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The acromegaly registry of ten different centers in Turkey

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ABSTRACT

Objectives: To describe biochemical and clinical features, and therapeutic outcomes of acromegaly patients in Turkey.
Methods: Retrospective multicenter epidemiological study of 547 patients followed in 10 centers of the Turkish Acromegaly registry.
Results: A total of 547 acromegaly patients (55% female) with a median age of 41 was included in this study. Majority of patients had a macroadenoma (78%). Transsphenoidal surgery was performed as primary treatment in 92% of the patients ($n = 503$). Surgical remission rate was 39% (197/503) in all operated patients. Overall disease control was achieved in 70% of patients. Remission group were significantly older than non-remission group ($p = .002$). Patients with microadenomas had significantly higher remission rates than patients with macroadenomas ($p < .001$). Patients with microadenomas were significantly older at the time of diagnosis when compared to patients with macroadenomas ($p < .001$). Preoperative growth hormone (GH) and insulin-like growth factor 1 (IGF-1) levels were significantly lower in the remission group ($p < .001$). Initial IGF-1 and GH levels were significantly higher in macroadenomas compared to microadenomas ($p < .001$). Medical treatment was administered as a second-line treatment (97%) in almost all patients without remission. Radiotherapy was preferred in 21% of the patients mostly as a third line treatment.
Conclusions: This is one of the largest real life studies evaluating the epidemiological characteristics and treatment outcomes of patients with acromegaly who were followed in different centers in Turkey. Transsphenoidal surgery in the treatment of acromegaly still remains the most valid method. Medical treatment options may improve long-term disease outcomes in patients who cannot be controlled with surgical treatment (up to 70%).

1. Introduction

Acromegaly is a chronic multisystem disease caused by growth hormone (GH)-secreting pituitary adenomas. According to the epidemiological data obtained from different populations, the prevalence of acromegaly is 2.8–13.7 cases/100000 [1,2]. Morbidity and mortality are common in acromegaly patients and predominantly due to cardiovascular and respiratory complications [3]. Transsphenoidal pituitary surgery is the gold standard for the treatment of acromegaly [4]. Many patients will not be cured by surgery alone and will need lifelong surveillance. Although significant advances in treatment and diagnostic methods is available, real life data related to the outcome of acromegaly patients is limited. Longitudinal studies of patients with acromegaly usually are only conducted in a single center [5]. Even though these studies are valuable in terms of homogeneity of results, multicentered studies are needed to show real life data. Surgical cure rates in single centers are significantly higher than in multicenter studies [6–10]. The aim of this study was to evaluate clinical outcomes of acromegaly patients followed in ten different centers and operated by different surgeons in Turkey.

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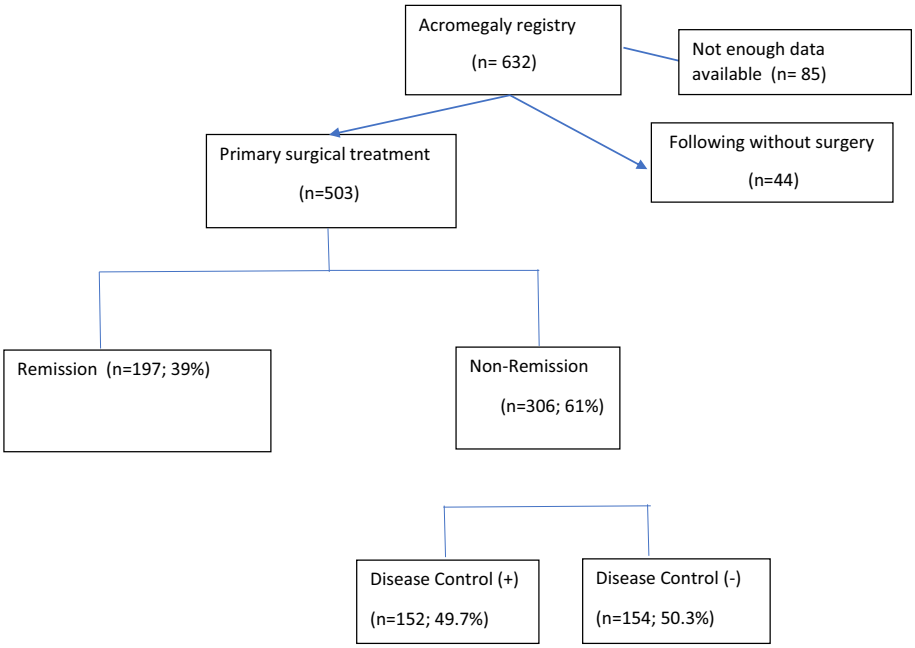

