ORIGINAL RESEARCH

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Characterization of management and outcomes of patients with acromegaly in Vancouver over 30 years

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Abstract

Purpose: The purpose of this study was to characterize the management and outcomes of patients with acromegaly seen in single center in Vancouver, British Columbia, Canada over a 30 year period.

Methods: The study involved retrospective data collection from charts of patients diagnosed with acromegaly since 1980: 130 patients (63 male and 67 female) were included in the analysis, with a mean age at diagnosis of 43 years (male) and 47 years (female).

Results: The most common presenting features included acral enlargement, coarse facial features, sweating/oily skin and headache. All cases were caused by pituitary adenomas, of which 58.5% were macroadenomas and of these, 30.8% were invasive. The most common co-morbidities were hypertension 31.5%, arthralgia 28%, diabetes 27.7% and sleep apnea 23.8%. The vast majority (88.5%) of patients was treated surgically and of these patients, 21.5% also received radiotherapy and 66.9% received medical therapy. When stringent cure criteria were applied (based on latest growth hormone (GH) and IGF-1 results) the outcomes were 35.4% cured or controlled, 30% remained active, 15.4 discordant results and 19.2 % with no results reported. Twenty eight percent of patients who underwent surgery and 32% of patients who underwent radiotherapy were not cured but symptoms were moderately well controlled with medical therapy.

Conclusion: Based on the size of population studied, this study showed a prevalence of acromegaly of 29 per million. The cure rate was low following surgery but with adjuvant medical treatment disease control was achieved in most individuals.

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Acromegaly is the result of prolonged growth hormone (GH) hypersecretion, and consequently raised insulin-like growth factor 1 (IGF-1) [1]. The cause is, most commonly, an autonomously functioning pituitary adenoma secreting GH or GH in combination with prolactin (PRL) or, very rarely, thyroid stimulating hormone (TSH) or adrenocorticotrophin hormone (ACTH). Extra-pituitary causes, including hypothalamic or ectopic growth hormone releasing hormone (GHRH) hypersecretion and ectopic pituitary adenomas secreting GH have also been reported [2,3]. McCune-Albright syndrome, multiple endocrine neoplasia type 1 (MEN1) and Carney complex are genetic syndromes associated with acromegaly and, with familial acromegaly, have been recently reviewed [4].

With an incidence of 3-4 per million per year and prevalence of 60 per million, acromegaly is a rare disease [1]. A recent study, based on raised IGF-1 levels, suggests under-diagnosis of acromegaly and, thus, a higher prevalence of 1034 per million [5,6]. Acromegaly remains associated with significant morbidity and mortality and, left untreated, patients die from a range of systemic complications 10 years younger than their healthy counterparts [6,7].

The low incidence of the disease has prompted the initiation of several registries in Europe and the generation of valuable epidemiological data; however, similar studies have not been reported in North America [8-11]. Here, we set out to analyse the management and outcomes of patients with acromegaly in a single tertiary center, in Vancouver, British Columbia (BC), Canada over the last 30 years, and to characterize the demography and epidemiology of acromegaly, the presence of co-morbidities and the effectiveness of treatments used.

Materials and Methods

Patient Selection

Patients with a diagnosis of acromegaly 1980-2008, based on clinical records, were included in the study. The Division of Neurosurgery and the Department of Pathology at Vancouver General Hospital were involved in the diagnosis and management of majority of patients. Information was extracted from clinical and laboratory databases. A survey of all licenced endocrinologists in BC identified additional cases. The cross-referencing between databases was accomplished using only patients' personal health number to ensure patient confidentiality. Each patient was assigned a unique code for use in the study database, which included no other identifiable data. The Committee for Research and Ethical Behavior at UBC (CREB) approved the study.

TABLE 1. Number of patients and participating endocrinologists from each hospital

Hospital	Participating Endocrinologists	Number of Cases
Vancouver General Hospital	5	27
St. Paul's Hospital	4	80
Royal Columbian	6	23

Between 5th January 2009 and 1st February 2011, 130 patients who had been diagnosed with acromegaly since 1980 were identified from 15 participating endocrinologists, representing three hospitals in BC (Table 1).

