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Clinical Presentation, Treatment, and Outcome of Acromegaly in the United Arab Emirates

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ABSTRACT

Objectives: We sought to ascertain the clinical characteristics and control rate of acromegaly in the UAE. ***Methods***: We conducted a multicenter retrospective analysis of all patients presenting with acromegaly to six endocrine centers in the UAE between November 2010 and December 2018. Demographic, clinical, biochemical, and radiologic data were collected. Patients were considered controlled if normal insulin-like growth factor-1 (IGF-1) level and growth hormone < 1 mcg/L were achieved at their last visit. ***Results:*** A total of 75 patients were included in the study (60.0% males, 33.3% native UAE nationals). The mean age at diagnosis was 37.2 (range: 12–69) years. Common clinical features at diagnosis were headache (82.4%), coarse facial features (82.4%), acral enlargement (79.7%), and sweating (31.3%). Diabetes mellitus/prediabetes and hypertension were present in 45.2% and 35.5% of patients, respectively. About 82.2% had pituitary macroadenoma on pituitary magnetic resonance imaging. At presentation, 27.0% and 3.2% of the patients had secondary hypogonadism and diabetes insipidus, respectively. Overall, 76.7% of the patients underwent surgery, 20.8% received radiotherapy, and 50.7% received medical therapy. At their last clinic visit, only 43.7% of all patients achieved disease control. ***Conclusions:*** Our study shows a high prevalence of pituitary macroadenoma in our acromegalic population, suggesting a delayed diagnosis. Also, a significant proportion of patients remained uncontrolled. Efforts to increase physician's awareness of acromegaly and to improve disease control are underway.

Acromegaly is the second most common functioning pituitary adenoma, with a prevalence of 60–125 cases/million.[1,2] It is characterized by excessive growth hormone (GH) release and is caused by pituitary macroadenoma in the vast majority of patients.[3] Patients usually present with symptoms related to the trophic or metabolic effects of insulin-like growth factor-1 (IGF-1) and GH, symptoms of mass effect or occasionally incidentally.[3–5] Delay in diagnosis is common and is related to the gradual changes in facial features making it very challenging for family and even healthcare professional to recognize, especially when the disease is mild.[3]

Uncontrolled acromegaly is associated with significant morbidities as well as increased mortality.[6] Achieving biochemical control is one of the main treatment goals in acromegaly and has been associated with improvement in several of the acromegaly comorbidities as well as a lowering of mortality to that of the general population.[7] Nonetheless, approximately 40% of patients from 19 national acromegaly registries remain uncontrolled.[8]

As data on acromegaly is primarily derived from studies in Europe, patients from the Middle East and North Africa (MENA) region are underrepresented. This study aimed to assess the clinical characteristics and control rate of patients with acromegaly in the UAE.

METHODS

We conducted a multicenter, retrospective study of all patients diagnosed with acromegaly between

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2010 and 2018. Six centers participated in the study; three from Al Ain city, two from Abu Dhabi city, and one from Dubai city. Four facilities are public (Tawam Hospital, Sheikh Khalifa Medical City, Al Ain Hospital, and Dubai Hospital), and two are independent (New Medical Center in Abu Dhabi and Al Ain). In all centers, the essential components of neuroendocrine care are available. However, radiotherapy was only available in one center (Tawam Hospital). Furthermore, multidisciplinary teams are not consistently functional in all centers except Tawam Hospital. In most parts of the UAE, health care is provided on the basis of health insurance system coverage for all residents in the UAE. It is freely provided by the state for UAE nationals and is a legal requirement for residence permits for expatriates mostly covered by employers (or other sponsors). Different health insurance tiers provide different levels of insurance coverage in different localities with two tiers readily recognized; a high tier and a standard tier.

We also compared our results with corresponding data available in published acromegaly series from the MENA region (Saudi Arabia, Oman, Iraq, Morocco, Jordan, Turkey, Iran, Pakistan, and India). Data were extracted from the corresponding publications.[9–19]

The cases were identified using ICD 9 and ICD 10 codes or according to other methods in each center. Demographic data in addition to symptoms, biochemical status, other pituitary hormones, tumor size at presentation, treatment modality(s) used, and the medical therapy at last visit were collected. Cases with incomplete data or insufficient information were excluded. Data were cross-checked using gender, tumor size, date of birth, and nationality to exclude duplicates. The disease status at last visit was established using IGF-1 and GH levels. Patients were considered controlled if normal IGF-1 level and GH < 1mcg/L were achieved at the last point of assessment.

