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Original Research

Investigation of the Relationship between Adenoma Volume and Perioperative Hormone Levels in Patients with Acromegaly

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ABSTRACT

Objective: Current pituitary adenomas classifications and surgical treatment results are made only with two-dimensional radiological sections and hormonal measurements. This study investigated the relationship between hormone levels and volumetric tumor burden by measuring tumor volumes before and after surgery in patients with acromegaly.

Methods: In a retrospective clinical study, clinical and radiologically measured volumetric, hormonal and surgical results of 52 patients who were operated on with the diagnosis of acromegaly due to pituitary adenoma were examined. Radiological measurements were obtained using the ImageJ software package version 1.47 and the measure-stack plug-in. In statistical analysis, the relationship between tumor volumes, growth horomone (GH) and insulin-like growth factor (IGF-I) levels was analyzed during and after surgery.

Results: Of the 52 cases, 22 (42.3%) were male, 30 (57.7%) were female, and the mean age of the patients was 43.40±11.40 years. 45 cases (86.53%) were macroadenoma, 7 cases (13.47%) were microadenoma. All patients were operated by the transnasal-transseptal-transsphenoidal route. When the early preoperative and postoperative hormone results of the patients were compared, significant decreases were observed in GH (82.1%), volume (67%), and IGF-1 (50%) levels in the postoperative period. While there was a significant positive correlation between preoperative GH levels and tumor volumes (r: 0.516, $p<0.05$), there was also a significant positive correlation between postoperative GH levels and tumor volumes (r: 0.755, $p<0.05$). No correlation was observed between IGF-I levels and volume in the preoperative and postoperative period (r:-0.051, $p>0.05$) (r:0.259, $p>0.05$). A significant positive correlation was found between postoperative GH levels and IGF-1 levels (r: 0.303, $p<0.05$).

Conclusion: Both GH and IGF-I levels increase significantly as tumor volume increases in patients with pituitary adenoma before and after surgical treatment. Volumetric measurements may be necessary for classifying patients with acromegaly before and after surgery and in the more objective and quantitative determination of postoperative residual and/or recurrence. For this reason, we believe that it is more accurate to evaluate tumor tissues occupying a 3-dimensional volume with volumetric measurements.

Keywords: Pituitary adenoma, Acromegaly, Volume, Transsphenoidal

INTRODUCTION

Acromegaly is a rare disease often caused by pituitary tumor synthesizing growth hormone (GH) with increased circulating GH and insulin-like growth factor-1 (IGF-1) levels, somatic disorders, and systemic involvement [1-3]. Its prevalence is 40-70 per million, and its incidence is 3-4/year per million [1, 2].

In 98% of acromegaly cases, it develops due to a pituitary adenoma (somatotroph adenoma) that synthesizes GH, and these adenomas are usually benign. Somatotropic adenomas in the pituitary gland consist of sparse or dense granular cells [3, 4]. In 25% of cases, prolactin (PRL) is secreted in addition to GH, with the presence of mammosomatotroph or acidophilic stem cells [1]. Rarely, plurihormonal adenomas in which other anterior pituitary hormones [thyroid stimulating hormone (TSH), adrenocorticotropic hormone ACTH)] are secreted are seen [1]. Overt heart failure can be seen in the advanced stages of the disease in patients who remain untreated. As GH and IGF-1 levels decrease with treatment, improvement in cardiac mass and left ventricular functions is observed.

In this retrospective study, magnetic resonance imaging (MRI) and GH, IGF-1 levels of patients with acromegaly before and after transsphenoidal surgery were compared, and the relationship between pituitary adenoma volume and hormone levels was tried to be determined.

MATERIALS AND METHODS

This study included 52 patients who were operated on for acromegaly in our clinic between 2010 and 2016 and the relationship between preoperative-postoperative hormone profile and preoperative-postoperative tumor volume was investigated. In the endocrinological evaluation, all cases' anterior pituitary function data were obtained by examining preoperative and postoperative GH and IGF 1 levels. In the radiological evaluation, data on tumor volume in all cases were obtained by examining preoperative and postoperative pituitary MRIs (1.5 Tesla Dynamic Pituitary MRI cross-sectional interval 1mm) and calculating volume values with the ImageJ [5-7] computer program (Figure 1).

