Characteristics and outcome of surgically treated acromegaly patients attending an endocrinology clinic at a tertiary referral centre in Durban, South Africa over a period of 10 years

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Introduction

Acromegaly is an acquired endocrine disease due to overproduction of growth hormone (GH), most often from a pituitary somatotropinoma and characterised by progressive somatic and systemic manifestations.1–3

Excess GH and the subsequent elevation of insulin-like growth factor-1 (IGF-1) are the biochemical hallmarks of the disease and lead to the characteristic multi-system, often disfiguring, physical manifestations as well as the co-morbidities including diabetes mellitus (DM), hypertension (HT), arthritis, sleep apnoea and cardiovascular disease.4,5

Acromegaly is due to a pituitary adenoma in over 98% of cases, either purely GH-secreting (60%) or as part of a pluri-hormonal secretory adenoma. In rare cases, acromegaly is caused by ectopic secretion of growth-hormone-releasing hormone (GHRH) or GH.6 It may present with the following manifestations: symptoms and signs of GH hyper-secretion, tumour expansion with compression of the adjacent structures (optic chiasm, and cavernous sinus) and with the diagnosis of a co-morbid condition.7

Treatment strategies for acromegaly aim at reduction in tumour size or control of tumour growth, inhibition of GH hyper-secretion, and normalisation of IGF-1 levels. The three approaches to treatment are surgery, medical management and radiotherapy.8 The primary treatment is surgical, either trans-sphenoidal or trans-cranial. Trans-sphenoidal surgery is the treatment of choice for intra-sellar microadenomas and non-invasive macroadenomas. Trans-cranial surgery is reserved for patients with invasive or supra-sellar macroadenoma.8

Medical therapy includes three classes of drugs: dopamine agonists (DAs), somatostatin receptor ligands (SRL) and GH receptor antagonist (GHRA). These are usually adjunctive to primary surgical management.8

Radiation treatment (conventional, stereotactic) is rarely used as primary therapy and is usually employed following surgical debulking of non-resectable tumours.8

Biochemical criteria for cure of acromegaly have been debated over a number of years.9,10 With the improvements in GH assay performance, recent guidelines state that patients with random serum GH < 2.5 μg/l (measured by standard radio-immunoassay) after treatment do not have increased mortality and such patients are reported to have a standardised mortality rate (SMR) of 1.1 (95% CI 0.9–1.4), compared with an SMR of 1.9 (95% CI 1.5–2.4) in patients with random GH levels > 2.5 μg/l.8

The achievement of a ‘safe’ GH level and corresponding reduction in mortality is influenced by a number of factors, including the availability of a skilled and experienced dedicated pituitary surgeon and the judicious use of new therapeutic agents.11

In the developed world, acromegaly is able to be cured with a combination of surgery, medical therapy and radiotherapy in over 60% of subjects. An earlier study of 103 patients in Canada, treated with initial surgery, followed by medical therapy or
radiotherapy, reported a cure rate of 63%, defined by random GH < 2.5 μg/l, or GH nadir in a 75 g oral GTT < 1.0 μg/l and normal IGF-1. More recently, the large German Acromegaly Register study reported on disease control in 1 344 patients, using normal or low age- and gender-adjusted IGF-1 as the criterion. At the last follow up visit, IGF-1 was available for 1 275 subjects and, of these, 917 (71.9%) fulfilled the criterion for disease control. Results from the Spanish Acromegaly Register were similar, with 76% of 698 subjects regarded as controlled, as defined by a normal IGF-1 level.

Whilst acromegaly is well characterised in the developed world, there is a paucity of information from Africa and South Africa. The available literature from South Africa is limited to a single publication. This was a review of the 20-year experience (1974–1993) of acromegaly at a teaching hospital in Cape Town. Of the 72 patients in that study, the majority (79%) had a pituitary macroadenoma at diagnosis, and after a mean follow-up of 8.7 years only 43% were deemed to have been cured. After follow-up, 23 of 62 (37%) traced patients had died. The most frequent cause of death was cerebrovascular disease, although in 22% the cause was not defined. Only one report is available from Africa. In this report, acromegaly patients were addressed as part of pituitary tumours in general.