Continuous data are presented as means and standard deviations (SDs) or median and ranges according to the studied variable. Categorical comparisons were performed with the chi-square test. Simple binary logistic regression was used to find the degree of association with independent and dependent variables. A statistical significance level of p-value < 0.050 was used. No statistical analysis was applied to the regional comparison.

RESULTS

Seventy-five patients were included in the study [Table 1]. In brief, 45 (60.0%) were men, and the mean age at diagnosis was 37.2+11.6 years (range: 12–69). The three most common clinical features at diagnoses were headache (82.4%), coarse facial features (82.4%), and acral changes (79.7%). Among 62 patients with available data, 28 (45.2%) had diabetes mellitus (DM)/prediabetes, while 22 (35.5%) had hypertension. Endocrinologists suspected the diagnosis of acromegaly in 36 out of 51 (70.6%) patients with available data while other specialties contributed less in detecting the disease. The vast majority (82.2%) of patients had macroadenoma as a cause of acromegaly, while empty sella syndrome was noted in two (2.7%) patients. Both of the latter patients had normal levels of growth hormone-releasing hormone and normal thoracoabdominal imaging. None of the patients in our cohort was diagnosed with an extra-pituitary source of GH excess.

Fifty-six out of 73 (76.6%) patients with available data underwent surgery [Table 2]. Transsphenoidal (TSS) (microscopic/endoscopic) approach was used in 49 patients, craniotomy in one patient, and the combined approach in one patient. Data on the exact type of surgery was not available in five patients. Repeat surgery was performed in five patients. Data on medical therapy (at last visit) was available for 69 patients. Of those, 28 patients were on monotherapy (25 octreotide long-acting release (LAR), three pegvisomant), seven on combination therapy (six octreotide LAR and cabergoline (CAB), one patient on pegvisomant and CAB), and 34 patients were not on any medications. No patients in our cohort were on dopamine agonists alone as monotherapy or a combination of pegvisomant and somatostatin analog. Radiotherapy was used in 15 out of 72 (20.8%) patients with available data; six stereotactic, six conventional, and the exact modality was unknown in three. None of the patients received radiotherapy as an initial modality of treatment.

Seventy-one patients were eligible for assessment of disease control at the last visit. Of those, 31 (43.7%) had normal IGF-1 and GH < 1 mcg/L and were considered controlled. The only predictor for disease control was high insurance coverage, whereas tumor size did not predict outcome [Table 3]. Of the remaining 40 uncontrolled patients, 19 were not on medications, 15 were on octreotide

Table 1: The demographic, clinical, and radiological characteristics of 75 patients with acromegaly in the UAE.

Characteristics	Results*
Demographics	
Age at diagnosis, years	37.2 ± 11.6
Male, gender	45/75 (60.0)
UAE, nationality	25/75 (33.3)
Clinical manifestations	
Headache	56/68 (82.4)
Acral changes	55/69 (79.7)
Facial features	56/68 (82.4)
Sweating	21/67 (31.3)
Diabetes mellitus	28/62 (45.2)
Arterial hypertension	22/62 (35.5)
Who first suspected the diagnosis of acromegaly?	
Endocrinologist	36/51 (70.6)
Internal medicine	3/51 (5.9)
Family physician	4/51 (7.8)
Neurologist	3/51 (5.9)
Orthopedic surgeon	2/51 (3.9)
Others	3/51 (5.9)
Unknown	24/75 (32.0)
Pituitary morphology on imaging	
Macroadenoma	60/73 (82.2)
Microadenoma	11/73 (15.1)
Empty sella	2/73 (2.7)
Unknown	2/75 (2.7)
Components of hypopituitarism	
Hypogonadism	17/63 (27.0)
Hypothyroidism	12/60 (20.0)
Secondary adrenal insufficiency	12/61 (19.7)
Cranial diabetes insipidus	2/62 (3.2)

**Results given as mean ± standard deviation or proportion (percentage).*

LAR monotherapy, four were on a combination of octreotide LAR and CAB, and data on medical therapy was unknown in two. Only 13/40 underwent surgery, while radiotherapy was utilized in five patients only.

The characteristics, management, and outcomes of 831 cases of acromegaly described in either specific acromegaly series or acromegaly patients included in pituitary disorders series reported from Saudi Arabia, Iraq, Iran, Turkey, Pakistan, Jordan, Oman, Morocco, and India between 2004 and 2019 are summarized in Table 4. The comparison was limited by the two different models employed (acromegaly only versus all pituitary diseases) but included homogenous treatment unselected acromegaly

Table 2: Frequency of the treatment modality and acromegaly control rate at the last documented visit.

