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ORIGINAL ARTICLE

Clinical features and therapeutic outcomes of patients with acromegaly in Saudi Arabia: a retrospective analysis

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Abstract

Background Acromegaly is a rare disease resulting in clinical sequelae with significant morbidity and mortality due to the central tumor mass effect and prolonged growth hormone (GH) hypersecretion.

Objectives The goal is to describe the epidemiology, clinical features, presence of comorbidities, and treatment outcomes of acromegaly in Saudi Arabia.

Methods Data was collected through a retrospective review of the charts of all patients diagnosed with acromegaly from nine major hospitals in Saudi Arabia over a period of more than 25 years.

Results A total of 195 patients (116 males and 79 females), with a mean age at diagnosis of 43 ± 12 (males) and 46 ± 14 years (females), from nine major hospitals were identified and included in the analysis. All cases were caused by pituitary adenomas, of which 92.4% were macroadenomas. Headache, coarse facial features, acral growth, and sweating/oily skin were by far the most frequent presenting complaints. The most common comorbidities were diabetes mellitus (51.7%), followed by hypertension (50%) and visual field defect (30.5%). The vast majority (95%) of patients were treated surgically (98%). Twenty-four percent also received radiotherapy, and 74.4% received medical therapy. When stringent criteria were applied for assessment of outcomes of therapy, 28.7% of the patients were cured and 30.1% had their disease under control, while 28.7% were found to have active disease despite receiving multimodal therapy.

Conclusions Our findings highlight the need for a national acromegaly registry to enable early identification, evaluation, and selection of the best therapeutic approaches to improve the outcome and remission rate of the disease.

Keywords Pituitary adenoma · Acromegaly · Epidemiology · Transsphenoidal surgery · Radiotherapy · Medical therapy and outcome

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Introduction

Acromegaly is a rare disease resulting from prolonged growth hormone (GH) hypersecretion, and consequently raised insulin-like growth factor 1 (IGF-1). More than 95% of cases are due to an autonomously functioning pituitary adenoma either purely secreting GH or in combination with other hormones, commonly prolactin (PRL) [1].

The annual incidence is around 3–4 per million per year, with a worldwide prevalence of 40–130 cases per million [2]. However, a recent study based on raised IGF-1 levels suggests underdiagnoses and a higher prevalence of 1034 cases per million [2, 3]. Acromegaly is associated with significant morbidity and mortality and if left untreated; patients would die approximately 10 years younger than their healthy counterparts from a range of systemic complications. [2–4].

The diagnosis of acromegaly is delayed for a variable number of years due to its indolent and insidious nature [5]. The duration between onset of symptoms and diagnosis of acromegaly ranges from 6.6 to 10.2 years, with a mean delay of around 9 years [6]. This latency period to diagnosis appears to have shortened, likely reflecting enhanced physician awareness, availability of more sensitive diagnostic tools, and increased use of MRI [7]. Approximately 60% of acromegalic patients die from cardiovascular disease, 25% of respiratory disease, and 15% from malignancies, as indicated by analysis of determinants of mortality outcome [8–14].

The nadir GH value likely constitutes the most predictive survival index, regardless of the cause of death [8–11]. There is compelling evidence indicating that control of GH levels and/or IGF-I levels, normalized for age, is associated with the improvement of adverse mortality rates, independent of the type of associated complications [13]. Suppression of GH below 1 ng/dl has previously been shown to portend a favorable mortality outcome [12–15]. In fact, it has been suggested that overall mortality in patients with acromegaly is correlated with the degree of GH control [8]; mortality rates for cancer can be stratified according to posttreatment GH levels [9]; and, if GH secretion is controlled, mortality rates become similar to those recorded in the non-acromegalic population [8, 9].

Surgery is generally considered the primary therapy, with initial remission rates of 85% for microadenoma and 40%–50% for macroadenomas [16, 17]. However, 40–60% of patients will experience recurrent or persistent disease after surgery, necessitating additional therapy [4].

Medical therapy or radiotherapy is generally reserved for a tumor that cannot be resected completely by surgery because of extensive cavernous sinus invasion, or in a patient who is a poor surgical candidate [18]. The low incidence of acromegaly has prompted the formation of several registries in Europe and Mexico in order to collect structured information and to generate valuable epidemiological, specific clinical, and outcome data [6–8, 19, 20]; however, studies of such magnitude have not been conducted so far in the Kingdom of Saudi Arabia.