Fig. 1. Study population flowchart diagram.

2. Subjects and methods

This study consists of the consortium of 10 centers throughout Turkey. All centers shared their data with the Local Pituitary Working Group-Society of Endocrinology and Metabolism of Turkey in 2016 and were able to access the data at any time. Participating investigators were asked for the information of their patients who had been diagnosed and treated as acromegaly and who had at least one recorded visit in the last two years. Data were collected retrospectively by local investigators in a computarized database form and reviewed by a previously assigned team. Inclusion criteria were: (1) age at diagnosis > 18 years, (2) abnormal nadir GH levels (> 1 ng/ml) during a 75-g oral glucose tolerance test (OGTT) and/or abnormal IGF-1 levels for age and gender, (3) confirmed pituitary tumor on magnetic resonance imaging, (4) typical clinical feature of acromegaly at diagnosis, (5) in operated patients at least 6 months of follow-up after surgery.

The study cohort included 547 acromegaly patients diagnosed between January 1984 and December 2016. Demographics, estimated duration of acromegaly, tumor size on pituitary MRI, initial random GH and IGF-1 levels, treatment modality and remission status of the patients were evaluated retrospectively.

Remission criteria was based on 2010 consensus report (Insulin like growth factor levels normal for age and sex and a postoperative random GH level of < 1 ng/ml or GH level of < 0.4 ng/ml after an OGTT [11]. Disease control was achieved if the patient had normal IGF-1 levels according to age and sex.

Statistical analysis was performed with SPSS software version 20. Simple descriptive statistics were expressed as median with ranges. The frequency distribution of categorical variables between subgroups was compared by the chi-square test. Numerical variables were compared by unpaired *t*-tests. Statistically significant results obtained from univariate analysis were submitted to multivariate logistic regression. $P < .05$ was accepted as significant.

This study was approved by the Ethics Committee of the Abant Izzet Baysal University in Turkey. Informed consent was obtained from all participants.

3. Results

3.1. Clinical assessment

A total of 547 acromegaly patients [Gender, n (%): female, 300 (55); male: 247 (45)] from 10 different centers were included in the study with a median follow-up of 8 years (0 − 32). The median age at diagnosis was 41 (16–76), and the median time to diagnosis was 48 months (1 − 300). The median GH and IGF-1 level were 7.8 ng/ml (0.2–192) and 707 ng/ml (107–4000) at the time of diagnosis respectively. Macroadenoma was found in 78% of the patients ($n = 426$). No significant difference was found between genders in terms of the age at diagnosis and adenoma size. Initial GH and IGF-1 levels were higher in males than females [GH levels, ng/ml (range): male, 10.5 (0.1–192); female, 6.1 (0.1–143); $p = .035$; IGF-1 levels, ng/ml: male, 748 (107–4000); female, 676 (130–3800); $p = .023$]. The median delay from first symptoms to diagnosis was 24 months longer in females than males [Time from symptoms to diagnosis, months (range): female, 60 (1–240); male, 36 (1–249); $p = .008$]. Patients with microadenomas were significantly older at the time of diagnosis than patients with macroadenomas [Age, yrs. (range): microadenomas, 47 (17–76); acromegaly, 39 (16–76); $p < .001$]. In addition, a significant negative correlation was found between maximal adenoma diameter and age at diagnosis ($r = -0.233, p < 0{,}001$). Furthermore, initial GH and IGF-1 levels were significantly higher in macroadenomas compared to microadenomas [GH levels, ng/ml (range): macroadenomas, 9.3 (0.1–192); microadenomas, 5.6 (0.1–111); $p = .007$); (IGF-1 levels, ng/ml: macroadenomas, 743 (107–4000); microadenomas, 545 (174–1331); $p < .001$)].