Reports are available from other developing countries. A retrospective study of 15 patients with pituitary macroadenomas at a tertiary care hospital in eastern India over a period of four years (2007–2011) reported that 10 (66%) patients had trans-sphenoidal surgery and, of these, cure was achieved in four (40%) subjects with no recurrence in the follow-up period. The remaining five (33%) subjects had no surgery: three (19.8%) of the five patients declined surgery and two (13.2%) had comorbidities precluding surgery. Five subjects received radiotherapy as a primary therapy. All five failed to respond to conventional radiotherapy and three (60%) subjects developed hypopituitarism.

The clinical profile and treatment outcome of patients with acromegaly in the developed world contrasts with these reports from the developing world. There are no studies of patients with acromegaly from KwaZulu-Natal to compare with more recent reports from the developed world and since Inkosi Albert Luthuli Central Hospital (IALCH) is a referral centre for a large catchment population, it is important to review the clinical profile and treatment outcomes of this disease.

**Aim**

The aim of the current study was to determine the clinical, radiologic and biochemical characteristics before and after treatment of all patients with acromegaly attending the endocrinology clinic at IALCH between January 2003 and January 2013.

**Material and methods**

**Study population and patient selection**

The study was a retrospective record review of all patients with acromegaly who attended the endocrinology clinic at Inkosi Albert Luthuli Central Hospital (IALCH) over a 10-year period: 2003–2013. IALCH is a public-sector referral hospital in Durban, KwaZulu-Natal, providing specialised neurosurgery and endocrinology services for the population of KwaZulu-Natal and part of the Eastern Cape in South Africa. The population residing in these regions exceeds 10 million. Patients were identified at a regional level and referred to IALCH for diagnosis and treatment. Therefore, the majority of patients with acromegaly using public sector health facilities in this drainage area were managed at IALCH. The study was approved by the University of KwaZulu-Natal Biomedical Research Ethics Committee (Ref: BE306/13) and the College of Health Sciences Postgraduate Research Committee.

**Data collection**

For each patient, clinical, laboratory and radiologic data were collected from the time of diagnosis and at 3, 6 and 12 months post-surgery. Clinical data included demographic details, symptoms and signs, co-morbid conditions and medication use. Laboratory data included baseline pituitary function, the response of GH to glucose suppression in a 75 g oral glucose tolerance test (GTT) and measurement of serum IGF-1 levels. The criteria used to define cure included a normal age-matched and gender-matched IGF-1 and a random GH < 1.0 μg/l. Radiologic data included tumour size and characteristics as well as information on compression of adjacent structures on either computed tomography (CT) or magnetic resonance imaging (MRI). In addition, details of surgical procedures, including perioperative complications and histology findings, were recorded. The requirement for postoperative adjunctive medical therapy (including pituitary hormone replacement) or radiotherapy was recorded.

**Laboratory methods**

All the hormonal assays were performed by the Chemical Pathology Laboratory at IALCH. GH was measured by chemiluminescent immunoassay (Siemens HGH kit on the Siemens Immulite 2000 XPi; Siemens, Erlangen, Germany). The GH detection limit was 0.05 μg/l with normal reference range of 0–3 μg/l in males and 0–8 μg/l in females. Intra-assay and inter-assay coefficients of variation were 3.5% and 6.5% respectively. IGF-1 was measured by chemiluminescent immunoassay (Siemens IGF1 kit on the Siemens Immulite 2000 XPi). The IGF-1 detection limit was 20 μg/l and the intra-assay and inter-assay coefficients of variation were 3.9% and 8.1% respectively. Other hormone measurements included free T3, free T4, thyrotropin (TSH), prolactin, random and 8:00 am cortisol, prolactin, follicle-stimulating (FSH) and luteinising (LH) hormone, gonadal steroids and serum and urine osmolality.

**Pituitary imaging**

Magnetic resonance imaging (MRI) scans were performed in the radiology department at Inkosi Albert Luthuli Central Hospital with a Siemens symphony 1.5 tesla or Siemens skyra 3 tesla. Gadolinium enhancement was utilised routinely unless contra-indicated.

**Statistical methods**

Stata® 13.1 software package (StataCorp, College Station, TX, USA) was used for statistical analysis. Data were calculated as means, standard deviation, medians and inter-quartile ranges (IQR) for 4 time points: baseline, 3–6 months post-intervention, 12 months post-intervention and the most recent review. The difference between baseline and each subsequent period was calculated and a Wilcoxon sign rank test was used for any change. All p-values were two-sided and p < 0.05 was considered statistically significant.

