Original Article

Presentation, Morbidity and Treatment Outcome of Acromegaly Patients at a Single Centre

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Abstract

Introduction: The management of acromegaly, a rare and potentially curable disease, has undergone a paradigm shift in the past few decades. Many of the treatment modalities recommended for acromegaly are either too expensive or not available in many parts of India. There is a dearth of treatment and outcome data in Indian patients. **Aim:** Our aim was to study the clinical presentation, hormonal profile, radiology, management, and outcome of the disease at our center. **Materials and Methods:** Fifty one patients with acromegaly who attended the Department of Endocrinology, SKIMS, Srinagar, between October 2015 and April 2017, were included in the study. Clinical and hormonal profiles, comorbidities, treatment modalities, and outcome were evaluated. **Results:** The gender distribution was equal with the mean age of 42.3 ± 10.9 years at diagnosis. The majority (41) of the patients had macroadenoma. The most common presenting manifestations were acral enlargement and headache. Hypertension was present in 23, musculoskeletal manifestations in 19, and diabetes mellitus in 11 patients. Surgery was the most common method of treatment. Preoperatively only one patient with micro-adenoma had hypocortisolism, which was persistent in postoperative period, while no patient had preoperative or postoperative hypothyroidism or hypogonadism. As per the present consensus criteria, 23.7% patients achieved disease control (40% with microadenoma and only 19.5% with macroadenoma). The surgical complications occurred in 5 patients–CSF leak in 3 meningitis in 2 patients all except one having macroadenoma. **Conclusions:** The presentation of disease was generally comparable to that reported in literature. Cure rates were significantly lower than those reported from many large centers.

Keywords: Acromegaly, clinical presentation, pituitary macroadenoma

Introduction

Acromegaly is a disease of spectacular growth and metabolic disorders that has been intriguing and fascinating generations of physicians for centuries. Left untreated, the disease results in gross acral and facial disfigurement, musculoskeletal disability, cardiac failure, respiratory dysfunction, diabetes mellitus, and accelerated mortality.[1] The incidence of acromegaly is about three per million population per year with an estimated prevalence of 60 per million.[2] The incidence of acromegaly in India is 0.49 per lack person-years, which is reported in a cohort of service personnel who were followed for a long duration.[3]

This disease has no sex predilection and usually sets in during the fourth decade of life. In the majority of patients (>95%) it results from a growth hormone (GH) secreting pituitary adenoma.[1]

Acromegaly affects almost every organ and is associated with increased morbidity and mortality mainly because of the aggregate of cardiovascular risk factors such as hypertension, diabetes mellitus, and lipid disorders and to the appearance of cardiomyopathy associated with the disease.[4]

Transsphenoidal surgery (TSS) remains the treatment of choice to achieve disease control. Radiotherapy and medications are often required in addition to surgery or, when surgery is unavailable, contraindicated, or declined.

Given the lack of data about acromegaly from Kashmir Valley, we undertook this study on clinical profile and management of acromegaly, as seen at our center.

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Materials and Methods

This series includes 51 patients with acromegaly who visited department of Endocrinology, SKIMS Srinagar, between October 2015 and April 2017. These included: (a) patients first time suspected and proved to have acromegaly (new, prospective patients), and (b) patients with previously diagnosed acromegaly of whatever duration and whether treated or not (old, retrospective patients). Institutional Ethics Committee exempted the study from the ethical clearance as during the meeting it was found that the study involved collection of anonymous data of acromegaly patients.

The records of the retrospective patients were analyzed for clinical characteristics and the results of endocrine and radiological investigations. The prospective patients received a detailed clinical assessment. In addition to routine biochemical investigations, they received glucose suppression test (GST) for growth hormone (GH) using 75 g anhydrous glucose and taking samples for GH at 30, 60, 90, and 120 min. Acromegaly was diagnosed if the nadir plasma GH level during the GST was 1 ng/ml or more; and/or, IGF-1 levels above the upper limit of age matched range.[5]

In the case of patients with uncontrolled diabetes mellitus, this test was undertaken after achieving glycemic control for 2 weeks.[6] In addition to the routine preoperative biochemical investigations, hormone profile including 8 AM serum cortisol, T3, T4, thyroid stimulating hormone (TSH), luteinizing hormone (LH), follicle stimulating hormone (FSH), testosterone and prolactin, including GH were measured. All were measured by DXI 800, Beckman Coulter Chemiluminescence random access analyzer following manufacturer's protocol.

