Can immediate postoperative random growth hormone levels predict long-term cure in patients with acromegaly?

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Original Article

Clinical profile and outcome of patients with acromegaly according to the 2014 consensus guidelines: Impact of a multi-disciplinary team

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ABSTRACT

Aim: The diagnosis and treatment of acromegaly, a rare and possibly curable disease, has undergone a paradigm shift in the past few decades. Our aim was to study the changing trends in clinical presentation, management and outcome of the disease in the last fifteen years.

Methodology: 271 consecutive patients with acromegaly treated at the Departments of Endocrinology and Neurosurgery, PGIMER, Chandigarh, between 2000 and 2014, were included in the study. Clinical and hormonal profiles, comorbidities, treatment modalities, outcome and mortality data were evaluated. The cure rate was assessed according to the present consensus criteria.

Results: The gender distribution was equal with the mean age (±SD) of 37.1 ± 12.3 years at diagnosis. The average lag period to diagnosis was 4.7 ± 4.2 years. The most common presenting manifestations were acral enlargement and headache followed by visual deficits. The overall mortality rate was 5%, with the perioperative mortality being 1.5%. The most prevalent comorbidities in our series were hypertension (17.7%), diabetes mellitus (16.2%), arthropathy (11.8%) and obstructive sleep apnea (10.3%). Overall, 2 patients in our series suffered from extra-pituitary neoplasms and 12 patients had apoplexy as the presenting manifestation. As per the present consensus criteria, the cure rate in our series was 28.5%. The cure rate was only 7.9% when many surgeons were operating. It increased to 25.5% when surgeries were being performed by one surgeon exclusively; and, when a sub-specialty clinic exclusively for pituitary diseases was set up, the cure rates improved upto 56%.

Conclusion: Acromegaly has wide-ranging manifestations from acral enlargement to altered sensorium; incidental diagnosis was not prevalent in our series. Majority of the cases were due to the presence of a pituitary macroadenoma. Better cure rates can be achieved only when a dedicated group of multi-disciplinary team is involved.

Key words: Acromegaly; clinical features; outcome; somatotropinoma

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Introduction

Acromegaly, an uncommon disease, is caused by chronic hypersecretion of growth hormone (GH), usually by a pituitary adenoma. The annual incidence of acromegaly is 3 per million and the prevalence is 40 per million.[1] The disease has seen a paradigm shift in the diagnosis and treatment in the past few decades. We evaluated patients

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with acromegaly treated at PGIMER, Chandigarh, India over the past 15 years, with the aim to study their different clinical presentations, associated comorbidities and their outcome following treatment.

Patients and Methods

This series includes 271 acromegalic patients treated between January 2000 and December 2014 at the Departments of Endocrinology and Neurosurgery, PGIMER, Chandigarh. The inclusion criteria was the presence of nadir plasma GH level greater than (>) 1 ng/ml on oral glucose tolerance test (OGTT); and/or, IGF-1 levels above the upper limit of age-matched range.[2] In the presence of concomitant diabetes mellitus, the diagnosis was made if any two out of the following criteria was met: The nadir GH levels greater than or equal to (≥) 5 ng/ml and IGF-1 levels above the age matched range; or, the nadir GH levels > 0.4 ng/ml on OGTT performed after 2 weeks of glycemic control; or, a raised insulin-like growth factor-binding protein 3 (IGFBP-3) with the presence of clinical features of acromegaly and an adenoma on imaging.[3] At the time of inclusion, complete clinical details including the anthropometry were recorded for every patient. In addition to the routine preoperative biochemical investigations, the hormone profile including thyroid function tests (TFTs), luteinizing hormone (LH), follicle stimulating hormone (FSH) and prolactin (PRL) were measured by immunoradiometric assay on gamma counter (Perkin Elmer), while testosterone (T)/estradiol (E_2) and cortisol (F) were measured using radioimmunoassay on a Rack beta counter (Wallace) until 2008, and using electrochemiluminiscence on a COBAS 6000 machine (Roche, Hitachi) after that period. GH was measured by immunoradiometric assay on gamma counter (Perkin Elmer) until 2006, by electrochemiluminescence (IMMULITE, Siemens, Germany) until 2011, and finally on COBAS 6000 (Roche Hitachi) for the duration 2012-2014. IGF-1 was measured from 2000 to 2006 by enzyme immunoassay (DRG, Germany) kits and by chemiluminescence (JSD) for the period between 2007-2014. The WHO standard 98/574 was used for GH assay and 02/254 for IGF-1. HbA1c was measured by high performance liquid chromatography (BioRad variant II). Genetic analysis for aryl hydrocarbon receptor-interacting protein (AIP), multiple endocrine neoplasia (MEN)-1 and CDK1B was randomly done in 45 patients by Multiplex Ligation-dependent Probe Amplification (MLPA) using MRC-Holland kit P244-C1 (MK). The record keeping and audit of cure was done by the endocrinologists independent of the neurosurgeons ensuring the process of an external audit.

