

Improvement in Remission Rates of the First Operation in Acromegalic Patients

Akromegali Hastalarında İlk Cerrahi Tedavi Başarısındaki Artış

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ABSTRACT

AIM: The aim of the study was to determine the remission rates of the first operation with respect to the number of surgeons and the parameters important for the prediction of the success.

MATERIAL and METHODS: The study cohort consisted of 180 acromegalic patients who presented over a 29 year. All the patients had undergone transnasal transsphenoidal adenomectomy and then octreotide treatment and/or radiotherapy were applied to the patients who were not cured. Remission criteria was accepted as nadir GH<1 µg/L with oral glucose tolerance test (OGTT) and normal IGF-1 with respect to age and gender.

RESULTS: The postoperative median follow up period was 84 months (range 6-372 months). The remission rate of the first operation before 2003 was 20%, but this rate increased to 51% after 2003 (p=0.018). The most impressive improvement was due to the single experienced surgeon (49% vs. 5.3%) (p<0.001). The success of the first operation was determined by the tumor size, microadenomas were more successfully treated than macroadenomas (p=0.014). The prevalence of discordance between GH and IGF-1 was 24% in patients cured after first surgery.

CONCLUSION: The clinical recognition of acromegaly and outcomes of single experienced surgeons in specialized centers have significantly improved over the last years.

KEYWORDS: Acromegaly, Transnasal transsphenoidal adenomectomy, Microadenoma, Macroadenoma, Remission rate

ÖZ

AMAÇ: Akromegali tedavisinde ilk cerrahi tedavinin başarısını, beyin cerrahının deneyimine, sayısına ve remisyon oranlarını etkileyebilecek diğer parametrelere göre belirlemektir.

YÖNTEM ve GEREÇLER: 29 yıl süresince 180 akromegalik hasta (86 kadın, 94 erkek) değerlendirilmiştir. Tüm hastalara transnazal/transsfenoidal adenomektomi yapılmış, kür sağlanamayanlara octreotid tedavisi ve/veya radyoterapi uygulanmıştır. Remisyon kriteri olarak, IGF-1'in yaş ve cinsiyete göre normal sınırlarda olması ve Glukoz-büyüme hormonu baskılanma testinde büyüme hormonunun <1'e baskılanması kabul edilmiştir.

BULGULAR: Postoperatif ortalama (minimum-maksimum) takip süresi 84 (6-372) aydır. İlk operasyonun remisyon oranı 2003'ten önce %20 iken 2003'ten sonra %51'e yükselmiştir (p= 0,018). Oranlardaki en belirgin düzelme, tek deneyimli cerrah ile sağlanmıştır (%49 ve %5,3) (p<0,001). İlk operasyonun başarısı, tümör boyutundan etkilenmektedir. Mikroadenomlar, makroadenomlara göre ilk operasyon sonrası (p= 0,014) daha başarılı bir şekilde tedavi edilmektedir. Büyüme hormonu-IGF-1 diskordansı, ilk cerrahi sonrası kür olanlarda %24 oranında bulunmuştur.

SONUÇ: Hipofiz cerrahisinin, referans merkezlerinde tek deneyimli cerrah tarafından yapılması sıkı remisyon kriterleri kullanıldığında bile son yıllarda akromegali tedavisinde önemli gelişmeler sağlanmasına katkıda bulunmuştur.

ANAHTAR SÖZCÜKLER: Akromegali, Transnazal transsfenoidal adenomektomi, Mikroadenom, Makroadenom, Remisyon oranı

INTRODUCTION

Acromegaly is a rare disease that is due in almost all cases to a growth hormone (GH) secreting pituitary adenoma (31). Excess GH and the resultant elevations of insulin-like growth factor 1 (IGF-1), the biochemical hallmarks of the disease (19,31), produce its characteristic multisystem, physical manifestations as well as its clinically significant co-morbidities including diabetes mellitus, hypertension,

arthritis, sleep apnea and cardiovascular disease (3,32,36). When inadequately treated, acromegaly impairs patients' quality of life and leads to a 2-5 fold increase in mortality rate (4,13,36,38).