A gadolinium enhanced magnetic resonance imaging (MRI) of the hypothalamopituitary area was obtained in all new acromegaly patients and was interpreted by a single experienced radiologist. For the retrospective patients, all the available pre- and post-treatment MRI and CT films were reviewed.

The post treatment assessment was performed at 3 months to assess the results of treatment. This included clinical assessment, endocrine evaluation of pituitary functions as indicated, and MRI of the hypothalamopituitary area. Random GH followed by glucose suppression test for nadir GH values was performed at 3 months.

Statistical analysis

Statistical Package for Social Sciences, SPSS 22, was used for data analysis. The results were expressed as percentages or mean ± SD, as specified. Pearson's Chi-square method was used for comparing proportions and percentages whereas Student's *t*-test was used for comparison of continuous variables. A two-tailed *P* value was used for calculating statistical significance; a value of <0.05 was taken as significant.

Results

The series included 51 (28 prospective and 23 retrospective) patients, with the mean age at presentation being 42.3 ± 10.87 years (range 22--70 years). The mean height of the whole group was 167.3 ± 8.2 cms with a range of 152--187 cm. The average body mass index (BMI) was 27.0 kg/m^2. Imaging revealed a pituitary microadenoma in 10 and pituitary macroadenoma in 39 patients.

Clinical features

Our patients had a broad spectrum of presenting manifestations, ranging from acral enlargement, headache to musculoskeletal manifestations, and even diabetes mellitus. Overall, the three most common presentations were acral enlargement followed by headache and facial coarsening. All the clinical features encountered have been listed in Figure 1. Hypertension was present in 45.1% and diabetes mellitus in over a fifth (21.6%) of patients. One third of the females had menstrual disturbances.

Investigations

About a half (22/51) of our patients had glucose intolerance, including six, five, and eleven patients with impaired glucose tolerance, impaired fasting, and diabetes mellitus, respectively. Dyslipidemia was seen in more than two-thirds of our patients with elevated total cholesterol (>200 mg/dl) in 35.14% and triglycerides (>150 mg/dl) in 67.5%. Over a quarter of patients had evidence of ventricular hypertrophy, one-fifth had visceromegaly and two patients had colonic polyps [Table 1].

Pretreatment hormonal profile

Pretreatment growth hormone (GH) values at various intervals after a glucose load (75 g) revealed average GH levels at 30, 60, 90, and 120 min were 21.72 ± 12.83, 21.74 ± 12.92, 20.98 ± 11.85, and 19.27 ± 12.37 ng/ml, respectively. All the six patients who had a preoperative IGF-1 estimation had clearly elevated levels. Gonadotropin deficiency was the commonest associated pituitary deficit [Table 2]. Preoperatively only one patient with micro-adenoma had hypocortisolism, which was persistent in postoperative period, while no patient had pre- or postoperative hypothyroidism or hypogonadism.

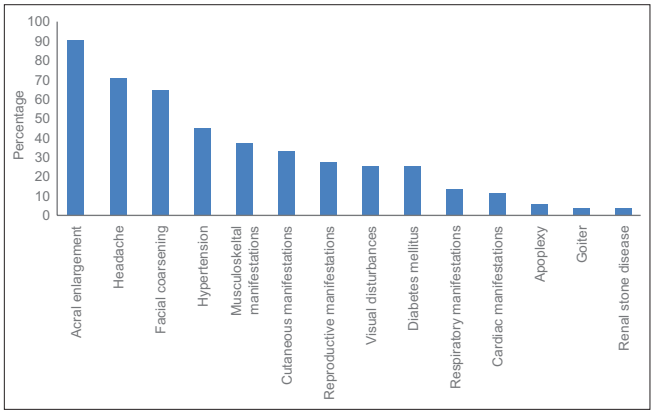

Figure 1: Bar diagram showing frequency of various clinical features in patients at presentation

Treatment modalities used

An overwhelming majority (88.2%) of the patients received surgery as primary modality of treatment; the approach was transnasal trans-sphenoidal in 93% and subfrontal in 7%. Three (5.9%) patients received primary medical therapy while three others declined any treatment.