OGTT (using 75 g anhydrous glucose) was performed for all patients and random GH values were measured pre-operatively, in the immediate post-operative period, at 6 hours post-surgery, on the post-operative day 1 to 5, and 6 weeks later. IGF-1 was measured pre-operatively and at 12 weeks post-operatively for all patients in the last 8 years. Gadolinium enhanced cranial MRI focusing on the sella turcica with MR angiography of the circle of Willis was done as a routine departmental protocol. This is because the incidence of aneurysms is higher in these patients compared to the general population. Imaging was repeated during follow-up to look for any residual tumor. Optical colonoscopy was performed for all patients until 2004, following which it was replaced by a multidetector CT (MDCT) colonoscopy.[4] Multiple neurosurgeons (n = 5) operated upon these patients till 2005. However thereafter, only a single dedicated pituitary surgeon (KKM) performed most (55%) of the surgeries. All biopsy specimens were sent for histopathology and immunostaining (after 2006), using antibodies against anterior pituitary hormones (LH, FSH, GH, PRL, ACTH, TSH). The criteria for cure was the random GH less than (<) 1 ng/ml or nadir GH during OGTT being less than (<) 0.4 ng/ml; and, the IGF-1 levels within the normal range for age.

Statistics

The groups were compared using Student T test or Mann-Whitney U test depending on their distribution. Multivariate analysis was used to predict factors affecting cure. The data was analyzed on SPSS software version 15 (Chicago, IL). The data was expressed as mean ± standard deviation, unless specified and a P value of < 0.05 was considered as significant.

Results

The series included 134 male and 137 female patients, with the mean age at presentation being 37 ± 12.5 years (range 4 – 73 years) [Figure 1]. The average lag period (from the onset of symptoms to diagnosis) was 56.3 ± 50.2 months (4.7 years) and the average body mass index (BMI) was 26.32 kg/m^2. The mean height of the whole group was 167.2 cm and in the adolescent patients, it was 176.6 ± 13.6 cm (the average Indian standard height being 157.5 cm).

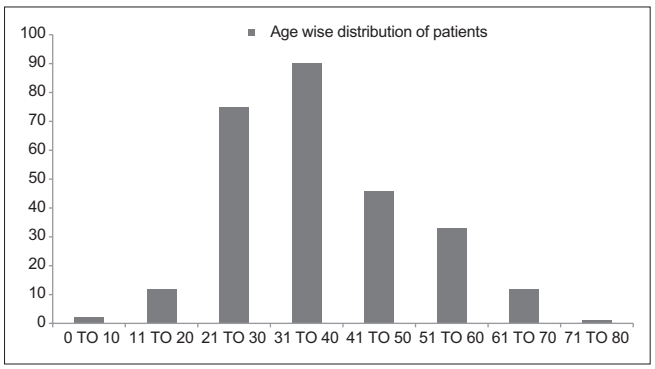

Figure 1: Age wise distribution of patients

Aetiology

Majority of the cases were due to pituitary adenomas with two cases being due to ectopic GH and growth hormone-releasing hormone (GHRH) secretion.[5,6] Out of the 271 patients, 18 (6.6%) had a microadenoma, 26 (9.6%) had a mesoadenoma (intrasellar microadenoma) while the rest (83%) harbored a pituitary macroadenoma (including 44 (19.5%) patients with a giant adenoma (≥4 cms in any diameter). One patient had an adenoma in an ectopic location (a pharyngeal pituitary adenoma). One patient had a choriostoma and another had a gangliocytoma accompanying the pituitary adenoma.[7] Seventy one (26.2%) adenomas had a suprasellar, 25 (9.2%) had a parasellar and 9 (3.3%) patients had an infrasellar extension. McCune-Albright syndrome was the cause of acromegaly in 8 patients and all of them had underlying fibrous dysplasia.[8] The Knosp grading was available for the last 100 patients [grade 0 – 20%, grade 1 – 20%, grade 2 – 20%, grade 3 – 15% and grade 4 – 25%][9] [Table 1].