**Results**

**Patient characteristics**

The study group included 27 subjects, 11 (41%) male and 16 (59%) female, mean age 44.2 ± 14.0 years.
Clinical features at diagnosis

Table 1 indicates the clinical characteristics at the time of presentation. The majority of patients (n = 25, 92.6%) noted a change in appearance. The commonest symptom was headache, reported by 24 (88.9%) of patients.

Symptoms of hypopituitarism were reported in 10 (37.4%) subjects. Three (27.3%) male patients had erectile dysfunction and 7 (43.8%) female subjects had menstrual disturbance. The predominant physical changes that occurred were increased size of hands or feet, and prominent supraorbital ridge. Visual field defects were recorded in 17 (62.9%) patients at diagnosis and blindness was not reported in any subject.

Comorbidities at presentation

The prevalence of co-morbid medical diagnoses at presentation is given in Table 1. The two commonest co-morbid conditions were hypertension (n = 14, 51.8%) and diabetes mellitus (n = 7, 25.9%). Of the subjects with diabetes mellitus, four were treated with oral anti-hyperglycaemic therapy, one patient was on insulin and two were on both oral therapy and insulin. Other co-morbidities, diagnosed in fewer subjects, included osteoarthritis, goitre and sleep apnoea. In subjects with osteoarthritis, the predominant joints affected were knees and hips.

Biochemical tests at baseline

GH and IGF-1 values were available in all patients. At presentation, the mean random GH was 57.58 ± 33.54 μg/l, and the mean IGF-1 was 956.8 ± 432.91 μg/l. Mean IGF-1 was 3.5 times above the normal glucose tolerance, 7 (25.9%) had impaired glucose tolerance or impaired fasting glucose and 4 (14.8%) had diabetes. None of the patients suppressed GH to < 1.0 μg/l during the GTT. The mean GH nadir during the GTT was 34.88 ± 28.43 μg/l. In subjects with pituitary macroadenoma, mean GH nadir in the GTT was 35.5 ± 29.8 μg/l, as compared with those who had pituitary microadenoma in whom the mean GH nadir was 29.3 ± 14 μg/l (p = ns).

Hyperprolactinaemia was found in 18 (66.6%) patients; the mean prolactin level was 16 times above the reference range. Of these 15 (83%) had a pituitary macroadenoma. Hypopituitarism was present in nine (33.3%) patients at baseline. Of these, secondary hypothyroidism was found in eight (89%), secondary hypogonadism in four (44.4%) and secondary hypoadrenalism in one (11%). None had diabetes insipidus at the time of diagnosis (Table 2).

Radiological results at baseline

MRI was performed in 23 (85.1%) of the patients and 4 (14.9%) had pituitary CT scan. A pituitary adenoma was identified in 27 (100%) patients; of these, pituitary macroadenoma was found in 92.5% (n = 25) subjects. Precise measurement of the maximal tumour size was reported in 22 (81.4%) patients. Where the tumour size was available, the mean (± SD) was 3.0 ± 0.75 cm. Of the 25 patients with a pituitary macroadenoma, 18 (72%) demonstrated extension beyond the confines of the sella, with optic chiasm compression occurring in all these 18 patients; extension into the cavernous sinus was reported in 12 of these 18 patients. Pituitary microadenoma was diagnosed in 2 (7.4%) patients. No patients were diagnosed with ectopic GH-secreting or GHRH-secreting tumours.

Treatment modalities

Table 3 outlines the mode of therapy. Pituitary surgery was the primary therapy in 96.3% (n = 26). All 26 were treated with initial trans-sphenoidal surgery and 1 (3.7%) patient was treated with medical therapy only. Sixteen (61.5%) patients had a single surgical procedure, seven (26.9%) had two surgical procedures, two (7.7%) patients underwent three operations and one (3.8%) patient required four surgical procedures. Patients with pituitary macroadenoma were subjected to a mean of 1.4 ± 0.86 surgical procedures as compared with 2.0 ± 0 in those with microadenomas (p = 0.1).

Adjunctive medical therapy was administered to 23 (88.5%) of the 26 patients who underwent initial surgery. Of these, 6 (26.1%) received a somatostatin analogue (SSA) (octreotide) alone, 7 (30.4%) were treated with a dopamine agonist (DA) (5 with bromocriptine and 2 with cabergoline) and 10 (43.5%) received both octreotide and a dopamine agonist either sequentially or in combination.