As a surgical procedure, the standard endonasal transsphenoidal intervention was performed in 52 patients.

Main Points;

- GH and IGF-I levels increase significantly as tumor volume increases in patients with pituitary adenoma.
- Postoperative volumetric evaluation may be important in the evaluation of postoperative residual and functional tumor remnants.
- For this reason, we believe that it is more accurate to evaluate tumor tissues occupying a 3-dimensional volume with volumetric measurements.

Statistical Analysis

The quantitative data obtained in the study were made with the SPSS statistical program (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp., our university license). When the data were evaluated in terms of homogeneity and normal distribution compatibility, it was observed that all the data obtained both preoperatively and postoperatively did not comply with the normal distribution (Kolmogorov-Smirnov test, $p<0.001$) (Table 1).

Because the data could not meet the parametric test assumptions, Wilcoxon signed-rank test (Table 2) was used for comparisons investigating within-group differences (dependent group). A bivariate correlation test (Pearson's Correlation) (Table 3) was used to determine the relationship between variables. Variable comparisons with a p-value below 0.05 in all tests were considered statistically significant.

RESULTS

Of the 52 patients included in the study, 30 (57.7%) were female, and 22 (42.3%) were male. The mean age of women was 42.10±11.53, and the mean age of men was 45.18±11.23. In the study, the preoperative tumor tissue volume measurement was 166.00±16.92 mm3, while the postoperative measurement was 55.50±10.65 mm3, and a volume decrease of 67% was detected in the postoperative period (Table 1, 2).

In the study, the preoperative GH level was 13.9±2.09 µg/L, while the postoperative level was 2.5±1.0 µg/L, and 82.1% low GH was detected in the postoperative period (Table 1, 2).

In the study, the preoperative IGF-1 level was 948±41 ng/ml, while the level was 474±42 ng/ml in the early postoperative period, and a 50% decrease in IGF-1 was detected in the postoperative period (Table 1, 2).