Variables	Results*, n (%)
Surgery	
Yes	56/73 (76.7)
No	17/73 (23.3)
Unknown	2/75 (2.7)
Radiotherapy	
Yes	15/72 (20.8)
No	57/72 (79.2)
Unknown	3/75 (4.0)
Medical therapy	
Octreotide LAR	25/69 (36.2)
Octreotide LAR and cabergoline	6/69 (8.7)
Pegvisomant	3/69 (4.3)
Pegvisomant and cabergoline	1/69 (1.4)
None	34/69 (49.3)
Unknown	6/75 (8.0)
Control status**	
Controlled	31/71 (43.7)
Uncontrolled	40/71 (56.3)
Unknown	4/75 (5.3)

LAR: long-acting release.
**Results are given as absolute and relative frequencies.*
***Control was defined as normal serum insulin-like growth factor-1 and serum growth hormone < 1 mcg/L.*

cohort. The largest series (either single study or combined) were reported from India, Iraq, Iran, and the present study. The mean ages fell between the third and fifth decades of life. Where reported, somatic effects were common, while metabolic abnormalities were variable. Macroadenomas were

Table 3: Predictors of acromegaly control using simple binary logistic regression analysis used to find the degree of association with independent and dependent variables.

Predictor	*p*-value
Age	0.450
Gender	0.310
High tier insurance coverage*	< 0.010
Tumor size	0.600
History of surgery	0.240
History of radiation therapy	0.220

**Based on cure rates of 16/23 (69.6%) in the higher tier insurance coverage vs. 12/47 (25.5%) in the standard insurance coverage. Data on the remaining variables is not shown due to statistical non-significance.*

Table 4: Descriptive comparison of seven acromegaly series from the Middle East and three nearby countries (Pakistan, India, and Turkey) presented in reverse chronological order.*

Country	UAE	Morocco	Iraq	Saudi Arabia	Iran	Pakistan	India	Turkey	Jordan	Oman
First author	Al Dahmani K	Askaoui S	Mansour A/ Al-Yasseri B	Hussein S	Khamseh M	Tabassum S	Dutta P	Evran M/ Nuhoglu I	Malkawi O	Al-Futaisi A
Year of publication	2019	2019	2018/2019	2018	2017	2017	2015	2014/2009	2008	2007
Reference	This study	9	10/11	12	13	14	15	16/17	18	19
Patients, n	75	30	124	30	85	53	271	104	51	8
Mean age	37.2	42.4	46.4	42.4	43.9	39.7	37.1	40.4	43.4	42
Acral changes, %	79.7	-	-	83.3	81.3	96.2	88.9	87.5	-	75
Coarse facial features, %	82.4	-	-	-	-	96.2	13.7	92	-	-
Headache, %	82.4	-	-	40	63.5	-	49.1	6.5	-	-
Visual field defect, %	-	-	-	16.6	29.4	-	27.3	27.9	-	-
Diabetes mellitus, %	45.2	34	70	45.6	-	-	16.2	33	-	-
Hypertension, %	35.5	23.4	61.7	50	-	-	17.7	21	-	-
Macroadenoma, %	82.2	93.3	75.9	83.3	72.9	76.7	83	83	90	75
Surgery, %	76.6	90	30.6	86.7	100	94.3	98.9	90.3	-	75
Radiotherapy, %	20.8	56.7	3.2	-	11.7	49.1	12.6	32.3	15.7	-
Medical treatment, %	92.0	NA	85.7	-	27.1	17.0	14.8	-	33.3	-
Control rate, %	43.7	6.7	68.3	43.3	36.5	-	28.5	-	33.3	-
Settings	Multicenter	Single center	Two studies from two referral centers	Single center	National registry	Single center	Single center	Two studies from two referral centers	Single center	Single center
Limitations	Data from tertiary referral centers in three emirates only.	Low number, insufficient presentations features, very low control rate. Control rate criteria not defined.	Different criteria for disease control.	Insufficient data on presentation and nonsurgical treatment modalities.	Small sample for large population.	Poster abstract, insufficient data on presentation and control rate.	May not be representative of the whole country.	When available, data on treatment modalities and control rate derived from one study only.	Poster abstract only, insufficient data on presentation. Criteria for control not mentioned.	Few patients, with insufficient data on presentation, nonsurgical treatment modalities and control rate.

**No formal statistical analysis was applied due to variation of in availability of comparative data from all the series. Studies were presented in chronological order to take consideration of changing practices overtime.*

fairly frequent, and surgery was the most commonly used modality of therapy. Surgery was the primary line of management in all series (75–100%) except for Iraq (only 30.6%).