3.2. Treatment

Transsphenoidal surgery was performed as primary treatment in 92% of the patients ($n = 503$). Two or more surgical interventions were performed in 23% of the patients ($n = 115$). Only 8% of the patient ($n = 44$) were not treated with surgery (due to the patient preference) and were followed-up with only medical treatment, radiotherapy or combination of both (Fig. 1). In the vast majority of patients without remission, medical treatment is administered as a second-line treatment (97%) (Fig. 2). Sixty percent of patients were only treated with

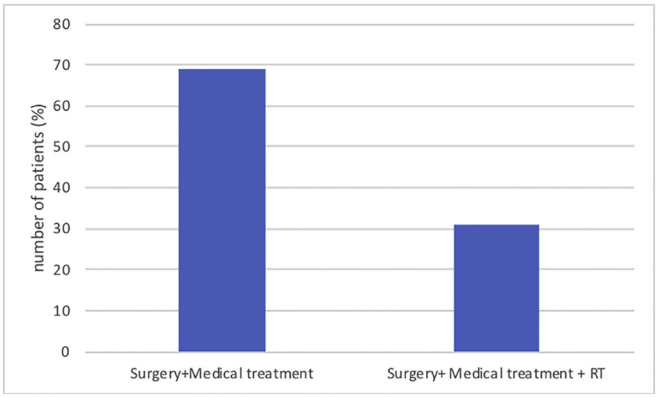

Fig. 2. Distribution of second and third-line treatments in patients without remission after surgery. RT, radiotherapy.

somatostatin receptor analogues (SRL) while 40% were treated with a combination of medications (32% with SRL and Cabergoline; 4% with cabergoline alone, 2% with SRL and pegvisomant and 2% with SRL and pegvisomant and cabergoline). Around 21% (n = 114) received radiotherapy (Fig. 3).

3.3. Outcome analysis

Long term surgical remission rate was 39% (n = 197) in all operated patients. Based on IGF-1 levels alone, disease control was achieved in 70% of patients at the last visit. Remission group were significantly older than non-remission group [median (range): remission, 42 (18–68); non-remission, 38 (16–76); p = .002] (Table 1). Patients with single pituitary surgery had significantly higher remission rates than patients with two or more hypophyseal surgeries (p = .03). Patients with microadenomas had significantly higher remission rates than patients with macroadenomas (p < .001) (Fig. 4). Patients achieving remission had significantly smaller maximal tumor diameters than patients not at remission [Tumor size, mm (range): remission, 14 (5–45); non-remission, 18 (3–70); p < 0,001)]. Preoperative GH and IGF-1

Table 1
Clinical and laboratory characteristics of patients that underwent surgery.

	Remission (n = 197)	Non-remission (n = 306)	*P value*
Age at diagnosis (years)	42 (18–68)	38 (16–76)	**0.002**
Sex (Female/Male)	116/81	160/146	0.26
Adenoma diameter (mm)	14 (5–45)	18 (3–70)	< **0.001**
Baseline IGF-1 (ng/mL)	650 (107–1800)	743 (297–4000)	< **0.001**
Baseline GH (ng/mL)	5.8 (0.1–61)	8.6 (0.1–192)	< **0.001**