The aim of acromegaly treatment is to eliminate local and secretory effects of the tumor. Different cure criteria have been used in the treatment of acromegaly but in recent years it is generally accepted that cure of acromegaly is to achieve

serum nadir GH levels less than 1 µg/L during an oral glucose tolerance test and normal levels of plasma IGF-1 for age and gender (22). However, some evidence in healthy subjects and acromegalic patients, using highly sensitive assays, has recently suggested that the cut-off value for the nadir GH after oral glucose administration is much lower than 1 µg/L such as 0.4 µg/L (23).

Transsphenoidal surgery is currently considered as the first line treatment of choice but cure rates vary with both patient characteristics and with the surgeon's experience. Published surgical success rates are between 42% and 76%, these rates being modified by tumor size, infiltration of cavernous sinus, preoperative levels of GH and IGF-1 and experience of the surgeon (1,35). Clearly, the smaller the tumor, the more likely is the possibility of remission, and small noninvasive tumors (microadenomas) are the most favorable category of tumor for surgical remission (15,20,26,36, 37). Moreover, the basal GH level before surgical treatment predicts the outcome, with favorable results occurring in those patients with basal GH levels of less than 45 µg/L (10). One of the most important factors favoring good outcome is the experience of the surgeon and the surgical team (2,8,9,21). Studies have shown that surgeons who are actively involved on a regular basis in performance of pituitary surgical procedures achieve better outcomes (7). Patients who are not cured with neurosurgery require medical treatment and/or radiotherapy.

In this retrospective study, the medical records of acromegalic patients treated in a third stage reference endocrinology center since 1980 were analyzed to determine the remission rates of the first operation with respect to the number of surgeons and the parameters important for the prediction of the success.

MATERIAL and METHODS

The study cohort consisted of 180 acromegalic patients (86 female and 94 male) who presented over a 29 year period from January 1980 to May 2009 and followed in Ankara University, Endocrinology and Metabolic Diseases Department. Collected data include estimated data of the time from the beginning of symptoms till diagnosis, GH and IGF-1 levels at diagnosis, results of pituitary imaging, presence of cavernous sinus invasion and visual field defects, the treatment modalities and the remission rates, presence of hypopituitarism. All the patients had undergone transnasal transsphenoidal adenomectomy at least once and then octreotide treatment and/or radiotherapy were applied to the patients who were not cured. The patients were classified into three groups: Group 1: The ones operated by different surgeons at different centers before the year 2003, group 2: The ones operated by the same experienced surgeon at the single center and group 3: The ones operated by different surgeons after the year 2003.

Remission criteria was accepted as nadir GH<1 µg/L with oral glucose tolerance test (OGTT) and normal IGF-1 with respect to age and gender (22).

Patients were evaluated 1, 3 and 6 months after neurosurgery and in six months intervals afterwards with physical examination, laboratory tests of hypothalamo-hypophysial-adrenal axis and hypophysis MR was done 3 and 6 months after the operation and in 1 year intervals afterwards if remission could not be achieved or there was residual adenoma. Hypopituitarism was defined as clinical and biochemical evidence of pituitary dysfunction or requirement for hormone replacement.

Serum GH were measured with chemiluminescent enzyme immunometric assay (Diagnostic Products Corporation DPC[®], Los Angeles, CA) before 2000 and immunoradiometric assay (IRMA) (Immunotech SAS[®]; A Beckman Coulter Company, France) after 2000. IGF-1 levels were determined by radioimmunoassay (Medgenix Diagnostics SA[®], Fleurs, Belgium) and (Diagnostic Systems Laboratories DSL[®], Texas, USA) before 2000; immunoradiometric assay (IRMA) (Immunotech SAS[®]; A Beckman Coulter Company, France) after 2000. Data were reported as median (minimum-maximum). Chi square test, Kruskal-Wallis test and Mann-Whitney test were used for statistical analysis.

RESULTS

The mean age at diagnosis was 44 ± 13 years. The median time from the beginning of symptoms to the diagnosis was 24 months (range 1-120 months) before 2003 whereas it was 12 months (range 1-96 months) after 2003. The decrease was 12 months. Before the year 2003, 41 macroadenomas and 19 microadenomas were operated by different neurosurgeons in different centers, but after year 2003, 60 macroadenomas and 28 microadenomas were operated by one experienced neurosurgeon whereas 28 macroadenomas and 4 microadenomas were operated by different neurosurgeons in different centers. The postoperative median follow up period was 84 months (range 6-372 months).