DISCUSSION

Acromegaly is a rare disorder of GH overproduction and is usually diagnosed in the fourth decade of life.[3] Our findings concur with this with the mean age at diagnosis being 37.2 years and most patients aged between 30–50 years at diagnosis. Approximately 80.0% of our patients had enlargement of the extremities and coarse facial features similar to previous studies reporting morphological changes in 80–90% of patients.[4,13,20] In the Liege Acromegaly Survey (LAS) reporting on 3163 patients with acromegaly, hypertension and diabetes were present at diagnosis in 27.7% and 28.8% of the patients, respectively.[21] While our rate of hypertension was similar, diabetes and prediabetes were more prevalent in our sample (45.2%). Thus, our patients are similar to the Mexican patients with acromegaly, whose diabetes and prediabetes rates were 30% and 32.9%, respectively.[4]

Acromegaly is a systemic disease, and patients may have variable presentations that might include, but are not limited to, osteoarthritis, carpal tunnel syndrome, sleep apnea, cardiovascular complications, and jaw dysfunction. Hence, physicians from different subspecialties could encounter those patients. In two recent studies, non-endocrinologists suspected the diagnosis of acromegaly in 55.1–71% of the patients.[20,21] In contrast, only 32.0% of our patients were suspected of having acromegaly by non-endocrinologists. This suggests low awareness of the disease among physicians in other specialties, and it might indicate under-diagnosis of this condition in our population.

Acromegaly results from pituitary macroadenoma in the vast majority of patients. A recent report, including data from 16/19 national acromegaly registries with data on tumor size at diagnosis, showed that approximately 75% of acromegalic patients had macroadenoma (range: 67–84%).[8] The high prevalence of macroadenoma (82.2%) in our study is greater than most of the studies included in the above report[8], ranking third after studies from New Zealand (84%) and South Korea (83%).[4,22] This high prevalence of macroadenoma may reflect a delayed diagnosis of acromegaly in these studies and our own.

In our study, nearly three-quarters of the patients underwent at least one operation, typically, TSS, while a minority required additional surgery. This practice conforms with current guidelines recommending surgery as a first treatment modality in most patients with acromegaly.[7] It also highlights the fact that surgery is the only effective modality resulting in a potentially effective cure of the disease without the need for additional treatments.

Medical therapy is commonly used in patients with active acromegaly. In our study, nearly half of all patients were on active medical therapy at their last visit. Most of these patients were treated with somatostatin analogs (SSAs) either as monotherapy or in combination with CAB. None of the patients was on CAB monotherapy, probably reflecting its established lower efficacy rate in acromegaly. Few of our patients were on pegvisomant, which is costly and a non-formulary medication in our country. The lack of SSAs and pegvisomant combinations may reflect the cost of such medications, concerns related to the liver enzyme abnormalities, fear of non-compliance and/or the limited experience of treating physicians. About half of all patients were not on medical therapy, reflecting possible disease cure, patient's non-adherence to follow-up or therapy, medical insurance limitations and/or physicians' failure to evaluate after surgery or radiotherapy. Lack of properly structured and consistently functioning neuroendocrine multidisciplinary teams in many of the centers observed in the settings of acromegaly care may have deprived some patients of the collective wisdom of several experts needed in complex cases.

Radiation therapy was the least common (20.8%) modality used in our patients, typically as an adjunct therapy in patients with active disease despite surgery and medical therapy, as suggested by the guidelines.[7] In France, the use of radiation therapy has declined over the last three decades.[23] This reflects improvements in medical therapy, thus avoiding the potential downsides of radiation such as its delayed effect and higher hypopituitarism risk as well as its association with increased stroke and malignancy risk.[24]

Globally, the rate of acromegaly control is 63%, but it varies between 37% to 76% across different registries.[8] This large variation in disease control