(p < 0.05) is considered as statistically significant

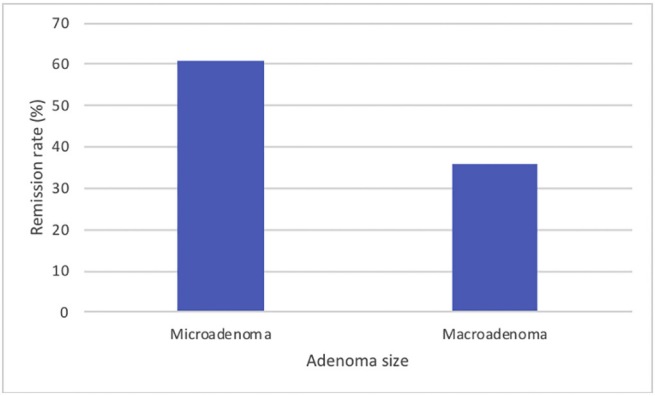

Fig. 4. Surgical cure rates of patients according to adenoma size.

levels were significantly lower in the remission group [GH levels, ng/ml (range): remission, 5.8 (0.1–61); non-remission, 8.6 (0.1–192); p < 0,001); IGF-1 levels, ng/ml: remission, 650 (107–1800); non-remission, 743 (297–4000); p < .001)] (Table 1). The remission rate of individuals < 40 years of age at diagnosis was lower than patients older than 40 years at the time of diagnosis (p < .001). Median follow-up time was significantly lower in the remission group compared to the non-remission group [Follow-up time; years (range): Remission group,

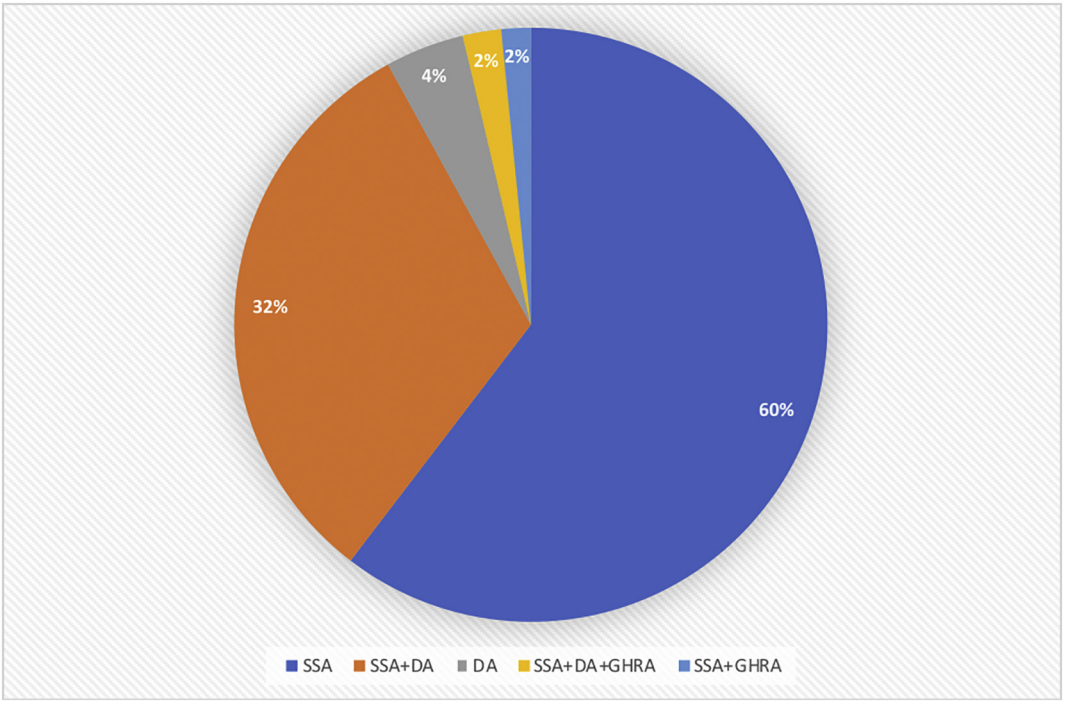

Fig. 3. Medical treatment regimens in patients with non-remission. SSA, somatostatin analog; DA, dopamine agonist; GHRA, GH receptor antagonist.