Objectives

The primary objectives are to describe the demography and epidemiology of acromegaly, the presence of comorbidities, and outcomes of patients with acromegaly in a multicenter setting in Saudi Arabia.

Methods

The study was retrospective in nature, carried out at nine tertiary care centers over the entire kingdom, in which all Saudi nationals are eligible for treatment. All these nine centers have been operating for more than 10 years, and a few of them for more than 25 years.The diagnosis of acromegaly was established by the presence of clinical features of acromegaly, elevated age-adjusted IGF-1, and serum GH levels not suppressible below 1 ng/dl after a 75-g oral glucose load. All patients with a diagnosis of acromegaly based on clinical records were included in the study, whether diagnosed in that particular center or referred from other secondary and primary care centers. All endocrinologists involved in the care of patients with acromegaly in Saudi Arabia were invited to submit their data. All data were collected directly from the charts and assembled. Date of diagnosis is not available for all the patients, as some of them were diagnosed and managed around 20 years ago, when the electronic medical file system was not available at some of these centers and hard copies were the only methods of storing clinical records.

The data analysis was performed retrospectively and did so with no interference in the patient's management. The study was approved by a research ethics committee of the King Fahad MedicalCity (KFMC) research center, Riyadh and King Faisal Specialist Hospital and Research Center (KFSH&RC), Riyadh, Saudi Arabia.

Data collection

Data on demographic features (age and gender), a comprehensive clinical evaluation, tumor size (microadenoma and macroadenoma), invasiveness, and visual field assessment were collected, as were details of hormonal levels (initial and follow-up), and treatment, as follows: route(s) of surgical treatment(s), method(s) and radiotherapy, and types of medical treatment (dopaminergic drugs, somatostatin analogs, and GH receptor antagonists) and therapeutic outcome. Finally, data collection included morbidity related to the disease or to its treatment.

Participating hospitals

One hundred and ninety-five patients with a diagnosis of acromegaly from nine different governmental and academic hospital settings in the country were included.

Outcome analysis: definitions

The criteria used to determine the effectiveness of treatment as described in the treatment outcome and a consensus statement were based on the latest GH and IGF-1 results. [19, 20]. The cure was defined as a normal value for IGF-1 for age and sex and a mean GH value less than 1 ng/dl, as a result of previous surgery or/and radiation therapy. Controlled disease was considered as a normal IGF-1 value for age and sex and a mean GH value less than 1 ng/dl, obtained with medical therapy irrespective of previous therapy. Active disease was defined as a value more than the normal range for IGF-1 and more than 1 ng/dl, for GH.

Data analysis

All data collected were analyzed using descriptive statistics. Demographic and clinical characteristics of study patients were reported as mean or median (25th and 75th percentiles) for normally and non-normally distributed continuous variables, respectively. Additionally, categorical variables were reported as counts (percentage). Differences between the two arms were compared using the chi-square test. All analyses were performed using the SPSS 24.0 software (SPSS Inc., Chicago, IL, USA) package; a two-tailed p value of 0.05 was considered significant. Spearman's rank correlation coefficient (r) was calculated to define the relationship between variables.

Results

Demographic characteristics

Between January 2017 and January 2019, a total of 195 patients with acromegaly from nine major participating hospitals (Table 1), of whom 116 (59.5%) were males and 79 (40.5%) females, with a mean age of 43 ± 12 years with SD (standard deviation) 11.72 years and 46 ± 14 years with SD 13.57 years, respectively, at diagnosis, were identified and included in the study analysis. The youngest and oldest male patients at the time of diagnosis were 16 and 61 years old, respectively. Corresponding figures for females were 19 and 63 years, respectively. The estimated prevalence of the disease among the Saudi Arabia population of 33.4 million [21] is approximately 5.9 cases per 1 million inhabitants.

