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Original article

Clinical characteristics and management outcomes of acromegaly in a Tunisian university hospital: A retrospective study

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Abstract

Introduction: Acromegaly is a rare endocrine disorder characterized by excessive growth hormone (GH) secretion, primarily caused by pituitary adenomas. If untreated, it leads to significant morbidity and increased mortality. This study investigates the clinical characteristics and treatment outcomes of acromegaly patients in a Tunisian University Hospital.

Methods: We conducted a retrospective review of medical records for patients diagnosed with acromegaly in the Endocrinology Department of a University Hospital in Central Tunisia over 20 years. Data on clinical features, imaging, comorbidities, and treatment outcomes were collected and analyzed.

Results: Among 41 patients included, the mean age at diagnosis was 37±11 years. MRI revealed macroadenomas in 93.9% of cases, with 58% displaying invasiveness. Adenomas co-secreting GH and prolactin were larger (35 mm vs. 21 mm; p=0.031) and more invasive (80% vs. 23%; p=0.02) compared to GH-only adenomas. Diabetes mellitus was the most common comorbidity (43%), and affected patients were older (42 vs. 34 years; p=0.03). Surgical treatment, primarily via the transsphenoidal route, was performed in 78% of patients. Medical therapy, including somatostatin analogs and dopamine agonists, was administered to 48%, with Lanreotide being the most frequently used agent. Multimodal therapy achieved a cure rate of 29%.

Conclusion: Despite therapeutic advances, managing acromegaly remains challenging. Early diagnosis and individualized treatment strategies are essential to improve patient outcomes.

Keywords: Acromegaly, Pituitary adenoma, Somatostatin analog, Comorbidities

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1. Introduction

Acromegaly is a rare endocrine disorder caused by excess growth hormone (GH) secretion, affecting men and women equally [1]. Its annual incidence ranges from 2 to 11 cases per million individuals, with a global prevalence of 28 to 137 cases per million [2]. Hypersecretion of GH and insulin-like growth factor 1 (IGF-I) leads to tissue remodeling, organ hypertrophy (organomegaly), and metabolic disturbances.

Most patients experience a delay of 4 to 10 years between symptom onset and diagnosis due to the disease's gradual onset [3, 4, 5]. This delay often diminishes quality of life and contributes to increased morbidity and mortality [6, 7]. Clinical features such as persistent headaches, diabetes mellitus, hypertension, or unexplained heart disease necessitate biochemical screening for GH and IGF-I to confirm the diagnosis. Magnetic resonance imaging (MRI) of the pituitary gland is recommended to identify the underlying cause [8].

Treatment options include transsphenoidal surgical resection, medical therapies (dopamine agonists, somatostatin analogues, and GH receptor antagonist pegvisomant), and radiotherapy [9]. Surgery is typically the first-line treatment, while medical therapy is employed to control hormone levels and manage tumor growth [10].

This study aims to characterize the demographics, comorbidities, and treatment outcomes of acromegaly in a single-center cohort from Tunisia.

2. Material and methods

We conducted a retrospective study at a University Hospital in Central Tunisia. The diagnosis of acromegaly was established based on characteristic clinical features, elevated age-adjusted IGF-1 levels, and serum GH levels that failed to suppress below 1 ng/mL following a 75 g oral glucose tolerance test.

All patients diagnosed with acromegaly at our center between 2003 and 2023 were included in the study. Data were analyzed retrospectively, ensuring no interference with patient management. Ethical approval was obtained from the Research Ethics Committee of the Faculty of Medicine in Sousse, Tunisia.

The collected data encompassed demographic characteristics (age and gender), clinical presentation, hormonal profiles, and tumor characteristics, including size (microadenoma or macroadenoma), invasiveness, and

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findings from visual examinations.

We evaluated disease-related morbidity and analyzed treatment modalities, including surgical interventions, radiotherapy, and medical therapies (dopaminergic drugs and somatostatin analogs), as well as therapeutic outcomes. Additionally, data on treatment-related morbidity and side effects were collected.

