

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SUMMARY

Objective: The aim of this study is to compare the olfactory functions of patients with active acromegaly and patients in biochemical remission.

Meterials and Methods: The study was conducted by forming 2 groups of patients diagnosed with acromegaly and a control group. Group 1 consisted of active acromegaly patients. Group 2 included patients who were determined to have biochemical remission. Group 3 were healthy volunteers. The olfactory functions were evaluated with the Brief Smell Identification Test(BSIT).

Results: A total of 69 patients were included in the study. The median value of blood insulin-like growth factor 1 (IGF-1) in Group 1 was statistically significantly higher than in Group 2(p <0.001). A statistically significant difference was found between the groups in respect of the BSIT scores(p <0.001). BSIT scores in Group 1 were observed to be significantly lower than both Group 2 and Group 3 (p = 0.001). There was no significant difference between Group 2 and Group 3(p = 1.000). A negative correlation was determined between the BSIT scores and IGF-1 values in Group 1(r = -0.983, p <0.001), (r = -0.629, p <0.01).

Conclusions: Active acromegaly causes a decrease in olfactory functions compared to the patients in biochemical remission and this function loss is negatively correlated with IGF-1 levels.

Keywords: Acromegaly, growth hormone, olfactory mucosa, smell

AKROMEGALİNİN KOKU FONKSİYONLARI ÜZERİNE ETKİSİ

ÖZET

Amaç: Bu çalışmanın amacı, aktif akromegali hastaları ile biyokimyasal remisyondaki hastaların koku alma fonksiyonlarını karşılaştırmaktır.

Yöntem ve Gereçler: Çalışma, akromegali tanısı almış 2 hasta grubu ve bir kontrol grubu oluşturularak gerçekleştirildi. Grup 1 aktif akromegali hastalarından oluşuyordu. Grup 2'de biyokimyasal remisyon olduğu belirlenen hastalar yer aldı. Grup 3 sağlıklı gönüllülerden oluşmaktaydı. Koku alma fonksiyonları Brief Smell Identification Test (BSIT) ile değerlendirildi.

Bulgular: Çalışmaya toplam 69 hasta dahil edildi. Grup 1'de kan insülin benzeri büyüme faktörü 1'in (IGF-1) medyan değeri, Grup 2'ye göre istatistiksel olarak anlamlı derecede yüksekti (p <0,001). BSIT skorları açısından gruplar arasında anlamlı fark bulundu (p <0,001). Grup 1'deki BSIT skorlarının, hem Grup 2, hem de Grup 3'den anlamlı düzeyde düşük olduğu görüldü (p = 0,001). Grup 2 ile Grup 3 arasında anlamlı fark yoktu (p = 1.000). Ayrıca, BSIT skorları ile IGF-1 değerleri arasında negatif korelasyon saptandı (r = -0.983, p <0.001), (r = -0.629, p <0.01).

Sonuç: Aktif akromegalili hastaların, biyokimyasal remisyondakilere göre koku alma fonksiyonlarında azalma mevcuttur ve bu fonksiyon kaybı IGF-1 seviyeleri ile negatif korelasyon gösterir.

Anahtar Sözcükler: Akromegali, büyüme hormonu, olfaktör mukoza, koku

INTRODUCTION

Acromegaly is an endocrine disease that can affect the soft tissue and bone tissue and cause somatic deformities in the face and extremities as a result of excessive and continuous growth hormone (GH) secretion [1,2]. Although the prevalence has been reported to be 4-7 per 100.000, new data show a higher rate [3]. The age of diagnosis is 40-45 years, and the average time to diagnosis has been reported to be 7-10 years from the onset of the disease. Benign pituitary adenoma causes 98% of cases.

Systemic clinical signs of acromegaly are due to the effects of both GH and insulin-like growth factor 1 (IGF-1) on peripheral tissue [2,4,5]. Increases in the number of gloves, hats, and shoes, and dental malocclusion due to growth in the skull, mandibular growth and frontal prominence are the most common findings of the disease [4,5]. The effects of the disease in the

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craniofacial region generally occur due to the mucosal and soft tissue hypertrophy of the nose, uvula and parapharyngeal region, and the increase in tongue size in particular causes obstruction in the upper respiratory tract [6,8].