The median GH level was 18.4 µg/L (range 1.6-236.8 µg/L) for macroadenomas and 12.8 µg/L (range 1.9-60 µg/L) for microadenomas preoperatively. The median IGF-1 level was 1000 µg/L (range 323-3900 µg/L) for macroadenomas and 983 µg/L (range 150-4500 µg/L) for microadenomas preoperatively.

The frequency of invasive macroadenomas was 27% (11/41) before 2003 and 40% (35/88) after 2003.

The remission rate of the first operation before 2003 was 20% (4% for macroadenomas, 27% for microadenomas), but this rate increased to 51% after 2003 and this increase was statistically significant (p=0.018). After the year 2003, the success of the first operation done in the same center by the same experienced neurosurgeon (49%) was much more higher than the first operation done in different centers by different neurosurgeons (5.3%) (p<0.001). Remission rates with respect to the adenoma size, the time of operation and the number of surgeons were given in Table I.

Before 2003, 51% (21/41) of the macroadenomas and 37% (9/19) of the microadenomas undergone second surgery; 12% (5/41) of the macroadenomas and 11% (2/19) of the

Table I: Remission Rates of Operations with Respect to the Adenoma Size, the Time of Operation and the Number of Surgeons

Adenoma size	# of operation	Remission rates		
		Before 2003	After 2003	After 2003
			>3 surgeon	Single surgeon
Macroadenoma (n=129)	1st operation (n=129)	4% (n=41)	12.5% (n=28)	47% (n=60)
	2nd operation (n=48)	8% (n=21)	0% (n=9)	10% (n=18)
Microadenoma (n=51)	1st operation (n=51)	27% (n=19)	0% (n=4)	50% (n=28)
	2nd operation (n=9)	25%	-	-

microadenomas undergone third operation. After 2003, 30% (18/60) of the macroadenomas operated by the single experienced surgeon undergone second surgery; 32% (9/28) of the macroadenomas operated by different surgeons at different centers undergone second surgery, one of those patients operated for the third time.

Octreotide treatment of a mean 20 mg was given to the patients for a median period of 24 months (range 1-108 month) if remission was not achieved by surgery. Radiotherapy (conventional or gamma-knife) was applied to the patients as the second or the third line therapy and the median duration of the follow-up period was 6 years (range 2-31 years) after radiotherapy.

The median GH and IGF-1 levels at the time of diagnosis was 19.4 µg/L (range 4-237 µg/L) and 1133 µg/L (range 640-2500 µg/L) for the patients who were not cured whereas it was 8.95 µg/L (range 2-56 µg/L) and 966 µg/L (range 302-3900 µg/L) for the patients who were cured after the first operation respectively. Although the level of GH and IGF-1 at the time of diagnosis was much higher for the patients who were not cured than the ones who were cured after first operation they did not reach statistical significance ($p=0.055$ and $p=0.599$). The GH and IGF-1 levels at the time of diagnosis were not predictive for the success of the treatment. The success of the first operation and the multiple treatment modalities were determined by the tumor size, microadenomas were more successfully treated than macroadenomas ($p=0.014$ and $p=0.016$). Cavernous sinus infiltration also did not differ the remission rates after the first operation and other treatment modalities ($p=0.091$ and $p=0.392$).

The median decrease in GH and IGF-1 levels after the first operation were 8.41 µg/L and 728 µg/L in the patients who were cured; 15.16 µg/L and 384 µg/L in the patients who were not cured respectively and this was not meaningful ($p=0.650$ for decrease in GH, $p=0.074$ for decrease in IGF-1). But in the subgroup analysis, the decrease in IGF-1 (after the first operation done by the same experienced neurosurgeon after the year 2003 was statistically significant ($p=0.036$) whereas the decrease in GH was still not significant ($p=0.509$).