Radiotherapy was delivered to six (22.2%) patients. In three (50%), conventional fractionated external beam radiotherapy was administered, with a mean daily dose of 2.0 ± 0 Gy and mean total dose of 49.75 ± 3.68 Gy. In the other three (50%) patients, stereotactic radiosurgery was administered as a single treatment with a mean dose of 11.5 ± 2.12 Gy. Three of the six (50%) patients who had received radiotherapy had hypopituitarism at the most recent follow-up. Table 4 indicates the major and minor complications of surgery. No record of post-surgical visual loss or perioperative mortality was reported. Twelve patients (46.2%) had new onset hypopituitarism as a result of surgery.
Surgical complications
Thirteen of the 26 (50%) patients experienced a complication as a result of surgery. The most common complications were transient diabetes insipidus (10 patients; 38.5%) and cerebrospinal fluid leak (9 patients, 34.6%).

Cure and disease control at final follow-up
The final review occurred at a mean follow up period of 4.4 ± 3.4 years (median follow-up: 3 years; range 0.5–10 years), with total cure rate of 33.3% (9 subjects).

IGF-1 levels
All 27 patients had IGF-1 levels done at the most recent visit. Mean IGF-1 at final review was 527.76 ± 395.45 μg/l. Nine (33.3%) subjects had a normal age-matched and gender-matched IGF-1 level.

Random GH
All 27 patients had random GH available at the final review. The mean GH was 18.60 ± 10.67 μg/l. Twenty (74.1%) subjects had a random GH < 5.0 μg/l, 15 (55.5%) < 2.5 μg/l and 9 (33.3%) < 1.0 μg/l. Seven (25.9%) patients had random GH level above 5.0 μg/l.

GH nadir in GTT
Only 2 subjects had a GTT at the final follow-up. In these subjects, the mean nadir GH was 10.03 ± 3.77 μg/l. Serum IGF-1 in these subjects was 1077 μg/l and 181 μg/l, respectively.

MRI scan
At the final review 18 (67%) patients had an MRI scan. In these patients, the median tumour reduction compared with baseline was –1.2 cm (IQR –1.2 to –0.6), p = 0.012.

Hypopituitarism
Twenty-two of 27 (81.5%) patients required pituitary hormone replacement therapy at the final review. Of these, five (22.7%) subjects had combined hypothyroidism, hypoadrenalism and diabetes insipidus and five (22.7%) had both hypothyroidism and hypoadrenalism. The remaining patients required varying combinations of replacement therapy.

IGF-1, Random GH levels and pituitary function
Nine (33.3%) of 27 subjects had normal age-matched and gender-matched IGF-1 level with random GH level of < 1.0 μg/l at the most recent visit. Of the nine subjects with biochemical cure of acromegaly, only two subjects had normal pituitary function; the remaining patients all required pituitary hormone replacement. The only difference between the group who achieved cure and those who did not was in baseline skull X-ray findings (vault thickening, p = 0.018; sinus enlargement, p = 0.021). No significant difference was found for baseline GH, IGF1 or size of tumours between those cured and those with persistent active disease at the final review.

Discussion
The current study evaluated the clinical, biochemical and radiological features of 27 patients with acromegaly at four different periods in order to assess treatment outcome. The majority of patients presented with symptoms of the tumour mass and pituitary macroadenoma was present in all but two of the subjects. Hypopituitarism was present in one-third of subjects prior to treatment and this increased to 81.5% after a mean follow-up of 4.4 years. Trans-sphenoidal surgery was used as the primary treatment modality in 96.3% of the patients, and...
adjunctive medical and radiotherapy in 88.5% and 22.2% respectively. All patients had a baseline random GH above 5.0 μg/l and elevated age-matched and gender-matched IGF-I. At the last follow-up, 55.5% had a random GH < 2.5 μg/l, 33.3% < 1.0 μg/l and 33.3% had a normal age-matched and gender-matched IGF-I level. In addition, serial MRI scans showed significant tumour reduction during the follow-up period.

The presenting features of patients in the current study related primarily to tumour mass effect and this was corroborated by the finding of pituitary macroadenoma on MRI in all but two of the patients. In other studies, a lower prevalence of these symptoms has been reported: headache in 47% and visual field defects in 18–21% and, in these studies, 79.6% of patients had macroadenoma.5 The high prevalence of macroadenoma at the time of diagnosis in the current study reflects presentation with advanced disease and delayed diagnosis in many patients. This may be due to the insidious nature of the disease, low index of suspicion in peripheral hospitals and clinics and the specifics of the referral system in KwaZulu-Natal.