In order to smell, the odor molecules must be transported to the olfactory mucosa and dissolve in this mucosa to reach the olfactory receptor. Olfactory receptors are distributed in the superior cleft between the middle and upper conchas and the septum in the nasal cavity [9]. It is thought that the air to the olfactory cleft passes through the medial or anterior of the middle turbinate. Mucosal edema, hypertrophy, polyp, tumor or nasal bone deformities in this region may cause loss of olfactory function by causing a nasal obstruction [10]. In a similar way, nasal mucosal hypertrophy and associated nasal obstruction seen in patients with acromegaly are thought to affect olfactory functions. However, there is no study in the literature comparing the olfactory functions of patients with active acromegaly and patients with biochemical remission. Therefore, the aim of this study is to compare the olfactory functions of patients with active acromegaly and patients in biochemical remission and to evaluate the results.

MATERIAL and METHODS

Study design

This prospective study was carried out between October 2018 and December 2019 at the Ankara Training and Research Hospital with the approval of the Clinical Research Ethics Committee of the hospital (protocol no:20/2019). The study was conducted in the Endocrinology and Metabolic Diseases clinic by forming 2 groups of patients with pituitary adenomas diagnosed with acromegaly and a control group.

Group 1 consisted of active acromegaly patients with high GH and IGF-1 values. 14 patients in Group 1 were diagnosed in the last 1 month and none of them received treatment. Transsphenoidal pituitary surgery was applied to 6 patients in Group 1, but it was found that remission could not be achieved after surgery. Group 2 consisted of patients who were previously diagnosed with acromegaly, had transsphenoidal pituitary surgery more than 1 year ago, and determined to have biochemical remission according to their GH and IGF 1 levels. Group 3 were healthy volunteers.

Patients were excluded if they had nasal cavity pathologies such as nasal septum deviation, nasal polyp, concha bullosa, had maxillofacial trauma, had a history of smoking or had undergone nasal surgery other than transsphenoidal pituitary surgery, or if they had acromegaly without a pituitary adenoma.

In all cases, IGF-1 values were analyzed from blood samples at the beginning of the study. The blood IGF-I normal range was accepted in our laboratory as 87-252 ng/Ml and high values were accepted according to reference values determined by age and gender.

Detailed otolaryngological examinations (anterior rhinoscopy and nasal endoscopic examination) of all patients were performed by the same ear, nose and throat (ENT) doctor in the ENT clinic. The Brief Smell Identification test (BSIT) was used, which is an easy to carry, store and apply test, consisting of 12 odorants, with proven reliability and validity [11,12].

The patients were asked to identify 12 different odors that were exposed by scraping the BSIT scent strips. After each strip was scraped, the strip was sniffed for an average of 1 minute and was noted on the basis of the scent it defined first. The test was completed in 67 minutes, with a 5-minute rest interval between 2 scent strips. Scoring was applied according to the patient's answers as 1 point for each odor recognised.

The research was carried out in accordance with the principles of the Helsinki Declaration. Informed voluntary consent for participation in the study was obtained from all the participants.

Statistical analysis

Data obtained in the study were analyzed statistically using SPSS® v20.0 software (SPSS Inc., Chicago, USA). In the descriptive statistics, continuous data were stated as mean±standard deviation, median, minimum, and maximum values and discrete data were given as number and percentage. The conformity of the data to normal distribution was examined with the Shapiro-Wilk test. Kruskal Wallis Variance Analysis was used to examine the differences in data not conforming to normal distribution in 3 groups. The Mann Whitney U test was used to compare the difference of IGF-1 values in acromegaly patient groups. The Spearman correlation coefficient was used to determine the relationship between BSIT scores and IGF-1 values. A value of $p < 0.05$ was accepted as statistically significant.

RESULTS

Evaluation was made of a total of 69 patients who met the study criteria. Group 1 comprised 20 patients (55% female, 45% male) with an average age of 45.7 ± 10.5 years (range, 20-64 years), Group 2 comprised 24 patients (62.5% female, 37.5% male) with an average age of 46.8 ± 12 years (range, 26-68 years) and Group 3, the control group, was formed of 25 patients (60% female, 40% male) with an average age of 46.2 ± 9.1 years (range, 26-60 years). No statistically significant difference was determined between the groups in terms of age and gender distribution ($p > 0.05$) (Table 1).