could be attributed to different factors such as the varying definition of disease control (based on IGF-1 levels, GH < 1, GH < 2.5 or combination of normal IGF-1 and different GH cutoff values) and the availability of different treatment modalities. In our study, we used the most stringent criteria for disease control (normal IGF-1 and GH < 1 mcg/L) and we included all patients who visited the study centers even if they were lost to follow-up or declined other treatment modalities. Disease control was achieved in 43.7% of our patients, which is similar to a study from Saudi Arabia (43.3%) but higher than that reported in Iran (36.5%).[12,13] However, this rate is lower than many recently reported series from Europe.[8] Additionally, our observed higher rate of pituitary macroadenomas may have adversely impacted our results since tumor size is an important predictor of surgical cure. Remission rates of 75.3%, 48.6%, and 8.3% in patients with acromegaly due to microadenomas, macroadenomas, and giant adenomas, respectively, have been reported.[25] However, in our cohort, tumor size did not predict the outcome, perhaps because vast majority of the patients had macroadenomas. While the experience of the neurosurgeon is crucial to achieving a cure, this data was lacking in our study. The 120 patients with uncontrolled disease in the German acromegaly registry were attributed to patient-related factors (declining to escalate therapy in 23.3% and non-compliance in 20.6% as the primary reasons for persistently elevated serum IGF-1 levels).[26] Many of our patients with the uncontrolled disease were on monotherapy alone, and only a couple on pegvisomant. This suggests that physician inertia, drug availability, and cost as possible reasons for uncontrolled disease. In line with this, higher tier insurance coverage was the only predictor of disease control in our study. This could be attributed to the variable access to expensive medical treatment between different insurance tiers. Moreover, a recent survey of physicians treating acromegaly in the MENA region reported medication cost and lack of physicians' awareness as the biggest barriers to optimal disease control.[27] Another factor leading to uncontrolled disease may be the underutilization of radiotherapy; a valuable modality for disease control when surgery and medical therapy fail. However, radiotherapy is only available in one center (Tawam), which may have discouraged physicians and patients from considering this option on the basis of access and the inconvenience of traveling. Future prospective studies should focus on identifying the different factors responsible for suboptimal acromegaly control in our region.

Including our patients, only 831 cases of acromegaly could be retrieved from studies based in the MENA and surrounding regions [Table 4]. However, these series are inhomogeneous, whereby some included acromegaly patients only and others described acromegaly patients among other patients with other pituitary disorders series reported from 10 countries over 15 years (2004 to 2019) [Table 4]. Only a scoping narration was possible as no formal comparisons were feasible due to the differences in samples reported and study design (from clinic to regional and national cohorts). Also, we did not take account of studies evaluating the single efficacy of single treatment modalities (surgery or radiotherapy). Similarly, single case reports, which may have specific peculiarities, were not included. All the studies were retrospective in nature and mostly derived from tertiary referral centers. Data from three countries (Jordan, Pakistan, and Morocco) were derived from poster abstracts presented at international meetings while the rest were published in regional indexed journals in the last five years. A national acromegaly registry existed only in one country (Iran). The mean ages of patients ranged from 32.1 to 46.4 years. Where reported, somatic effects were common and metabolic abnormalities were variable. Macroadenomas were present in 72.2–93.3% of the patients with about a quarter having visual field defects suggesting delayed presentation. Except in Iraq, surgery was the most commonly used modality of therapy, probably being the most readily available treatment option. This perhaps reflects a lack of surgical skills or other attributes of the reported cohort. Such a practice cannot be supported by tumor size since high proportion of macroadenomas (75.9%) were reported. Medical therapy was used less frequently in India and Pakistan, possibly limited by cost. Radiation was the least commonly used treatment modalities in most countries. Cure rates, differently defined in many studies, varied between one- and two-thirds, clearly lagging behind international expectations. In our attempt at the narration of the data from the regions, we are cognizant of the recent developments over the time of studies, and the differences in care structure and resources in different countries.

There are a few limitations of our study that are noteworthy. The retrospective nature depending on the quality of routine clinic-based documentation, could not fully track all comorbidities and hormonal analysis consistently. Also, the number of patients in this study similar to those from the MENA and neighboring regions is smaller than other studies reported in the international literature. However, acromegaly is a rare disease and is most likely under-diagnosed in our region. Furthermore, the study included only six centers which may not reflect disease status in the whole country and those natives and expatriates who may have chosen to be treated elsewhere outside the country. Lastly, the participating centers in this study are mostly tertiary referral centers where complicated cases are usually encountered, and it is possible that other cases of presumed controlled acromegaly were not referred to these centers. Nevertheless, this study is the second most comprehensive study addressing acromegaly in the MENA region and provides important information to guide additional educational and interventional activities in the region.

CONCLUSION

Our study showed that a significant proportion of patients with acromegaly have macroadenomas. Endocrinologists suspected most of the cases. However, less than half of the patients are biochemically controlled. Educational activities are needed to increase the awareness of the disease among health care providers for early detection. Clear care pathways for referral and access optimal management at specialist services disregarding the insurance tiers are also needed to achieve internationally recommended outcomes. A nationwide register should help ascertain and continuously monitor the quality of care and map the volume managed, expertise and outcomes of professionals, and available resource centers involved. The pooling of cases and specific designation/accreditation may also need to be enforced by regulators and funders. Also, further studies should explore the disease- and care-related factors leading to the observed relatively high rate of uncontrolled disease in this study.

Disclosure

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