Familial Acromegaly and Other Syndromes

In our series, 5 families (13 members, 4.5%) were having familial acromegaly with at least 2 affected members in each family [Figure 2]. Genetic analysis was performed in 45 patients randomly. Two patients from one family were found to be positive for the aryl hydrocarbon receptor interacting protein (AIP) mutation and another member from the same family was an unaffected carrier. One young boy (aged 3 years) was positive for germline AIP mutation, and one of his sisters and father were silent carriers. Two of our patients had genetically proven multiple endocrine neoplasia (MEN-1) syndrome. Both of them subsequently presented with a primary hyperparathyroidism.

Clinical Features

Our patients had a broad spectrum of presenting manifestations, ranging from acral enlargement, headache to lower gastrointestinal bleed and even diabetes mellitus. Overall, the 3 most common presentations were acral enlargement followed by headache and visual deficits. In the females, the third most common presentation was amenorrhea. All the clinical features have been listed in Table 2 while the malignancies/tumors observed are listed in Table 3. In all except one patient, malignancy was diagnosed synchronously with acromegaly, while it was metachronous in a patient with carcinoma of the ovary. As previously mentioned, the prevalence of colonic polyps was not increased.[10]

Acrogigantism was present in 45 (16.2%) patients (height >97th percentile for age). As stated in our previous series, these patients had higher GH levels and excepting for one patient, all other had a macroadenoma.[11] Two of these patients belonged to the same family (first cousins) and were diagnosed as cases of Familial Isolated Pituitary Adenoma (FIPA).

Unusual Presentations

A few patients presented with some unusual features like tonsillomegaly; seizures and auditory hallucinations (due to the tumor extension into the temporal lobe); and, hypotension and bleeding per rectum due to multiple colonic polyps. One patient presented with epistaxis due to apoplexy in the pituitary macroadenoma with an infrasellar extension.

Pre-treatment Hormonal Profile

Complete anterior pituitary hormone profile was available for 215 patients. The most common abnormality was cortisol deficiency followed by hypogonadism [Table 4]. Preoperatively, the average nadir GH level was 51.5 ng/ml (2.5-1250 ng/ml) and only 10 (3.7%) patients had GH levels in the safe range (<2.5 ng/ml). Paradoxically, 7 patients had raised GH levels but normal IGF-1 levels matched for age. 183 (85.1%) patients had one or more anterior pituitary hormone deficiencies, with 106 patients

Table 1: Different types of adenomas in our series

Adenoma size	Age <30 years (*n*=78) (%)	Age >30 years (*n*=191) (%)	*P* value
Microadenoma	1 (1.3)	17 (8.9)	0.03
Mesoadenoma	6 (7.7)	20 (10.5)	0.47
Macroadenoma	71 (91)	154 (80.6)	0.01
Giant adenoma	17 (21.8)	27 (14.1)	0.14

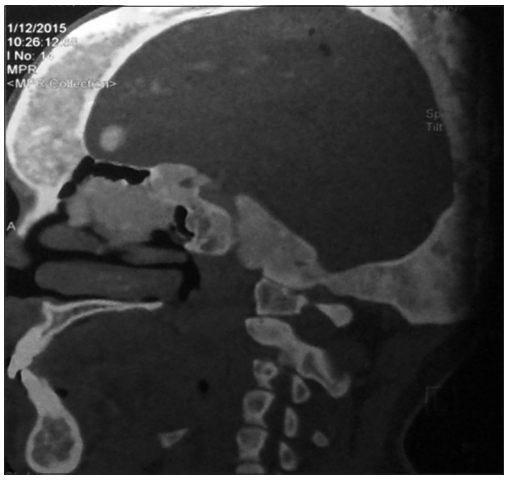

Figure 2: Sagittal section of CT scan of head showing McCune – Albright syndrome as the cause of acromegaly. Gamma knife was given as primary therapy