Treatment efficacy was assessed in accordance with consensus guidelines based on GH and IGF-1 levels [11, 12]. A cure was defined as achieving a normal age- and sex-adjusted IGF-1 level, along with a mean GH level of less than 1 ng/mL, after surgery and/or radiotherapy. Controlled disease was defined as maintaining a normal age- and sex-adjusted IGF-1 level, with a mean GH level below 1 ng/mL, achieved through medical therapy regardless of prior treatments. Active disease was characterized by IGF-1 levels above the normal range and GH levels exceeding 1 ng/mL.

Statistical analysis was conducted using GNU PSPP software. Demographic and clinical characteristics were summarized as means or medians (with interquartile ranges) for continuous variables and as counts (percentages) for categorical variables.

Independent samples t-tests were used to compare means between groups, while Pearson's chi-square tests were applied to compare percentages. Spearman's rank correlation coefficient (r) was calculated to assess relationships between variables.

3. Results

Demographic characteristics: A total of 41 patients with acromegaly were included in the study. Among them, 17 (42%) were male, and 24 (58%) were female. The mean age at diagnosis was 37±11 years, with male patients being significantly younger on average (36 years) compared to female patients (39 years) (p=0.001). The age at diagnosis ranged from 13 to 61 years for male patients and from 23 to 63 years for female patients.

The average delay between symptom onset and diagnosis was 6.8±4.7 years. Most patients (48.5%) experienced symptoms for 5 to 10 years before being diagnosed, while 24.2% had symptoms for more than 10 years prior to diagnosis.

Endocrinologists were the primary specialists to suspect acromegaly and referred 63.6% of the cases for further investigation. Otolaryngologists accounted for 12.4% of referrals, while general practitioners referred 9.1% of the cases. In all instances, the suspicion of acromegaly was based on the presence of acrofacial dysmorphism.

Biochemical and imaging data: IGF-1 assessments were available for many cases (75.6%, n=31), all of which showed elevated levels. Additionally, 19 patients (46.3% of the cohort) exhibited elevated serum GH levels that failed to suppress below 1 ng/mL following a 75-g oral glucose load.

At the time of diagnosis, the mean GH level was 22.34 mIU/L. Mean IGF-1 levels were 847 ng/mL for males and 782 ng/mL for females, with no statistically significant difference between the two groups (p=0.8).

Among the cohort, 29 patients (70%) had pituitary adenomas secreting only GH, while 12 patients (30%) had adenomas secreting both GH and prolactin (PRL).

Magnetic resonance imaging (MRI) data were available for 33 patients (80.5%). Of these, 31 patients (93.9%) presented with macroadenomas, while 2 (6%) had microadenomas. MRI findings revealed that 58% of patients (n=24) had invasive adenomas.

Mean IGF-1 levels were significantly higher in cases of invasive pituitary adenomas (372 vs. 293 ng/mL; p=0.001). Adenomas co-secreting GH and PRL were notably larger (35 vs. 21 mm; p=0.031) and more invasive, with a significantly higher frequency of optic chiasm invasion (80% vs. 23%; p=0.02) (Table 1).

Table 1. Clinical presentation of adenomas secreting both GH and PRL

	Adenomas secreting both GH and PRL (n=12)	**Adenomas secreting GH (n=29)**	**p**
Mean age (years)	38	39	0.001
Tumor size (mm)	35	21	0.031
Optic chiasma invasion n (%)	10 (80)	7 (23)	0.020
Insulin-like growth factor (ng/ml)	796	831	0.001

GH: Growth Hormone ; PRL: Prolactin ;p: p-value

The reported clinical features at diagnosis are summarized in Table 2. The most common complaints included headaches, coarse facial features, and acral growth.

Table 2. The initial clinical presentation of acromegaly

Symptoms	**Patients n (%)**
Headache	29 (70)
Coarse facial features	24 (58)
Acral enlargement	29 (70)
Prognathism	28 (68)
Arthralgia	18 (43)
Increased denture size	12 (29)
Loss of libido	13 (31)
Macroglossia	13 (31)
Sweating	20 (48)
Snoring/sleep apnea	19 (46)

The prevalence of associated comorbidities is presented in Table 3. Diabetes mellitus was the most frequently reported comorbidity, while hypertension and visual field disorders were less common. Patients with diabetes mellitus were significantly older than those without (42±12 vs. 34±8 years; p=0.03).