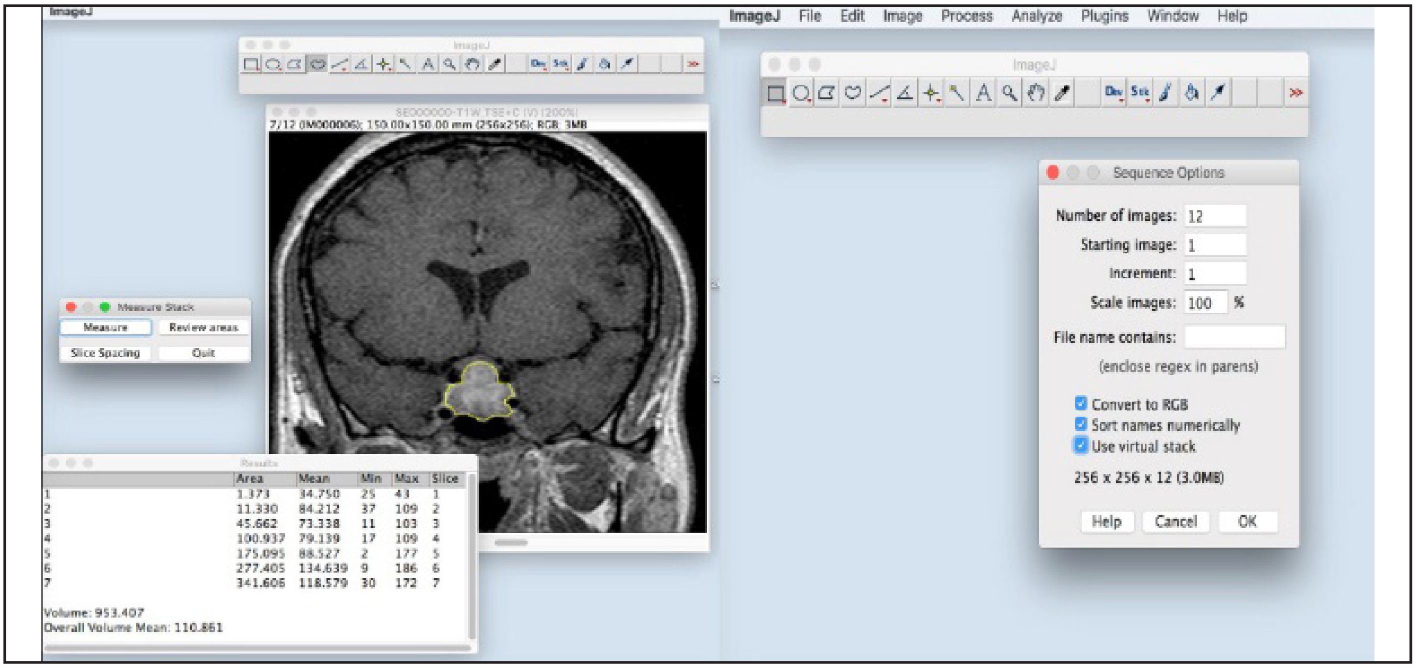

Figure 1. Volume measurement example

Table 1. The descriptive statistical results of preoperative-postoperative variables

	Preop. GH	Postop. GH	Preop. Volume	Postop. Volume	Preop. IGF-1	Postop. IGF-1
Median		2.53	166.00	55.50	948.50	474.00
Std. Error (S.E.)	2.09	1.00	16.92	10.65	41.26	42.45

Table 2. Wilcoxon signed rank test

Parameter	Median	SE	p-value*
Preop GH	13.95	2.09	
Postop GH (%82 decrease)	2.53	1.00	0.001
Preop volume	166.00	16.92	
Postop volume (%67decrease)	55.50	10.65	0.001
Preop IGF-1	948.50	41.26	
Postop IGF-1(%50 decrease)	474.00	42.45	0.001

* p value was considered as significant if less than 0.05

Table 3. The Correlation test results

Parameter-1	Parameter-2	r value	p value*
Preoperative tumor volume	Preop GH	0.516	0.001*
Preoperative tumor volume	Preop IGF-1	-0.51	0.722
Postoperative tumor volume	Postop GH	0.755	0.001*
Postoperative tumor volume	Postop IGF-1	0.259	0.064
Preoperative GH	Preop IGF-1	-0.90	0.524
Postoperative GH	Postop IGF-1	0.303	0.029*

* p value was

DISCUSSION

This study is one of the first retrospective studies investigating the effect of surgical treatment on volume and hormonal profile by measuring the tumor volume in the perioperative period before and after surgical treatment in patients with acromegaly. In this study, we investigated the relationship between volume measurements and hormone values, with the thought that adenoma volume would be more meaningful than the adenoma diameter used in previous studies and classifications [8, 9]. This is because current classifications attempt to classify a three-dimensional tumor in a two-dimensional environment. Because the fact that the classifications made by evaluating a three-dimensional structure that can show invasion and/or invagination to the surrounding structures only with coronal sections, where the sella and ICAs are best displayed, are insufficient is understood as different opinions have emerged over the years regarding these classifications and a common consensus has not been formed [8-10]. In addition, the operation's success is still evaluated with qualitative and not so objective methods, not quantitatively [11]. In this study, it is planned that these methods will play an important role in objectification and perhaps lead to an important way in terms of classification. Tumor volume assessment was performed with the help of a high-standard and high-resolution software application and software plug-in [12].

Colao et al. previously stated that tumor size increases and IGF-I levels are unrelated [13]. In this study, we also observed no relationship with IGF-1, which is consistent with this publication, but a positive relationship, or correctly put, a significant correlation between the volumetric load of the tumor and GH production, especially in the preoperative and postoperative periods. In addition, we observed a significant decrease in postoperative GH and IGF-1 in the postoperative period, which has not been reported in any study before and correlated with each other in the early postoperative period.