Table 2: Clinical features at presentation in our series

Presenting manifestation	Total cases (*N*=271)	Percent	Age <30 years (*n*=78) (%)	Age >30 years (*n*=193) (%)	*P* value
Acral enlargement	241	88.9	70 (29)	171 (71)	0.78
Headache	133	49.1	42 (31.6)	91 (68.4)	0.32
Visual deficit	74	27.3	24 (32.4)	50 (67.6)	0.43
Hypertension	48	17.7	1 (2.1%)	47 (97.9)	<0.001
Diabetes mellitus	44	16.23	8 (18.2%)	36 (81.8%)	0.06
Amenorrhea	54	19.93	20 (37)	34 (67)	0.02
Facial coarsening	37	13.65	9 (24.3)	28 (75.7)	0.5
Loss of libido/Erectile dysfunction	32	11.8	6 (18.8)	26 (81.2)	0.14
Goitre	18	6.64	5 (27.8)	13 (72.2)	0.92
Galactorrhea	16	5.9	7 (43.8)	9 (56.2)	0.23
Apoplexy	13	4.8	1 (7.7)	12 (92.3)	0.12
Altered sensorium	7	2.58	1 (14.3)	6 (85.7)	0.68
Diabetic ketoacidosis	6	2.2	0	6 (100)	0.19
Diplopia	2	0.74	2 (100)	0	0.08
Incidental	2	0.74	2 (100)	0	0.08
Respiratory manifestations					
Sleep apnea	28	10.3	8	20	
Nasal polyps	2	0.74	2	0	
Cutaneous manifestations					
Acanthosis nigricans	24	8.9	8	16	
Skin tags	27	9.9	7	20	
Hirsutism	9	3.3	4	5	
Seborrhea	31	11.4	10	21	
Cutis verticis gyrata (bull dog scalp)	2	0.74	0	2	
Granulomatous cheilitis	1	0.37	0	1	
Musculoskeletal manifestations					
Back ache	7	2.6	2	5	
Arthralgia	32	11.8	11	21	
Crippling proximal myopathy	5	1.8	2	3	
Quadriparesis	1	0.37	1	0	
Paraparesis	2	0.74	1	1	
Poliomyelitis (Figure 3)	2	0.74	2	0	
Carpel tunnel syndrome	6	2.2	0	6	
Fibrous dysplasia (Figure 4)	8	2.9	5	3	
Mimicking motor neuron disease	1	0.37	0	1	
Renal stone disease	8	2.9	6	2	
Cardiovascular dysfunction					
Cardiac dysfunction	10[$]	3.6	3	7	
Valvular lesions	5	1.8	3	2	
Coronary artery disease	1	0.37	0	1	

[$]Of these, the initial 4 were operated without optimization of cardiac function and all of them died. The rest were optimized with octreotide for at least 6 months

having one, 49 having two, and the remaining 28 having three hormone deficiencies.

Treatment Modalities Used

Majority of the patients underwent transsphenoidal surgery, performed by multiple pituitary surgeons till 2006 and after that mostly by a single surgeon (KKM). Five patients underwent surgery twice; four had a residual tumor, while one patient had a recurrent adenoma. Subfrontal approach was used for 14 invasive adenomas with suprasellar and parasellar extensions. Only 1 patient received gamma knife radiosurgery as a primary therapy [Table 5]. At follow-up, 15 patients received radiotherapy, 16 patients underwent gamma knife radiosurgery and 20 were on monthly octreotide depot preparation. Besides these, another 20 patients were prescribed cabergoline in the follow-up period.

Post-treatment Hormone Profile

146 patients with a complete postoperative anterior pituitary hormone profile were included for analysis. In the

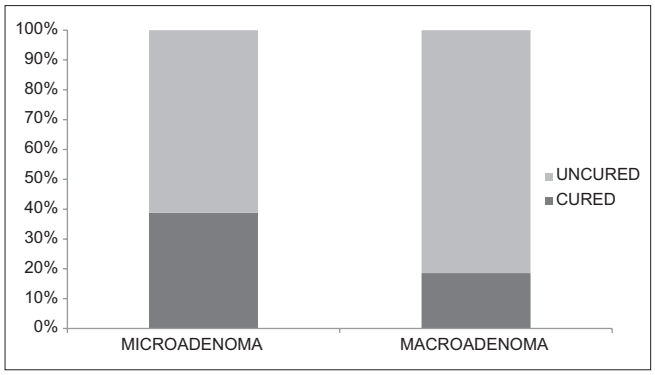

Figure 3: Cure rate in microadenomas versus macroadenomas

Table 3: Different neoplasms present in acromegalic patients in our series

Neoplasms	No. of subjects
Colon cancer	4
Meningioma	2
Breast cancer	2
Ovarian cancer	1
Papillary thyroid carcinoma	1
Chronic myeloid leukemia (BCR-Abl positive)	1
Pleomorphic adenoma of parotid gland	1