5 (0–36); Non-remission group, 7 (0–40); $p = .005$]. There was no significant gender difference in terms of remission status ($p = .26$). Multivariate analysis showed that a smaller adenoma size (OR 1041, 95% CI 1003–1081; $p = .035$) was an independent predictor of remission in patients with acromegaly.

4. Discussion

This study is important in several aspects; (1) this is the first multicenter study to evaluate the clinical features and treatment outcomes of acromegaly patients in Turkey, (2) transsphenoidal surgery was applied as a first line therapy in accordance with international guidelines and majority of the patients received surgical therapy (92%) with a success rate of 39% (3), secondary and tertiary treatment options significantly increased the chance of disease control in patients not in remission.

Acromegaly is a rare endocrine disorder therefore a multicenter approach is needed to better understand the clinical outcome of such rare disease. In our study the surgical remission rate of patients with acromegaly was 39% which was similar to the Belgian (34%) and German registry (38.8%), but lower than the South Korea cohort (46.2%) [7,12–14]. Other cohorts have shown a surgical cure rate between 32% and 71% as real-life data depends on the experience of the centers [5,15–18]. In our study, the remission rate for microadenomas was 61% and the remission rate for macroadenomas was 36%. In previous studies, 75–95% of patients with microadenoma and 40–69% of patients with macroadenomas had normalization of IGF-1 after surgery was performed in experienced centers [19–23]. Portocarreto-Ortizis et al. showed a 34% remission rate in patients with macroadenomas and 50% remission rate in patients with microadenomas (Table 2) [6].

This study defined disease controls as patient with an IGF-I normalization at last visit (adjusted for age and sex). Based on IGF-1 levels alone, our overall disease control was achieved in 70% of the patients which is similar to Italian cohort (65%) but higher than the Belgian registry (49%) and lower than German and Spanish registries (72% and 76%) (Table 2) [7,12,13,20].

Approximately 92% of our cohort had at least one pituitary surgery which is similar with German and South Corea registries (89.3% and 90.4%) but higher than Spanish and Belgian registries (81% and 68%) [7,12–14]. In the present study, transsphenoidal surgery was the first choice of therapy in most of the patients due to the fact that surgery is the gold standard for acromegaly if performed by experience surgeons. The high surgical cure rates reported in the literature may not always reflect real-life data since most of the data comes from experience surgical sites [5–18]. The relatively low remission rates in our study may be related to (1) the fact that the operations were performed by different surgeons in 10 different centers with different surgical experience levels and (2) by the more stringent definition of remission in all centers due to 2010 consensus report. The first consensus conference in 1999 defined cure criteria as followed: normal IGF-1 level when adjusted for age and sex and random GH value below 2.5 ng/ml or GH value below 1 ng/ml during an oral glucose tolerance test. These criteria were tightened with the development of more sensitive GH assays over the years.

The incidence of acromegaly is considered to be equal in both genders. Our cohort had a small female predominance (55%), which is close to the proportion reported in other registries. It is not possible to conclude that acromegaly is more common in women. In most published cohorts the age of diagnosis is different between men and women. Men are mostly diagnosed at an earlier age than women. However in our cohort, the age at diagnosis was similar between women and men, which was also found in the Bulgarian cohort (age 41 of diagnosis in both genders) [23]. Older patients are generally presented with smaller adenomas and lower somatotropic activity suggesting that GH-secreting adenomas in older patients are less aggressive than in younger patients. This study showed that younger patients had larger adenomas and lower rate of remission when compared to older patients which is confirmed by other studies [24,25]. Also, surgical cure rates were less in patients with macroadenomas when compared to patients with microadenomas.