Table 1: Preoperative investigative profile

Parameter	Frequency	Percentage
ECG		
Normal	36	70.6
LVH	15	29.4
CXR		
Normal	45	88.2
Increased CTR	6	11.8
USG Abdomen		
Normal	41	80.4
Visceromegaly	10	19.6
Renal stones	2	3.9
Colonoscopy (18)±		
Normal	2	11.1
Polyp present	16	88.9
Echocardiography (29) ±		
Normal	17	58.6
LVH	8	27.6
Diastolic dysfunction	2	6.9
Dilated cardiomyopathy	2	6.9

±Number of patients

Table 2: Data of hormone evaluation, preoperative and postoperative

Parameter	Pretreatment	Post-treatment
GH levels (random) ng/ml	26.7±19.31	6.45±7.76
IGF-1 level ng/ml	801.3±453.8 (6)$^{\delta}$	439.33±215.7 (12)$^{\delta}$
Hypocortisolism	5/44 (11.6%)	13/44 (29.5%)
Hypogonadism	14/20 (70%)	14/23 (60.9%)
Hypothyroidism	6/41 (14.3%)	6/43 (14.0%)
Hyperprolactinemia	22/36 (61.1%)	6/37 (16.2%)

$^{\delta}$Number of patients

Post-treatment Hormone Profile and Imaging

Postoperatively, mean GH levels at 30, 60, 90, and 120 min after glucose load were 5.44 ± 8.72, 5.29 ± 8.43, 4.07 ± 6.18, and 4.64 ± 6.88 ng/ml, respectively. Postoperatively, the nadir GH following a glucose load was <1 ng/ml in 10 (27.3%), 1 to <2.5 ng/ml in 11 (29.73%), 2.5 to <5 ng/ml in 8 (21.62%), 5 to <10 ng/ml in 4 (10.81%), and 10 to 20 ng/ml in 4 (10.81%) of the 37 patients on whom the information was available.

Post-treatment, hypogonadism continued to be the most common pituitary hormone deficiency [Table 2]. As per the present consensus criteria, 23.7% patients achieved disease control (40% with microadenoma and only 19.5% with macroadenoma).

Postoperative MRI performed at variable periods (2--7 months) after treatment was available in 43 patients and revealed residual/recurrent disease in 24 (55.8%). Of the 24 patients with residual/recurrent disease, 12 (50%) were started on medical therapy (monthly octreotide depot preparation in 5 and cabergoline in 7 patients), while six (25%) were treated with repeat surgery and six patients received radiotherapy.

Complications

The surgical complications occurred in five (11.6%) of our operated patients and included postoperative CSF leak in three (6.96%) and postoperative meningitis in two (4.6%). All of these, except one, were having macroadenoma.

Discussion

This is a sizeable series evaluating the clinical presentations and outcome of acromegalic patients and has afforded a glimpse of the state of overall care of these patients from the Indian subcontinent. The mean age at presentation was

Table 3: Comparison between different acromegaly series

Characterstic	Present series	Dutta *et al*.[6] PGI Chandigarh, 2015	Sarkar S *et al*.[12] CMC Vellore, 2014	Belgian Registry[9], 2007
Number of patients	51	271	113	418
Mean Age (Years)	42.3	37.1	38.1	44
Male:Female ratio	1.04	0.98	0.98	1.03
Hypertention	45.1%	17.7%	37.1%	39.4%
Diabetes Mellitus	21.6%	16.23%	29.2%	25.3%
Arthropathy	37.3%	14.4%	-	46.7%
Sleep Apnea	13.7%	10.3%	-	17.1%
Any hormone deficiency	65%	85%	24.8%	39.7
Most common Hormone deficiency	Hypogonadism (65%)	Hypothyroidism (55.5%)	Hypocortisolism (24.4%)	-
Microadenoma	19.6%	16.2%	14%	16%
Postoperative Meningitis	4.6%	1.5%	2.7%	-
CSF Leak	7%	19.2%	2.7%	-
DI	0%	22.2%	7.1%	-
Remission rate	23.7%	28.5%	31.9%	27%