Table 4: Pre-treatment hormonal profile

Hormonal parameter	Total cases (n=215)	Percentage
Hypocortisolism	100	46.5
Hypogonadism	75	34.9
Hypothyroidism	49	22.8
Hyperprolactinemia	61	28.4

Table 5: Treatment modalities used in our series

Type of surgery done	Total cases (N=252)	Percentage
Transsphenoidal	233	92.5
Subfrontal approach	16	6.4
Primary gamma knife	1	0.4
Primary external beam radiotherapy	2	0.8

Table 6: Post-treatment hormonal profile

Hormone parameter	Total cases (%) (N=146)	New cases (%)*	Recovered (%)**
Hypocortisolism	81 (55.5)	26 (32)	17 (17)
Hypogonadism	56 (38.4)	11 (19.6)	13 (17.3)
Hypothyroidism	50 (34.2)	30 (60)	12 (24.5)
Hyperprolactinemia	11 (7.5)	2 (18.2)	27 (44.3)

*Percentage of new cases has been calculated by using the total cases of individual hormone parameters in the post-treatment period as denominator. **Percentage has been calculated for recovered cases using the total cases of individual hormone parameters in the pre-treatment period as denominator

post-treatment period, 129 (88.4%) patients had one or more hormonal deficiency, while 14 (5.2%) patients became GH deficient [Table 6].

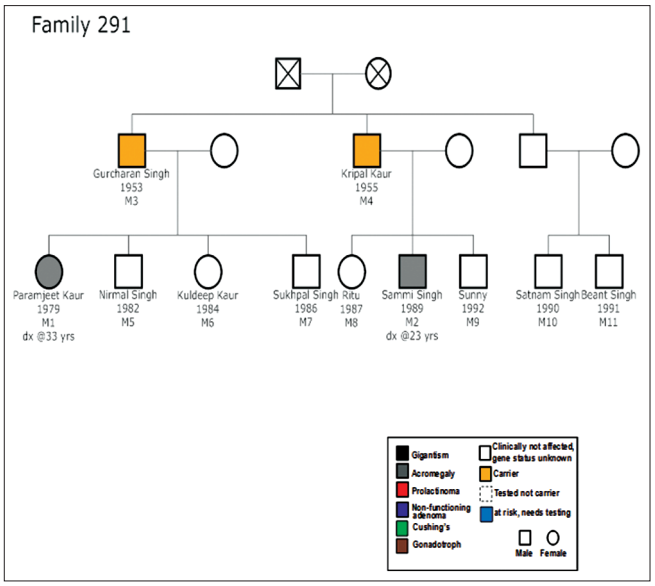

Figure 4: Pedigree of a family with familial acromegaly

Complications

The commonest complication in the postoperative period was CSF rhinorrhea followed by permanent diabetes insipidus [Table 7]. The complication rate for patients with a microadenoma was 35% while the same for those with a macroadenoma was 53.2%. Two patients suffered from sphenoditis, while one patient had a massive pulmonary thromboembolism that led to her demise. Fourteen (5.2%) patients had a classical triphasic response and 4 patients undergoing radiotherapy, developed radiation induced brain disorders in the form of encephalomalacia.[12]

Immunohistochemistry

Immunohistochemistry was available for 100 patients. Fifty biopsies were positive only for GH, 34 were positive for both GH and prolactin, 2 were positive only for prolactin, one biopsy was positive for ACTH and GH, while 13 were negative for all hormones. 7% of our patients had bone, dural or mucosal invasion.

Outcome

One hundered and seventy two patients were included for analysis as they had at least 6 months of follow-up. Only 49 (28.5%) subjects were cured. Out of 123 uncured patients, 22 had elevated random GH values with normal IGF-1 matched for age, while 6 had elevated IGF-1 rather than GH levels. Overall, 6 patients had a physiological cure, defined as intact pituitary hormones with random GH <1 ng/ml and IGF-1 levels normal for

age. The cure rate for microadenomas was 38.8% while that for macroadenomas was 18.6%. On multivariate analysis (n = 100), the cure was not influenced by pre treatment GH, IGF-1, Knosp grading and/or dural invasion, GH positivity alone or GH + prolactin positivity. It was rather dependent on the adequacy of surgery.