In addition, the present study has shown a higher rate of preoperative hypopituitarism (33.3%) than other studies.11 In other studies, one-fifth of patients had hypopituitarism at the time of diagnosis of acromegaly and, similar to the present study, the majority had a pituitary macroadenoma.11 The high rate of preoperative hypopituitarism in the current study is also considered to reflect the large tumour burden in the majority with compressive effects on the residual normal pituitary tissue.

Trans-sphenoidal surgery was the primary intervention in almost all (96.2%) subjects in the present study and this is similar to reports from Europe and USA.15,16 A slightly lower rate of primary pituitary surgery (92%) was reported by the Cape Town study, as 8% of the subjects were treated with radiotherapy alone.11 Repeat surgery was implemented in over a third (38.5%) of the patients in the current study, primarily as a means to achieve tumour removal; this is less than that reported in the Cape Town study (13.8%) although the indications for repeat surgery were similar (55.6% for tumour removal).11 Repeat surgery has been reported in up to 100% in other studies.17

Surgery-related complications occurred in 50% of patients in this study and this is higher than reported in another study. The reasons for the high rate of postoperative complications are attributable to tumour size, tumour invasiveness and the degree of surgical expertise at IALCH. A study reported from the USA described postoperative complications occurring in 28% of subjects.17

The majority of patients (88.5%) in the current study required adjunctive medical therapy in order to achieve disease control. Although pegvisomant is not available to state patients in KwaZulu-Natal, both octreotide and dopamine agonists are available and were used as treatment in the current study. Adjunctive medical therapy is reported to be required in 83.9% of patients in other studies and conventional radiotherapy has been used in up to 60% of subjects in other centres.14 In the Cape Town study adjunct therapy was confined to radiotherapy as dopamine agonists and somatostatin analogues were not available for use at that time.11

Definitions of cure of acromegaly have changed over time, related to improved assay sensitivity and improved treatment modalities. The Endocrine Society Guidelines define cure as a normal age-matched and gender-matched IGF-1 and a random GH < 1.0 μg/l.19 Other reports, such as the study of Mehtap et al. from Turkey, have used less stringent criteria for cure (random GH < 2.5 μg/l and nadir GH in GTT < 1.0 μg/l).18 The Cape Town study defined cure as random GH < 5 μU/l (1.7 μg/l), nadir GH in GTT < 2.0 μU/l (0.7 μg/l) and mean GH in GTT < 5 μU/l (1.7 μg/l).11

In the present study, application of the Endocrine Society criteria yielded a cure rate of 33.3% (nine subjects fulfilling both IGF-1 and GH criteria). However, if compared with the study of Mehtap et al., 55.5% (15 subjects) in the current study would be regarded as cured (based on random GH < 2.5 μg/l). The final GTT results in the present study are not able to be used as a means to define cure, in view of the small number of subjects who underwent this procedure at the final follow-up. The Cape Town study was reported in 2001 and older assay methods were used, thereby limiting direct comparison; however, using a random GH < 1.7 μg/l (as used in the Cape Town study), 44.4% (12 subjects) in the current study would be regarded as cured. IGF-1 was not reported in the Cape Town study. The Cape Town study reported a cure rate of 28% at the last visit.11 In the Mehtap study the cure rate after surgery and radiotherapy was 19.3%.18 In the USA and Europe the cure rate was 57% and 60% respectively.16,20 In the German and Spanish Register studies, disease control, defined as a normal IGF-1, was substantially higher than in the current study (71.9% and 76% respectively).12,14

The strict definition of cure, however, includes retention of normal pituitary function after surgery or radiotherapy. If the criteria of normal age-matched and gender-matched IGF-1 together with random GH < 1.0 μg/l and normal pituitary function are used; only 2 of 27 (7.4%) subjects would be regarded as cured.

Two important limitations of the current study should be mentioned. The first is the relatively small number of patients, which decreases the strength of statistical analysis. Second is that it was a retrospective study as all data were collected based on chart review.

Conclusion

Patients with acromegaly in KwaZulu-Natal present with advanced clinical features and large pituitary adenomata. The overall cure rate is lower than reported from developed countries.

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Declaration regarding authorship – We have the right to publish the paper.

Ethics committee approval – Ethics committee (Biomedical Research Ethics Committee of the University of KwaZulu-Natal) approval has been obtained for original study and is clearly stated in the methodology. (Reference: BE306/13).

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