"-" represents not mentioned

42.3 years with equal male:female ratio [Table 3]. The mean height at presentation was 167.3 ± 8.19 cm (the average Indian standard height being 157.5 cm), with BMI of 27 ± 3.24 kg/m^2 consistent with previous studies.[6-8] Earlier literature from national series as well as the registries from Spain and Belgium reported similar findings.[9,10]

Patients with acromegaly present with a wide spectrum of manifestations. In our series, the most common presenting manifestations were acral enlargement (90%) and headache (71%). Reid *et al.* reported headache at diagnosis in nearly half of the 324 patients with acromegaly.[11] In our study, the prevalence of headache was significantly lower in the prospectively studied 28 patients than in the retrospectively studied 23 patients (52.2 vs. 85.7%; *p* 0.008). We believe this to be due, at least partly, to relatively earlier diagnosis in the prospectively studied patients.

Table 3 compares the characteristics of our patients with that reported from PGI Chandigarh, CMC Vellore, and Belgian Registry. The prevalence of hypertension in acromegaly is variable, ranging from 18% to 60%.[13] Hypertension (45.1%) in our patients was more as compared with the overall prevalence of 29.8% in the Indian population. Hypertension is believed to contribute to the impaired cardiovascular function in acromegaly.[14] Hypertention, diabetes mellitus, and arthropathy incidence is similar, except from the series of PGI Chandigarh where it is lower, which could be due to abundance of younger patients in their series.

Sleep apnea were reported by 13.7% of our patients according to STOP BANG criteria. We did not perform sleep studies in our patients and this fact explains the low prevalence of sleep apnea in our patients as compared with other studies which reported a prevalence between 39 and 79%.[8,11]

In keeping with the increased incidence of micronephrolithiasis with acromegaly and its significant correlation with disease duration, four (7.6%) of our patients had renal stone disease.[15] Sixty five percent patients had deficiency of one or more anterior pituitary hormones (in whom hormone profile was available), which was less than reported by Dutta *et al*. but more as compared with 39.7% from the Belgian acromegaly registry.[6,9]

Hypogonadism was the most common hormone deficiency in our series which was different from reported by others. The remission rates in our study was less as compared with rest [Table 3] as well as to other reports that ranged from 57.3% to 64% when surgeries were performed by a single dedicated pituitary surgeon.[16,17] The cure and control in acromegaly is largely a function of the skill and experience of the operating surgeon.

The postoperative MRI done at least 3 months after surgery revealed residual disease in 55.8% of our patients. Abe reported residual disease in 40%.[18] Usually effective medical agents are used very infrequently in our patients with acromegaly. The main reason for this is poor affordability of our patients; inconsistent availability and accessibility to such medications also contribute.

Postoperative complications are reported in about 11% of patients and their incidence again depends on the experience of the operating surgeon. The lower figure in our study likely reflects inconsistency in documentation of seemingly innocuous events and inherent difficulties in "post-event" data collection.

Some of the limitations of our study include its retrospective cum prospective nature, relatively small number of patients, incomplete hormone profile, and heterogeneity of data given that some patients had evaluation at more than one place.

Conclusions

Acromegaly is a disabling but potentially curable disease. Our patients presented with an advanced and aggressive disease, and higher GH levels. The higher mean growth hormone levels in our series was likely due to late detection of the disease. The majority of them harbored a macroadenoma and had lower cure rates, due to lack of a dedicated pituitary surgeon. In a resource constrained nation like ours, it would be cost-effective to develop a dedicated surgical team focused on management of pituitary disorders, as administration of a prolonged medical therapy in the event of treatment failure is often unaffordable.

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Conflicts of interest

There are no conflicts of interest.

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