Mortality

Fourteen (5.2%) patients died due to different causes [Table 8], the commonest being cardiovascular dysfunction. Out of the 4 (1.5%) patients who died in the peri-operative period, two patients had congestive cardiac failure, one patient developed fatal pulmonary thromboembolism and another patient died due to massive pneumocephalus following an inadvertent opening of the lumbar drain.

Discussion

This is a large series evaluating the clinical presentations and outcome of acromegalic patients from the Indian subcontinent. Our patients presented at a younger age and the lag period prior to the treatment was less as compared to other series emanating from this area. Moreover, patients with macroadenomas far outnumbered those with microadenomas and GH levels were very high. The mortality was 4.8% and only 28.5% patients were cured.

Table 7: Postoperative complications in our series

Complication	Total cases	Percentage
CSF rhinorrhea	52	19.2
Diabetes Insipidus (permanent)	19	7
Diabetes Insipidus (transient)	41	15.2
Meningitis	4	1.5
VIth nerve palsy	2	0.75
Cavernous carotid artery injury	2	0.75
CSF overdrainage	1	0.37

Table 8: Causes of mortality in our series

Cause of mortality	No. of subjects (n=14)
Congestive cardiac failure	4
Pulmonary thromboembolism	1
Inadvertent opening of lumbar drain with massive pneumocephalus	1
Apoplexy with congestive cardiac failure	1
Refractory septic shock with diabetic ketoacidosis and seizures	1
Massive hematuria due to vesicle calculus	1
Colon carcinoma	1
Fulminant hepatic failure (Hepatitis B positive)	1
Sudden respiratory arrest and quadriplegia due to coexisting atlanto-axial dislocation	1
Carcinoma ovary with omental metastases, intestinal obstruction	1
Pulmonary tuberculosis	1

In the series by Nabarro, 18% patients had a microadenoma and 82% harbored a macroadenoma.[13] In our series, 6.6% had a microadenoma, 9.6% had a mesoadenoma, while 83% harbored a pituitary macroadenoma. Similar findings were seen in previous registries from Spain and Belgium where 73% and 79% patients harbored a macroadenoma, respectively.[14,15]

Patients with acromegaly may have a wide spectrum of presenting manifestations. In our series, the most common presenting manifestations were acral enlargement, headache and visual deficits. Although a previous review article mentions the incidence of apoplexy in pituitary adenomas ranging from 1% to 26%, the incidence of apoplexy in patients with acromegaly was 3.5% in the study by Nabarro and 4.8% in our series.[16,13] The prevalence of pigmented skin tags was 45% while that of acanthosis nigricans was 9% to 29% in their study, both being higher than our figures.[17] The prevalence of secondary amenorrhea and loss of libido in males was less in our study when compared to the the study by Nabarro.[13]

Arthropathy, hypertension and diabetes mellitus were the three most common comorbidities [Table 9]. The prevalence of hypertension in acromegaly is variable, ranging from 18% to 60%.[18] The prevalence of hypertension was 17% in our study, which was less as compared to the overall prevalence of 29.8% in the Indian population. It was, however, higher than the previous report of 14.5% from our institute.[19,20] Both genders were equally affected. This lesser prevalence of hypertension as compared to the overall prevalence in the Indian population could be due to abundance of younger patients in our series [Table 10].

The second most common comorbidity in our series was diabetes mellitus (16.23%). However, the incidence was less as compared to previous reports of 52.5% in a series from Russia and of 22.3% in the French registry. It was, however, comparable to Nabarro's series.[21,22,13] The lower prevalence of diabetes mellitus was probably due to a younger age at presentation, a shorter lag period in the detection of the disease, and the inclusion of lesser number of patients having a family history of diabetes.

Arthropathy was less than the previously mentioned figure of 60% to 70%; again, perhaps due to the younger age at presentation and a shorter lag period in our series.[23] Obstructive sleep apnea was less as compared to the previous literature where, the prevalence ranged from 19% to 79%, with a rising trend seen from 1980s to 1990s due to the increased use of polysomnography for diagnosis of the syndrome.[24] Cardiac dysfunction affected 3.7% patients,

Table 9: Cure rate for single versus multiple pituitary surgeons

Surgeon	2000 to 2004		2004 to 2009		2010 to 2014		Total		Since advent of pituitary clinic	
	surgery	cured (%)	surgery	cured (%)	surgery	cured (%)	surgery	cured (%)	surgery	cured (%)
Single dedicated surgeon	8	1 (12.5)	48	11 (22.9)	124	34 (27.4)	180	46 (25.5)	75	42 (56)
Others	11	1 (9)	24	2 (8.3)	3	0 (0)	38	3 (7.9)	nil	nil