The incidence of new anterior pituitary hormone deficiency of any axis developing postoperatively was 9% for macroadenomas before 2003; 12% for macroadenomas and 5% for microadenomas after 2003. There was no new anterior

pituitary hormone deficiency for microadenomas before 2003. Hypopituitarism incidence with all treatment modalities was 27.9% after 2003 whereas it was 41.7 % before 2003, but the difference was not statistically significant ($p=0.250$). There was no significant difference for the occurrence of hypopituitarism when the number of neurosurgeons, number of operations and cavernous sinus infiltration were considered ($p=0.432$, $p=0.06$, $p=0.184$). The tumor size and radiotherapy as the treatment modality were the factors that predicted hypopituitarism in one way analysis, but when we did logistic regression analysis radiotherapy remained as the only factor for hypopituitarism.

At the time of diagnosis, there was no discordance between GH and IGF-1. The prevalence of discordance was 24% in patients cured after first surgery and 33% in patients cured after multiple treatment modalities.

DISCUSSION

Acromegaly is a disease with ubiquitous facial and acral features, but the breadth and heterogeneity of the signs and symptoms that may be attributed to aging could contribute to delay in diagnosis (17,24,33,34). The delay in diagnosis is long. In most prior studies mean times from symptoms to diagnosis were 4 to 8 years (17,24,33), but in a recent series this was 2.5 years (34). This delay was shorter in our series with a median of 24 months (range 1-120 months) before 2003 and it was even shorter with a median of 12 months (range 1-96 months) after 2003. This may be because of the increasing awareness of the physicians with the disease.

Transsphenoidal surgery still remains the treatment of choice for the majority of the patients with acromegaly despite the increasing tendency to use somatostatin analogue treatment in developed countries. Our data are in keeping with the reports of the others that, in experienced hands, transsphenoidal surgery is a safe and effective first line treatment. Comparing previously reported results of surgery in acromegalic patients is not meaningful due to the variation in the selected criteria of cure and remission. These have been based on either single measures or various combinations of random/mean GH day profile levels (often with different cut-off values), nadir GH levels after OGTT and IGF-1 measurements. The results of primary surgery vary between 33% and less in non-specialized centers (16) and up to 70 % and more in specialized centers (29), overall success

rates being 50-60% (36). Our remission rates were lower than that had been reported by Law et al (27), Kreutzer et al (26) and De et al (14) whose remission criteria were similar to ours, but close to the overall success rates. The comparative results of transsphenoidal surgery for acromegaly in different centers were documented in Table II.

After the diagnosis of acromegaly there is a mean remaining lifespan of approximately 33 years; the success rates of surgery and somatostatin analogues in controlling the disease are approximately 60%; and the lifelong costs of different algorithms to control acromegaly in 100 patients ranged from 43 million euros (primary surgery and secondary somatostatin analogues) to 57 million euros (primary somatostatin analogues and secondary surgery) and even reached 95 million euros (medical treatment only). In algorithms that include trans-sphenoidal surgery, the lifetime treatment costs are almost 46-59% cheaper per 100 patients than in algorithms with medical treatment but without trans-sphenoidal surgery. Algorithms with primary surgery and secondary somatostatin analogs are 30% cheaper per 100 patients than algorithms with primary somatostatin analogues and secondary surgery (5). When we compare developing countries like Turkey with Europe, the cost of surgery is much more cheaper. The cost of transsphenoidal surgery is approximately 1000 euros in Turkey and this makes this treatment modality the cheapest besides its efficacy and safety.

When analysis of outcomes was compared, it is clear that results have improved over time with enhanced remission. The advances cannot be accounted for by changes in tumor size or in preoperative GH levels because there were no significant differences in these parameters over these years. The improvements may, however, be attributable to better preoperative imaging and a change in surgical approach, with increased emphasis on selective procedures wherever possible, but the most impressive improvement was due to the single experienced surgeon. Others have reported similar findings and reinforce the need for centers to employ dedicated, experienced pituitary surgeons in treating all patients with acromegaly (2,21,28,39). Quite reasonably, it has been suggested that pituitary surgery should be undertaken by specialists to achieve better surgical outcomes.