Table 3. Prevalence of comorbidities complicating acromegaly

Morbidity	**Prevalence n (%)**
Diabetes mellitus	18 (43)
Hypertension	10 (24)
Visual field defect	15 (36)
Cardiovascular	5 (12)
Arthropathy	18 (43)
Sleep apnea	8 (19)
Colonic polyps	1 (2)
Goiter	2 (5)

Sleep study data were available for 16 patients, 8 of whom were diagnosed with sleep apnea. Colonoscopy reports were available for 13 patients (31% of the cohort). One patient was found to have colonic polyps, while 4

patients had dolichocolon. Additionally, one patient presented with epigastric pain and was subsequently diagnosed with moderately differentiated ulcerated tubular gastric adenocarcinoma.

Cervical ultrasound results were available for 22 patients (53%), revealing nodular thyroid findings in 10 cases.

Therapy: Several therapeutic modalities were employed in the treatment of acromegaly in this cohort, including surgery, medical therapy, combined medical and surgical treatment, and radiotherapy.

Surgery was performed in 78% of patients (32/41), exclusively through the transsphenoidal approach. One patient refused the procedure, and surgical data were unavailable for 19% (8/41) of cases.

Radiotherapy was utilized in 24% of patients (10/41), primarily as an adjunctive treatment following surgery. However, radiotherapy data were not documented in 31% (13/41) of cases.

Medical therapy was administered as an adjunct to surgery in 48% of patients (20/41). Long-acting somatostatin analogs were the mainstay of medical treatment, with Lanreotide being the most frequently used agent (70%, 14/20). Dopamine agonists (DA), such as bromocriptine and cabergoline, were used in 7.3% of patients (3/41).

Biochemical outcome: The outcomes of the different treatment regimens were evaluated based on IGF-1 levels and random GH levels of less than 1 ng/mL. These data were available for 23 and 18 patients, respectively, from the total cohort.

The cure rate with multimodal treatment was 29% (n=12). Additionally, 7% of patients (n=3) who were not cured by surgery and radiotherapy achieved good control of symptoms and biochemical markers through medical therapy. However, 24% of patients (n=10) continued to have active disease despite treatment with long-acting somatostatin analogs and dopamine agonists. Mortality data were not available for inclusion in the analysis.

4. Discussion

The prevalence of acromegaly is often underestimated due to limited awareness among healthcare providers and patients, a low index of suspicion, and a substantial number of undiagnosed cases. In our department, among 41 patients with acromegaly, a female preponderance was observed, with 24 females (58%) and 17 males (42%).

The literature regarding sex distribution in acromegaly reveals considerable variability. While most studies report a female preponderance, notable exceptions exist. For instance, one study found a higher number of male patients than females. It has been suggested that both endogenous and exogenous estrogen may help suppress IGF-1, potentially offering a protective effect in females of reproductive age, which could delay the onset of clinical symptoms in acromegaly.

In our cohort, various specialists were consulted for different reasons, but the diagnosis was rarely made during the initial consultation. Endocrinologists were the primary clinicians who identified the diagnosis in most cases. Similar findings were reported by Aydin et al. in their study of 120 patients. Chraga found that in 43% of cases, the diagnosis was suggested by an endocrinologist, in 17% by a general practitioner, and in 10% by a neurosurgeon. In Azeiz's study, the diagnosing physician was a general practitioner in 40% of cases.

GH and PRL co-secreting adenomas account for approximately 20% of acromegaly cases. These tumors are typically more invasive, larger, and more likely to cause hypopituitarism compared to GH-only adenomas. Additionally, they are often diagnosed at an earlier age. Our findings are consistent with this, as adenomas secreting both GH and PRL were significantly larger (35 mm vs. 21 mm; p=0.031) and more invasive, with a higher frequency of optic chiasma invasion (80% vs. 23%, p=0.02).

MRI was the preferred imaging modality, with data available for 33 patients (80.5%). Of these, 93.9% were diagnosed with macroadenomas, and 6% had microadenomas. These findings align with those of most studies, including the Spanish Acromegaly Registry, where 70% of patients (842 out of 1196) were diagnosed with macroadenomas.

Cavernous sinus invasion is observed in 25% to 56% of macroadenomas, and tumors exhibiting this invasion are typically associated with worse disease outcomes.