The median values of blood IGF-1 were 812.5ng / ml (326-1625) in Group 1 and 91.5 ng / ml (10-270) in Group 2. The IGF-1 values in Group 1 were statistically significantly higher than those of Group 2 ($p < 0.001$) (Table 2).

The median values of the smell test scores were determined as 7 (4-11) in Group 1, 10 (6-12) in Group 2, and 10 (7-12) in Group 3. A statistically significant difference was determined between the groups in respect of the smell test scores ($p < 0.001$). Multiple comparisons showed a statistically significant difference between Group 1 and Group 2 ($p = 0.001$), between Group 1 and Group 3 ($p = 0.001$), and no significant difference between Group 2 and Group 3 ($p = 1.000$) (Table 3).

A negative correlation was found between the smell test scores and IGF-1 values ($r = -0.983$, $p < 0.001$), ($r = -0.629$, $p < 0.01$) (Table 4). In Group 1, which included patients with high blood IGF-1 values, it was observed that BSIT scores decreased as IGF -1 values increased.

Table 1: Age and gender distribution of groups

	Female		Male		Test Statistics p*	Age	Test Statistics p**
	n	%	n	%		mean±SD	
Group 1	11	55	9	45	$\chi^2=0.260$	45.70±10.52	F=0.063
Group 2	15	62.5	9	37.5	0.878	46.83±12.01	0.939
Group 3	15	60	10	40		46.20±9.14	

* Chi-square test, **Anova SD: standard deviation

Table 2: Comparison of blood IGF-1 values of group 1 and group 2

	Blood IGF-1 values		Test	
	Mean±SD	Median (Min-Max)	Statistics	p*
Group 1	913.55±426.27	812.5 (326-1625)	U=0.001	0.001
Group 2	122.33±84.26	91.5 (10-270)		

*Mann Whitney U Test

Table 3: Comparison of scent scores amoung three groups

	Smell test scores		Test	
	Mean±SD	Median (Min-Max)	Statistics	p*
Group 1	6.90±1.97	7 (4-11)		
Group 2	9.37±1.81	10 (6-12)	KW=21.000	0.001
Group 3	9.72±1,27	10 (7-12)		

* Kruskal Wallis Variance Analysis

Table 4: Correlation between group 1 and group 2 smell scores and blood IGF values

Kan IGF	Smell test scores	
	r*	p
Group 1	-0.983	0.001
Group 2	-0.629	0.001

* Spearman’s Correlation Coefficient

DISCUSSION

The significant findings of this study were that i) There is a decrease in olfactory function in patients with active acromegaly compared to the patients with biochemical remission, ii) the degree of olfactory dysfunction is negatively correlated with IGF-1 levels, iii) olfactory functions are similar to the normal population in patients with biochemical remission. To the best of our knowledge, this is the first study to have revealed that patients with active acromegaly have decreased olfactory functions compared to the patients with biochemical remission.

The primary reason for the decrease in olfactory function in acromegaly patients is thought to be that mucosal hypertrophy secondary to a high IGF-1 level may affect airflow to the nasal cavity and decrease the transportation of odor molecules to olfactory receptors by causing nasal obstruction. Keyhani et al. reported that the airflow in the olfactory region was closely related to the anatomy of the nasal valve [13]. In a three-dimensional computed tomography (CT) numerical simulation study in literature, it was shown that a 1.45% decrease in airway volume in the nasal valve region may cause a 76.9% decrease in olfactory airflow [14]. These studies in the literature show the importance of nasal obstruction and airflow in the olfactory function.

Another reason for the decrease in olfactory function in acromegaly patients is thought to be that high IGF-1 may cause possible narrowing of foramina in the cribriform plate and compression of the olfactory nerve fibers and/or alteration in the olfactory nerve structure. In a previous study, the median nerve was found to be thickened with delayed nerve conduction in patients with carpal tunnel syndrome in MR examinations, and it was reported that the disease findings (thickening of the carpal ligament) were not dependent on external factors but were related to internal factors [15]. Other studies in the literature have determined that IGF-1 causes the regenerative effect in the layers of nerve tissue [16,17]. It has also been shown that the effect of IGF-1 on nerve tissue returns quickly after treatment [15].