Table 1 Most common symptoms seen at the initial presentation of acromegaly

Presenting symptom	Patients presenting (%)
Acne	13 (31%)
Acral enlargement	72 (90%)
Arthralgia	41 (56.2%)
Coarse facial features	79 (89.8%)
Prognathism	65 (85.5%)
Deep voice	34 (54%)
Headache	99 (72.8%)
Increased denture size	48 (75%)
Loss of libido	33 (52.4%)
Macroglossia	46 (67.6%)
Menstrual disturbance	24 (31.2%)
Otological complaints	7 (14.6%)
Numbness	24 (48%)
Skin tags	17 (37.8%)
Snoring/sleep apnea	22 (47.8%)
Sweating	51 (70.8%)
Oily skin	34 (42.7%)
Weight gain	44 (68.8%)
Visual acuity disturbance	47 (51.6%)

Biochemical and imaging data

Data for elevated IGF-1 was available for 85.6% (167) patients, and elevated serum GH levels not suppressible below 1 ng/dl after a 75-g oral glucose load was seen in 30 patients (15.4%) of the whole cohort. The mean GH value at diagnosis was 51.17 mIU/L and 57.19 mIU/L for males and females, respectively, which did not show any significant difference ($p = 0.331$), while median GH values were 25.0 mIU/L and 30.75 mIU/L, respectively. Similarly, mean IGF-1 values at diagnosis were 763.92 ng/ml and 675.66 ng/ml for males and females, respectively, with no significant difference between them ($p = 0.546$). The corresponding median IGF-1 values were 709.5 ng/ml and 675.55 ng/ml for male and female patients, respectively. Magnetic resonance imaging information was available for 144 patients (73.8%), of whom 133 (92.4%) had macroadenomas and 11 (7.6%) had microadenomas. Concerning tumor invasiveness and pathology, details could not be determined.

Clinical features and comorbidities

The most commonly reported symptoms and signs at the time of diagnosis are summarized in Table 1. Headache, coarse facial features, acral growth, and sweating/oily skin were by far the most frequent presenting complaints.

The prevalence of associated morbidity, as reported in the patient's chart, is shown in Table 2. Diabetes mellitus was most frequently reported, followed by hypertension and visual field defects. Arthropathy and cardiovascular and cerebrovascular diseases were probably underreported. Associated cancer data were available for 95 cases, out of which malignant tumors were identified in eight cases only. Sleep study data were available for 46 patients only, out of whom 22 patients were found to have sleep apnea.

Colorectal cancer was reported in one case only, while the types of tumors were not known in the rest of the patients. The colonoscopy report was identified in 44 patients of the whole cohort. The prevalence of colonic polyps based on the available data was 22.7%.

Therapy

Several therapeutic modalities were employed for the treatment of acromegaly in this cohort, including medical, surgery, medical plus surgery, and radiotherapy, as listed in Table 3. Ninety-five percent (166/175) of the patients underwent surgery, mostly by the transsphenoidal route (98%); only three patients required the transcranial approach, while in 10.3% (20) of the cases, no surgical data were available. Radiotherapy was used in 24% of patients (42/174), mainly as adjunctive therapy after surgery, while in 10.7% (21), the radiotherapy information was not documented.

Medical treatment was used for the majority of patients mostly as adjunctive to surgery. Of these, 74.4% (122/164) had been treated with the long-acting somatostatin analogs (SSA), mostly octreotide LAR. Only three patients were treated with pasireotide after the failure of octreotide LAR, while dopamine agonists (DA), bromocriptine, or cabergoline were used in 3.2% (3/95) and 32% (44/139), respectively.

Also, where the data were available for 124 patients, 8% (10) of them were treated with the GH receptor antagonist (GHRA), pegvisomant, either sequentially or in combination with other medical therapy.

Table 2 Prevalence of comorbidities complicating acromegaly

Morbidity	Prevalence (%)
Arthropathy	17 (35.4%)
Cardiovascular	18 (20.2%)
Carpel tunnel	17 (31.5%)
Cerebrovascular	6 (11.3%)
Gallstone	18 (26.9%)
Colonic polyps	7 (22.7%)
Diabetes insipidus	9 (8.8%)
Diabetes mellitus	77 (51.7%)
Goiter	24 (37.5%)
Hypertension	70 (50%)
Sleep apnea	22 (47.8%)
Visual field defect	39 (30.5%)

Biochemical outcome

The outcome of the different treatment regimens was determined using both IGF-1 level and random GH < 1 ng/dl, where those data were available for 167 and 152 patients of the total cohort, respectively. Table 3 summarizes the outcome of the different treatment modalities in a patient with acromegaly, where the biochemical assay was done in respective hospital laboratories. The cure rate with multimodal treatment was 28.7% (52 patients). Furthermore, 30.1% of patients (55) were not cured by surgery and radiotherapy, but good control of symptoms and biochemical markers were achieved with medical therapy, while 28.2% of patients (51) still had active disease despite using multiple modalities of treatment. Unfortunately, mortality data were not available for analysis.