Table 10: Comparison between different acromegaly series

Characterstic	Present series	Nabarro's series , 1987[13]	Spanish registry, 2004[15]	French registry, 2011[22]	Belgian registry, 2007[14]	Ezzat S *et al*, 1994[1]	Sarkar S *et al*., 2014[41]
Place	India	London	Spain	France	Belgium	Multicentre	India
Authors	Dutta *et al*	Nabarro JD	Mestrón A *et al*	Fieffe S *et al*.	Bex M *et al*	Ezzat S *et al*	Sarkar S *et al*
No. of patients	271	256	1219	519	418	500	113
Male: female ratio	0.98	1.1	0.65	0.83	1.03	0.88	0.98
Mean age at diagnosis (years)	37.1	33.8	45	46.1	44	40	38.1
Diabetes mellitus prevalence	16.23%	18.8%	37.6%	22.35	25.3%	30%	29.2%
Hypertension prevalence	17.7%	30.5%	39.1%	33.7%	39.4%	51%	37.1%
Arthropathy prevalence	14.4%	18%	19.6%	55.7%	46.7%	45%	-#
Neoplasm prevalence	4%	10.2%	7.5%	-#	10.5%	-#	-#
Individual hormone parameters	Evaluated	Evaluated	-#	-#	-#	-#	Evaluated
Cure rate	28.5%	21.9%	40.3%	-#	27%	-#	31.9%
Mortality	5.2%	18.4%	4.6%	-#	6.7%	-#	-#

#Not known or not mentioned in the study

which is comparable to 3.5% in Nabarro's series.[13] Six patients also had an accompanying renal stone disease, in compliance with the available literature that points towards an increased incidence of micronephrolithiasis in acromegalics with a significant correlation with the disease duration.[25]

The notion of increased risk of malignancy in acromegalic patients, compared to the general population, is still controversial. There have been reports of development of colorectal carcinoma, breast cancer, prostatic cancer, thyroid cancer, and even hematological malignancies in acromegalics.[16,26] The most common neoplasm in our series was colorectal carcinoma having an incidence similar to that found in other large series; interestingly, majority of the neoplasms in our series were synchronous with the diagnosis of acromegaly. This could be due to GH – IGF-1 axis acting as a promoter of these malignancies in patients having an underlying genetic predisposition.

Eighty five percent patients had one or more anterior pituitary hormone deficiencies, as compared to 39.7% from the Belgian acromegaly registry and 25.7% from the Spanish acromegaly registry.[14,15] This figure increased to 88.4% in the post-treatment period which was again higher than the previous studies.[27] In another series from Germany, 48.7% patients had one or more hormonal deficiency after 3 months of surgery.[28] During follow-up, 5.2% patients became GH deficient, which was less as compared to a previous report (9%).[29]

Except for a few selected cases where other approaches were used, 92.5% of our patients underwent transsphenoidal surgery. The post-operative complication rate was higher in overall patients and in patients with a macroadenomas, as compared to the previous reports of 2% and 9.3%.[28,30]

The most important aspect in the management of acromegaly in past few years has been the revision of the criteria for endocrinological cure. A consensus statement released earlier this year recommends morning fasting GH and IGF-1 levels in the normal range as the aim of medical treatment.[31,32] Before 2006, using GH cut-off of 2.5 ng/ml by immunoradiometric assay, the cure rate was 26.6%, while subsequently, using a criteria of 1 ng/ml by chemiluminescence gave a cure rate of 28.8%. The overall cure rate in our series was 28.5%, which was low as compared to the previous reports that ranged from 57.3% to 64% when surgeries were performed by a single dedicated pituitary surgeon.[26,28] When multiple surgeons operated on these patients, the cure rate was 7.9%; while, the cure rate was 25.5% for the surgeries performed by a single dedicated pituitary surgeon (KKM) [Table 9]. Moreover, the cure rate increased dramatically after the first 100 surgeries done by one of the authors (KKM). If the last 75 patients operated after the setting up of the pituitary clinic are considered, the cure rate was 56%. meaning that a multi-disciplinary team may provide much better results. It is also possible that the superior results could have been due to the progressively increasing experience of the single neurosurgeon operating on these cases. The low cure rate might also be explained by the lower cut-off values

of GH taken by us as compared to the previously used high cut-off values when GH was measured by radioimmunoassay.[26] Besides, the higher proportion of macroadenomas also, in all probability, decreased the cure rate. The cure rate was higher in microadenomas than in macroadenomas [Figure 5], a result similar to that seen in previous studies. The cure was dependent on completeness of the surgery but not on the postoperative/ follow up MRI picture or the pattern of immunostaining, as stated previously by Minniti *et al*. [Figures 6 and 7].[33-35]