Data Collection

The following data were collected from medical records: demographic features, date of diagnosis, place of presentation (emergency, general practice, internal medicine, other specialist), presenting symptoms, tumor size and extension, pathology, visual fields, hormonal data (initial or follow-up GH, IGF-I concentration). Details on treatment were also collected: medical treatment, including current or previous and whether it was primary therapy, type and periods of medical treatment, radiotherapy treatment, including date, method and dose, number and route of surgical treatment(s) and co-morbidity related to the disease itself or to the treatment (gallstones, obstructive sleep apnea, visual defects, goiter, headache, hypopituitarism, diabetes mellitus, carpal tunnel syndrome, hypertension and neoplasms). No detailed information for mortality was available for this study.

Outcome Analysis: Definitions

Regarding the effectiveness of treatment, the 'Criteria For Cure' was utilized as described in a consensus statement and the treatment outcomes based on a previous study [11, 12]. "Cure" is defined as patients with previous surgery and/or radiotherapy and with both normalised IGF-1, as indicated by the individual lab reference range standardised for age and gender, and GH < 2 µg/l as indicated by their latest blood results. 'Controlled' uses the same criteria but for patients who were on primary medical therapy only (no surgery or radiotherapy). 'Active Disease' represented those patients with raised IGF-1 and GH ≥ 2 µg/l. Discordant GH and IGF-1 levels were also recorded, where present. It should also be noted that the GH and IGF-I assays have changed over time and results were presented based upon normal ranges used at the time of sample collection.

Results

Population and prevalence

A total of 130 patient's charts were reviewed, of which 48.5% (63) were male and 51.5% (67) female, with mean ages at diagnosis of 43 years and 47 years, respectively. The prevalence was 29 per million, based upon BC statistical data from 2007.

Clinical presentation location

When clearly documented, the medical setting where the patient presented was recorded: 30.8% (40) presented to their general practitioner; 3.1% (4) presented to Emergency; 3.1% (4) presented to an endocrinologist; 3.1% (4) in Internal Medicine; and, 60% (78) were unknown. Other specialists who suggested a diagnosis of acromegaly, with presenting diagnoses in brackets, were neurologists (carpal tunnel); opticians and ophthalmologists (visual acuity and visual field defects), orthopedic surgeries and rheumatologists (arthritis), endocrinologists (Facial characteristics), ENT specialists (snoring) and psychiatrists (depression and incidental MRI findings).

Presenting Symptoms

Table 2 lists the range of presenting symptoms recorded from the original patients' consultations, which were either the primary complaint(s), or elicited upon direct questioning.

Tumor Etiology and Pathology

All cases in this study were secondary to pituitary adenomas: 58.5% (76) were macroadenomas; 23.1% (30) were microadenomas; and, 18.5% (24) were unknown. The size, invasiveness and pathology were recorded from radiology and pathology reports, or where specifically recorded in patients' records. Of the macroadenomas, 47.1% (36) were invasive and of the microadenomas, 13.3% (4) were invasive. With respect to tumor etiology, 19.2% (25) were pure GH, 18.5% (24) were GH-prolactin secreting and 7.7% (10) were other mixed tumors, while 54.6% (71) were unknown.

Co-morbidities

The prevalence of co-morbidities, as reported in patients' charts, whether presenting before or after diagnosis, is shown in Table 3. Fifteen patients were followed up for neoplasia, including breast (1), colon (1), haematological (4), thyroid (5), rectal (1), malignant melanoma (1), bladder (1) and prostate (1). Patients with diabetes and arthropathy were, on average, 6 and 7 years older, respectively, than those without. Of the pa-

TABLE 2. Most common symptoms seen at the initial presentation of acromegaly

Presenting Symptom	Patients Presenting (%)
Acne	8 (6.2%)
Acral Enlargement	103 (79.2%)
Arthralgia	18 (13.8%)
Coarse Facial Features/Prognathism	88 (67.7%)
Deep Voice	12 (9.2%)
Headache	32 (24.6%)
Increase Denture Size	13 (10%)
Loss of Libido	8 (6.2%)
Macroglossia	17 (13.1%)
Menstrual Disturbance	11 (8.5%)
Otological Complaint	1 (10.8%)
Paraesthesia/Numbness	25 (19.2%)
Skin Tags	14 (10.8%)
Snoring/Sleep Apnea	28 (21.5%)
Sweating/Oily Skin	44 (33.8%)
Weight Gain	10 (7.7%)
Visual Acuity Disturbance	22 (16.9%)