Discussion

Given that the population of Saudi Arabia is about 33.4 million [21], the estimated prevalence of the disease is around 5.9 cases per million, which is well below the international figures [1–3]. All our study centers are tertiary care government hospitals fully equipped with facilities for management of acromegaly and as per healthcare policies; all citizens have access to these centers. Although diagnosis of acromegaly patients may occur in private hospitals outside major centers, patients are usually referred to these major centers with dedicated surgeons and specialists for treatment. Including patients from only nine tertiary care centers can be the main reason for the low prevalence value, as minority are estimated to be followed in hospitals other than these centers, and in private hospitals. Lack of awareness, among both physicians and patients, poor index of suspicion, and undiagnosed cases have further minimized the prevalence. Men accounted for 59.5% of the patients, with a mean age at diagnosis of 43 ± 12 years, with SD 11.72 years, SEM 1.088. Corresponding figures for women were 40.5% and 46 ± 14 years, with SD 13.57 years, SEM 1.527, respectively. As per the literature, data regarding sex distribution are variable. Most studies reviewed show female preponderance [20, 22–26]. However, one study has shown male patients to outnumber female ones [27], while another study has shown almost equal sex distribution [19]. As both endogenous and exogenous estrogen has been shown to suppress IGF-1, it has been hypothesized that estrogen may have a protective role in females of reproductive age, delaying the clinical presentation of acromegaly [28, 29].

At present, we have no evidence to conclude that acromegaly in Saudi Arabia is more common in males. The slight male predominance in our study is probably due to the reasons

Table 3 Treatments received and outcome

Treatment	Patient	Cured	Controlled	Active	Not available
Surgery, radiotherapy, and medical therapy	32	4	18	10	–
Surgery and medical therapy	75	17	29	29	-
Surgery	50	27	1	8	14
Medical therapy	14	-	7	2	5
Surgery and radiotherapy	9	4	-	1	4
Radiotherapy and medical therapy	1	-	-	1	-
Radiotherapy	-	-	-	-	-
Total available data	181	52	55	51	

mentioned above, reflecting the pool of missed cases, although earlier diagnosis in men and mean age are in accordance with those observed in earlier studies [20, 22–26].

GH and IGF-1 levels at diagnosis did not show any significant difference related to gender ($p = 0.311$ for GH and 0.546 for IGF-1, respectively); however, wide variations were observed in our study population as reflected by the standard error of the mean. This can be due to multiple factors, such as including patients diagnosed many years previously, changes in biochemical assay over the period, and lack of a centralized GH and IGF-1 assay facility. The small sample size and missing data could further have contributed to it.

Magnetic resonance imaging was the imaging modality of choice, and information was available for 144 patients (73.8%), out of whom 133 (92.4%) had macroadenomas and 11 (7.6%) had microadenomas, which is in accordance with most of the studies [19, 20, 23–25]. Concerning tumor invasiveness and pathology details could not be determined. This could be due to underreporting, as the data were extracted from the patient records.

Due to its insidious and indolent nature, the diagnosis of acromegaly is difficult and needs a high index of suspicion. Our data are in accordance with other studies. The common presenting features in our study were also in accordance with other studies: these can be easily overlooked or can be attributed to other common etiologies, again necessitating the importance of suspicion for early diagnosis. Increased sebum production is a recognized feature, but acne is often not considered as a presenting feature of acromegaly, although there are adequate literature data regarding their association [30]. In our study, only 13 patients (31%) presented with acne.

The comorbidity burden of acromegaly was also addressed in this study, as a prolonged unrecognized period of GH hypersecretion leads to its accumulation over the duration. Diabetes mellitus was the most common morbidity, along with hypertension, sleep apnea, goiter, and arthropathy, as seen in other registries [19, 20, 24, 25]. Compared with AcroBel, the Belgian registry on acromegaly and the Spanish Acromegaly Registry [19, 25], we found a higher prevalence of diabetes mellitus, hypertension, and sleep apnea. This is not surprising given that the prevalence of metabolic syndrome, DM, and obesity in Saudi Arabia is known to be one of the highest worldwide [31, 32].