The importance of preoperative GH levels on optimal outcome was evident with the previous studies taking different cut-off values (2,18,25,35). When we analyzed the relationship of preoperative GH levels and the remission rates in our patients, the level of GH at the time of diagnosis was much higher for the patients who were not cured than the ones who were cured after first operation and this difference was at the level of statistical significance ($p=0.055$).

The influence of tumor size on outcome is quite clearly borne out in our series with 79% of microadenomas achieving remission compared with 53% of macroadenomas. This compares well with the published series of De et al (14) which achieved a remission rate of 79% in microadenomas and 56% in macroadenomas. Although cavernous sinus infiltration decreased the remission rate after the first operation from 51.7% to 23.1%, more than 50%, the decrease could not reach statistical significance and different from the previously published data (2,14) cavernous sinus infiltration was not related with the remission rates in our study. The cavernous sinus infiltration was determined from the MR reports that did not classify the infiltration. As we know the higher the stage of infiltration the worse is the outcome of the surgery. Perhaps the most of the cavernous sinus infiltration detected in our patients were in early stages explaining the remission rates unrelated with the infiltration.

The incidence of new anterior pituitary hormone deficiency of any axis developing postoperatively was 12% for macroadenomas and 5% for microadenomas after 2003. This is comparable to the results of 14% of Ahmed et al (2) and better than 22% of De et al (14) and Sheaves et al (35). Although the results for the incidence of hypopituitarism seemed a bit worse when we compared the years after 2003 with the years before 2003 this may be because of the inefficient surgery which could be detected from the remission rates.

In the present study, we observed a 14% prevalence of discordant GH and IGF-1 levels at diagnosis, using 2.5 $\mu\text{g/L}$ as a cut off level for safe GH. This was similar with the results of Machado et al (13.7%) (36) and it was smaller than the results of Dimaraki et al (25%) (13). This discordance disappeared in our series and reduced to 3.9% in Machado et al (36) series when the cut off level was taken as 1 $\mu\text{g/L}$. The prevalence of discordance was 24% in our patients cured after first surgery

Table II: The Comparative Results of Transsphenoidal Surgery for Acromegaly at Different Centers

Study	Year	Total (micro/macro)	Remission rate Total (micro/macro)	No. of surgeons
Laws et al	2000	117 (N/A)	67% (87/51)	NS
Kreutzer et al	2001	57 (19/38)	70% (N/A)	1
De et al	2003	90 (29/61)	63% (79/56)	3
Present series	<2003	60 (19/41)	12% (27/4)	>3
	\geq 2003	88 (28/60)	49% (50/47)	1
		32 (4/28)	5% (0/13)	>3

OGTT values are nadir GH levels following OGTT. **N/A**, not available; **NS**, not stated.

and this was similar to the results of Costa et al (24%) (37) when the cut of level was 2.5 µg/L and higher than the results of Machado et al (13.8%) (30) and Costa et al (16%) (11) when the cut of level was 1 µg/L. 33% prevalence of discordant GH and IGF-1 levels was observed in patients cured after multiple treatment modalities for both cut off levels and this was similar to the results of Machado et al (33.3% for 2.5 µg/L, 28.4 for 1 µg/L) (30) and Cozzi et al (28.4% for 2.5 µg/L) (12).

Several factors related to GH as well as to IGF-1 may explain the occurrence of the discordance in acromegalics. It is thought that "safe" GH with elevated IGF-1 levels could be explained by the secretion of low but continuous (tonic secretion) of GH during the 24 hour or by the presence of GH molecules with biological activity, but with no immunoreactivity. There are several isoforms of GH, being the 22 KDa (22K GH) the predominant. However, the "non-22 K GH fraction", composed by a variety of monomers and oligomers, can be found in around 26% of the patients with active acromegaly and because of its smaller immunoreactivity it could, at least in part, explain the loss of correlation between GH and IGF-1 levels in these patients (6).

In conclusion, our data highlighted the importance of experience in the diagnosis and treatment of acromegaly. As we get experienced in time, the clinical recognition of acromegaly and surgical outcomes of single experienced surgeons in specialized centers have significantly improved over the last 5 years using stringent criteria of remission. Our data are in keeping with the reports of the others that, in experienced hands, transsphenoidal surgery is a safe, cheap and effective first line treatment for acromegaly patients.

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