In acromegaly disease, GH levels are related to the severity of the disease and the size of the adenoma [2]. In the clinic, GH measurements are not preferred in the diagnosis, treatment, and follow-up of acromegaly due to the pulsatile secretion of GH. Serum IGF-1 reflects the average 24-hour serum GH concentration. Therefore, IGF-I measurements are used in the clinical diagnosis and follow-up of acromegaly [18]. In the diagnosis of acromegaly, an increase in IGF-1 level is evaluated according to age and gender. In the normal population, IGF-1 values tend to increase up to the age of 15-18 years and decrease with advancing age (rising up to 366.2 ng/ml, decreasing to 99.5ng/ml [19,20]. Since it is the best predictor of disease control, it is also the main target in the treatment of acromegaly [21]. In the current study, diagnosis and follow-up of acromegaly patients was made with serum IGF-1 levels as described in the literatüre [18].

In acromegaly, disease duration and high IGF-1 value cause mucosal and soft tissue hypertrophy and can lead to congestion due to narrowing of the upper airways, problems such as breathing difficulties and sleep disturbances[2,7,22-25]. In a histopathological study of acromegaly patients, nasal mucosal hypertrophy and polyp formation were detected in 88% in the sphenoid sinus and 62% in the ethmoid sinus, although no specific signs of acromegaly disease were detected in the histopathological examination [26]. The current study is the first study in literature to show that acromegaly cause a decrease in olfactory functions. The results of this study also show that due to the negative correlation determined between IGF-1 levels and smell test scores, the increase in disease severity caused more deterioration in olfactory functions. Guo et al. reported that OSAS incidence increased due to thickening of soft tissues in patients with acromegaly, and a positive correlation was found between posterior pharyngeal soft tissue thickness and IGF-1levels [25]. The negative correlation between IGF-1 level and smell test scores in the current study suggests that there is a similar thickening in the nasal mucosa and this mucosa becomes thicker as IGF-1 level increases.

In a 2010 study by Actor et al. evaluating olfactory function before and after surgery in acromegaly patients, the olfactory functions of acromegaly patients were not compared with the active acromegaly and biochemical remission and the Sniffin sticks smell test (SST) was used as a smell test [27]. A 65% improvement in olfactory function was reported in patients with acromegaly postoperatively. In the current study, using the BSIT it was demonstrated that patients with active acromegaly had diminished olfactory function compared to the patients with biochemical remission, and in patients who had patients with biochemical remission, the olfactory function could be equal to that of the normal population. Studies have proved the reliability and validity of SST for olfactory assessment [28,29]. However, difficulties with transport, storage and application have limited the widespread use of this test compared with the University of Pennsylvania Fragrance Identification Test (UPSIT) and BSIT. Internationally, the most widely used smell test is the UPSIT, consisting of 40 different scents. To shorten the application time and ensure intercultural applicability, the BSIT is a simplified 12-item scent identification test version of the UPSIT. Many studies in the literature have used BSIT to evaluate olfactory functions [30,31]. A study in China showed that the specificity of BSIT was 64.1% and the sensitivity was 83.9% [11]. It is also known that BSIT provides a significant advantage in terms of cost and efficiency [30]. Furthermore, the short application time of 5 minutes makes this test valuable, especially in busy polyclinic conditions [12].

The most important limitation of this study is the small number of patients in the study groups. There is a need for further studies in this area with a higher number of patients.

CONCLUSION

In conclusion, active acromegaly causes a decrease in olfactory functions compared to the patients in biochemical remission and this function loss is negatively correlated with IGF-1 levels. However, patients in biochemical remission show olfactory functions similar to those of the normal population. Conflict of interest: There is no conflict of interest in this study.

ETHICAL APPROVAL:

The ethics committee approval was received from University of Health Sciences, Ankara Training and Research Hospital. (Prot No: 2019/20)

PATIENTS CONSENT:

Informed written consents were obtained from all the participants of this study.

CONFLICT OF INTEREST:

There is no conflict of interest.

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