Increasing age and male gender were observed to be more commonly associated with diabetes mellitus, as observed in another study [24]. In our study, we found a significant association between the increasing age of subjects and diabetes mellitus, with $p = 0.001$ and coefficient of correlation (r) as 0.331; however, we did not find any significant association between male gender and diabetes mellitus, $p = 0.768$ and $r = 0.011$. The small sample size could be a possible reason for this in our study. Hypertension, being another common comorbidity, was also assessed, and the association between hypertension and male gender was found to be nonsignificant ($p = 0.306$, $r = 0.081$).

Association of diabetes mellitus with elevated IGF-1 is well known from previous studies [33, 34], but we were unable to find any association or correlation between them ($p = 0.907$, $r = 0.01$), most likely due to the small sample size. There was, moreover, no association or correlation between diabetes mellitus and elevated GH level at diagnosis ($p = 0.187$, $r = 0.116$).

It was also observed that only elevated IGF-1 levels at diagnosis, and not GH, predicted the presence of diabetes [24]. Our findings are in accordance with these earlier studies.

Figures for arthropathy and cardiovascular and cerebrovascular disease were available for a smaller number of patients, suggesting underreporting. The prevalence of colonic polyps was only 22.7%, which is much lower than that of the AcroBel study [19]; however, data were available for only 44 patients. This is probably due to the underutilization of colonoscopy as well as underreporting. Out of 95 patients for whom malignancy data were available, only eight patients were identified as having cancer, and colorectal cancer was diagnosed in only one patient.

Treatment modalities did not vary between these institutes, as all of them have tertiary care facilities. Patients were treated as per international guidelines for the management of acromegaly [1].

Of the patients with available data in our study, not a single patient had cured disease status without undergoing surgery. In the whole cohort, multimodal therapy achieved a cure in 52 patients (28.7%). A further 55 patients (30.1%) were not cured by surgery and radiotherapy but had good control of biochemical markers with medical treatment, while around 51 patients (28.2%) still had active disease despite using multiple modalities of treatment. Compared with that of other studies [19, 25], the cure rate was lower in our study, which again reflects poor awareness leading to late diagnosis.

Our study is small when compared to other studies conducted round the globe [19, 20, 22–25]. Nevertheless, it is the first to be done in the Middle East region. There were a number of reasons for this. First, being limited to only nine tertiary care centers meant missing those patients followed up in smaller cities and outside these nine centers. Also, the study being multicenter and retrospective in nature, we did not have the privilege of centralized GH and IGF-1 measurement for standardized evaluation of the outcome of different treatment modalities. Compared with the general population, acromegaly has two- to threefold increased mortality, and successful treatment can reduce it [35], as revealed in a meta-analysis which showed, overall, 72% increased mortality [36]. Lack of mortality data also limited our assessment of the outcome of different treatment strategies. Finally, we acknowledge the lack of awareness concerning acromegaly diagnosis and management both among patients and physicians in our country. Nevertheless, despite all these pitfalls, our study was able to generate epidemiological data and reflect clinical, biochemical, and therapeutic outcomes which were very similar to those of other acromegaly registries round the world.

Conclusion

Our study is the first and largest of this rare disease reported to date in the region. The retrospective nature of our database has limitations, but the results provide important information about the clinical presentation, comorbidities, management, and therapeutic outcome of acromegalic patients under the conditions of the healthcare system in Saudi Arabia, as management of this disease is distributed over different hospital settings with variable resources. Overall, the therapeutic outcomes were analogous to those of other acromegaly registries around the world. We believe that the results of this study can be used as a step toward improving the surveillance protocol and therapeutic outcome. Furthermore, a comprehensive acromegaly registry to enable early identification, evaluation, and selection of the best therapeutic approaches to improve therapeutic outcomes is highly needed in our country/region.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by a research ethics committee of the King Fahad Medical City (KFMC) research center, Riyadh and King Faisal Specialist Hospital and Research Center (KFSH&RC), Riyadh, Saudi Arabia.

Informed consent Not applicable.

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