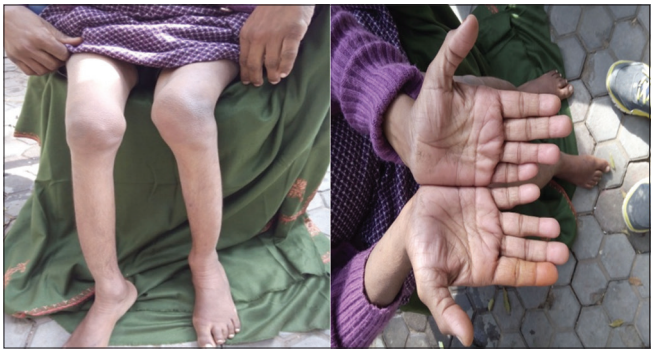

Figure 5: Differential growth of limbs in patients affected by acromegaly and pre-existing poliomyelitis; atrophic lower limbs and enlarged hands

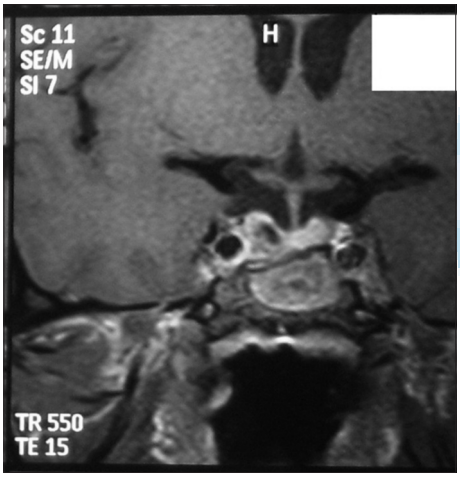

Figure 6: A patient with visible residue on pituitary MRI but clinically and biochemically cured. The GH was undetectable at 22 months of follow-up

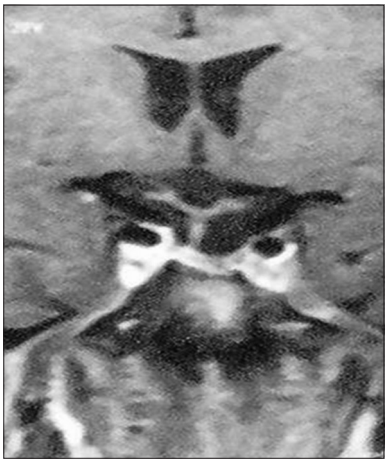

Figure 7: Postoperative imaging of a patient, without any radiologically visible tumor. However the patient is clinically and biochemically still not cured

Literature mentions an increased risk of early death in acromegalics, ranging from 34.6% to 39.4%, with major causes being cardiovascular, cerebrovascular and respiratory complications.[15,36-38] The overall mortality rate in our series (4.8%) was, however, much less than the crude death rate of 7% in the Indian population.[39] The most common cause of mortality was congestive cardiac failure, a fact that correlated with the previous literature.[38] The perioperative mortality was 1.5% (4 patients) in our series.

The limitation of our study was the lack of availability of complete hormonal profile in all the patients and the use of different assay systems over a period of time. The Immulite assay, even after recalibration, is 3 times higher than the Nichols assay and 6 times higher than the Diagnostic System Laboratories assay. Therefore, it might have underestimated the cure rate.[40] The other limitation was the non-availability of comparative GH values between the Immulite and Cobas e602 assays. The future will be of molecular biology and system biology to diagnose the disease at an early stage and predict the response to pharmacotherapy.[41,42]

Conclusions

Acromegaly is a disabling disease, but often curable. Our patients presented with an advanced and aggressive disease, and a higher GH level. The majority of them harbored a macroadenoma and had lower cure rates. The critical factor in achieving the desired results was the early diagnosis and treatment by a multi-disciplinary team dedicated to the management of pituitary disorders and performance of surgery by a dedicated neurosugeon. Moreover, a microadenoma is associated with lesser complications and a higher cure rate compared to larger tumors. 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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