Colao et al. reported higher IGF-1 levels in men but similar levels between the genders for GH levels [26]. The German registry reported significantly higher levels of GH and IGF-1 in males than females and attributed this difference to the earlier diagnosis of males [24]. In our cohort, there was no difference in age at diagnosis between gender, but the baseline GH and IGF-1 levels were higher in males. We believe that this difference could be related to hormone levels. Hence testosterone is a stimulation factor for IGF-1 and estrogen induced GH resistance in female. Furthermore, serum IGF-1 levels were significantly higher in males than in females in a large multicenter evaluation of a healthy population [27].

Medical therapy is normally the second treatment strategy in the management of acromegaly. However, if the center does not have experience pituitary surgeons, medical therapy is considered the first line therapy. In our cohort 61% of patients not in remission received SRL monotherapy and 32% received SRL with cabergoline. Pegvisomant is a valuable alternative in combined therapy or monotherapy in patients with resistant acromegaly. However, the use of pegvisomant was very low in our cohort. We speculated that the cost and low reimbursement rate of pegvisomant in Turkey may limit the use of the drug. In our cohort, 21% of patient ($n = 114$) received radiotherapy mostly as adjunctive therapy after surgery.

Acromegaly is a complex disease with an insidious onset that can take years to become clinically detectable leading to a delay in

Table 2
Treatment outcomes and disease characteristics of several national registries.

Country	Patients (n)	Age of diagnosis (years) (M/F)	Women (%)	Macroadenoma (%)	Surgery (%)	Surgical Cure (%)	Overall DC	Ref
Germany	1344	41M/47F	58	81	89	38.8	72	[12]
UK	2572	47	50	–	70	–	59	[21]
Spain	1658	46	61	75	54	32.3	76	[13]
Belgium	418	42M/46F	49	79	68	34	56	[7]
Mexico	2057	41	59	74	72	38.4	42	[6]
France	980	46	53	67	80	35	75	[25]
Canada	649	45	49	79	89	–	70	[19]
Italy	1512	43M/47F	59	70	80	–	65	[20]
Greece	115	47	61	74	79	41	52	[17]
South Korea	1350	42M/45F	54	83	90	46.2	–	[14]
Finland	334	45M/49F	52	67	87	–	76	[22]
Bulgaria	534	41M/41F	65	70	86	28.8	51	[23]
USA	166	50	69	–	80	–	72	[29]
Turkey	547	41M/41F	55	79	92	39	70	Present study

DC, Disease Control.

diagnosis. In our cohort the median time to diagnosis was 4 years which is similar with previous reports. The Liege Acromegaly Survey data (3173 patients from different countries) showed that time to diagnosis in females was significantly longer than males [28]. In our study the median delay from first symptoms to diagnosis was 24 months longer in females than males. Based on these results it is important to make awareness of acromegaly in women as well as in men that can lead to earlier diagnosis.

This study provides important real-life data of 547 acromegaly patients from ten centers in Turkey. Limitations of the study are as followed: (1) the data is collected retrospectively; (2) lack of standardization in preoperative imaging techniques among the centers and (3) the assays used to measure GH and IGF-1 level were different between centers causing some standardization problems. The strengths of the study: (1) the large number of patients from different centers reflecting real life data and (2) long follow-up period.

In conclusion the disease characteristics of our cohort were almost concordant with previously reported country registries [6,12,23]. Even though our acromegaly register has some limitations it is impressive because of reflecting the real-life outcome under routine conditions. Our study shows that the surgical cure rates in acromegaly are still moderate in Turkey. In order to increase surgical cure rates and decrease burden of additional medical treatments on the health system acromegaly patients should be referred to experienced centers.

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Disclosure statement

The authors have nothing to disclose.

Declaration of Competing Interest

The authors have no competing interests to declare.

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