The prevalence of diabetes in acromegaly patients ranges from 12% to 53% [27, 28]. In our study, diabetes was observed in 43% of cases, significantly higher than the 8.5% prevalence found in the general population. Furthermore, consistent with Warncke's study, which found that diabetes affects younger patients with acromegaly (average age 50.1 years) compared to the general population (average age 59 years) [29], our results show a similar pattern.

Chronic excess of GH/IGF-I significantly contributes to the development of hypertension, insulin resistance, diabetes, and obesity. These conditions are interrelated and can exacerbate one another [30, 31]. The elevated prevalence of arterial hypertension in the ACROSTUDY cohort, along with a high rate of IGF-I normalization, and its associations with age, higher BMI, smoking, and other comorbidities, underscores the complex, multifactorial nature of hypertension in acromegaly patients. This pattern mirrors that of the general population [32].

Data on colonic polyps were available for only 31% of patients, with only one case identified. This is significantly lower than the prevalence reported in the AcroBel study [11], and the discrepancy is likely due to both under-utilization of colonoscopy and underreporting.

The first-line treatment for acromegaly is transsphenoidal resection of the adenoma [33, 34]. The success of transsphenoidal surgery (TSS) largely depends on the surgeon's skill, with remission rates exceeding 70% for microadenomas or macroadenomas confined to the sella turcica. For non-invasive macroadenomas, remission rates range from 40% to 50%, while invasive macroadenomas have a remission rate of less than 20% [33, 34].

Regarding medical treatment, guidelines recommend somatostatin analogues as the first-line option, with dopamine agonists considered for less severe cases [10]. In Tunisia, the use of somatostatin analogues is highly regulated and restricted, typically reserved as a second-line treatment when surgery or dopamine agonists fail to manage the condition. While pegvisomant, a growth hormone receptor antagonist, is currently the most effective treatment

for acromegaly [29], it is not available in Tunisia.

Medical treatment was primarily used as an adjunct to surgery in 48% of patients, with Lanreotide being the most administered drug, used in 70% of these cases (14 out of 20). In Tunisia, radiotherapy for acromegaly patients is relatively infrequent, typically reserved for cases with residual or recurrent tumors that are high-risk for surgery, or when patients decline surgical options [10]. Although advances in medical treatments, such as somatostatin analogues and pegvisomant, have reduced the need for radiotherapy, it remains an important option for managing more complex cases [8, 10, 34]. While our study is smaller compared to global research [10, 22], it is the first conducted in central Tunisia.

According to our results, 24% of patients [10] still had active disease despite using multiple treatment modalities. The unavailability of pegvisomant in Tunisia represents a significant limitation in therapeutic options, which may contribute to the persistence of disease in these cases. The lack of this effective treatment option limits the ability to achieve optimal disease control and underscores the need for broader access to advanced therapies.

5. Conclusion

This study provides valuable insights into the management of acromegaly in a Tunisian University Hospital setting. Despite significant advances in treatment, a considerable proportion of patients continue to experience active diseases, highlighting the challenges in achieving optimal disease control. The high prevalence of comorbidities, particularly diabetes mellitus, underscores the need for comprehensive care and continuous monitoring. These findings emphasize the importance of improving diagnostic awareness and expanding access to advanced treatments, such as pegvisomant, which could potentially enhance therapeutic outcomes. Future research should focus on broadening treatment options and improving long-term disease management to address the persistent challenges observed in this cohort.

This study offers valuable insights into the management of acromegaly within a Tunisian University Hospital setting. Despite significant advances in treatment, a substantial proportion of patients continue to experience active disease, underscoring the challenges in achieving optimal disease control. The high prevalence of comorbidities, particularly diabetes mellitus, highlights the need for comprehensive care and ongoing monitoring. These findings emphasize the necessity for improved diagnostic awareness and enhanced access to advanced treatments, such as pegvisomant, which could potentially improve therapeutic outcomes. Future research should focus on expanding treatment options and improving long-term disease management to address the persistent challenges observed in this cohort.

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Ethical considerations

Ethical approval was obtained from the Research Ethics Committee of the Faculty of Medicine in Sousse, Tunisia.

Conflict of interest

The authors declare that there are no conflicts of interest that could be perceived as influencing the impartiality of the research presented.

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All authors contributed to the article and approved the submitted version.

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