In many studies, volumetric evaluation of pituitary tumors has often been done using simple volume calculation formulas. For example, the volume is calculated with the Di Chiro and Nelson formula by assuming that the tumor is mainly in an approximately ellipsoid configuration. This is also not sensitive and descriptive enough [14]. Although this formula is still a reliable method for formula-based volume calculation, especially in smooth round or ellipsoid form tumors, they do not have sufficient scientific precision since they cannot be calculated by subtracting the volumetric indentations and protrusions in the volume [14]. In addition, this and similar methods are far behind today's technical possibilities, and today there are more advanced and sensitive techniques with ROI (Range of Interest) based volumetric feature. Moreover, they are better evaluated with ROI-based volumetry, especially if cavernous sinus invasion or invagination is in question [6, 15-17]. Although volume measurement programs in MR devices, which normally contain embedded software, are intended for clinical studies, they cannot be applied in daily practice because they are very time-consuming and economically expensive [18, 19].

An interesting issue in the literature is that most of the volumetric publications on the pituitary are related to schizophrenia and similar psychiatric diseases [20, 21]. Few publications are associated with a hormonal profile and are primarily growth-developmental publications [22-24]. There are very few publications on such 3-dimensional measurements in pituitary tumors [25-27]. In almost all of these three-dimensional studies published on acromegaly, except for a few related to surgery [25, 26], the relationship between medical treatment and reduction in tumor volume was investigated [28-30].

This study shows us a serious relationship between the volumetric load of the tumor and the hormonal increase, especially in terms of GH. In the current literature, schemes based on location, invasion pattern, size in two dimensions, and relations with the cavernous sinus have been used to classify pituitary tumors [31, 32]. One of the most critical issues to be discussed here is describing a structure that occupies space in three dimensions with two-dimensional criteria. Ideally, a more objective approach can be made by adding three-dimensional volume measurements to the existing classification and follow-up criteria. Thus, more meaningful decisions can be made in the follow-up of tumor tissue and preoperative planning. In addition, in cases of residual and recurrence, follow-up can be done not only on the hormonal level but also on the volumetric plan. The fact that the reduction rate in GH levels after surgery is tightly correlated with the percentage of tumors resected has a potential practical impact. For example, the success of radiotherapy and medical treatment for GH-producing tumors depends on the degree of GH elevation. This means that as the tumor burden increases, the chance of success will decrease [33, 34].

Limitations

These measurements can also be used predictively in estimating the chance of achieving a normal GH and IGF-1 level with postsurgical medical or radiation therapy. Sometimes preoperative imaging will show whether the tumor can be removed entirely with surgery. In addition, knowing the relationship between the level of decrease in postoperative GH and the volume of the tumor fraction that can be surgically removed may provide additional information on whether the patient will need additional surgery. Although hormonally activated pathology was evaluated in our study, since it is known that pituitary tumors may not always be hormonally active, this causes the limitation of the study. Considering the evaluation of the hormone profile after effective pituitary surgery, the results of our study are also valuable in this respect. In our study, radiological studies will not replace endocrinological follow-up and evaluation in postoperative follow-up, but we think that surgical evaluation with endocrinological and 3D radiological studies may provide more advantages than 2D evaluation in the evaluation of space occupancy lesions."

CONCLUSIONS

Each GH-secreting tumor appears to have a unique level of GH production per tumor mass, and this level appears to be homogeneous over its tumor mass. Although the limitation of our study is that repetitive measurements of GH and IGF-1 values in the late postoperative period are not continued, if measurements can be made in a much larger case series, characteristic curves can be drawn between tumor volume and hormone levels. Therefore, when the volume or hormone levels are known, the quantity of the other parameter can be interpreted using this characteristic curve without measuring it. Expected hormone decline levels can be estimated from the volume removed after surgery. Volume measurements can be used as additional information in disease follow-up, residual, recurrence, and classification.

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