TABLE 3. Prevalence of co-morbidities complicating acromegaly

Morbidity	Prevalence (%)
Arthropathy	37 (28%)
Cardiovascular	8 (6.2%)
Carpel Tunnel	24 (18.5%)
Cerebrovascular	5 (3.8%)
Gall stone	8 (6.2%)
Colonic Polyps	11 (8.5%)
Diabetes Insipidus	4 (3.1%)
Diabetes Mellitus	36 (27.7%)
Goiter	10 (7.7%)
Any Hormone Deficiency	17 (13.1%)
Hormone Deficiency (multiple)	24 (18.5%)
Single ACTH Deficiency	5 (3.8%)
Single FSH/LH Deficiency	8 (6.2%)
Single PRL Deficiency	1 (0.8%)
Single TSH Deficiency	3 (3.2%)
Hypertension	41 (31.5%)
Sleep Apnea	31 (32.8%)
Visual Field Defect	6 (4.6%)

tients with hypopituitarism, 61.9% (13) had been treated with radiotherapy, and 28.9% (22) with surgery.

Treatment

Pituitary surgery was the primary therapy for the majority of the patients (88.5%, $N=115$), mostly by the transsphenoidal route (84.3%, $N=97$). Only five patients required second surgery. Radiotherapy was used as an adjunctive therapy after surgery for 21.5% (28) of cases. Eight cases underwent conventional and six cases used stereotactic approaches; however, in 50% (14) of the cases it is not known which methods were used.

Medical treatment was used for the majority of patients 66.9% (87) at some time, mostly as adjunctive to surgery. Of these, 73.6% had been treated with somatostatin analogues (SSA) alone and 26.4% with both dopamine agonists (DA) and SSA, either sequentially or in combination. Two patients were treated with the GH receptor antagonist (GHRA), pegvisomant.

The cure rate for surgery or radiotherapy was 13.1% (17). The majority 66.9% (87) of patients was not cured after surgery, but good control of symptoms was reported with medical therapy for 22.3% of the patients (Table 4).

Discussion

In this retrospective study, data contributed by 15 endocrinologists currently practicing in BC was analysed and 130 patients diagnosed with acromegaly since 1980 were identified. The majority of cases, 67%, were from St. Paul's Hospital and Vancouver General Hospital, where most pituitary tumors in BC were managed. Based on these data, the prevalence of acromegaly in BC is 29 per 1,000,000. This estimate is less than the prevalence previously described [6,11], and could be due non-recognition of some cases, or to patients being referred from out of province.

The suggested diagnosis of acromegaly was provided by a spectrum of medical specialties with 30.8% of known referrals from primary care. Due to the range of presenting complaints and complications associated with acromegaly spanning numerous specialties, it is a differential diagnosis that physicians outside of endocrinology should be aware of. This is of particular importance in light of its insidious onset and the recent suggestion of sub-clinical, under-diagnosed GH-producing pituitary tumors [5].

The mean age at diagnosis was 43 years (male) and 47 years (female) and did not differ from that reported in the other studies [10,11,13,14]. There was slight female preponderance

TABLE 4. Treatment outcomes

Criteria for Cure Category	Prevalence (%)
Cure	17 (13.1%)
Cure (GH only)	9 (6.9%)
Cure (IGF-1 only)	8 (6.2%)
Controlled	29 (22.3%)
Controlled (GH only)	22 (16.9%)
Controlled (IGF-1 only)	7 (5.4%)
Discordant Results	20 (15.4%)
Active Disease	39 (30%)
Unknown Latest Biochemistry	25 (19.2%)
Total Cure or Controlled	46 (35.4%)

(67 female), which is similar to what reported in Spanish Acromegaly Registry ($n=1219$ patients; 60.8% women) [10] and in the West Midlands Acromegaly database ($n=419$ patients; 57.5% women) [15]. In contrast, a slight male preponderance was reported by Beauregard *et al.* (58% men) [16] and no difference reported in the Belgian registry on acromegaly (418 patients: 51% men) [11].

Acromegaly is difficult to diagnose. The most common presenting symptoms (acral enlargement; coarsening facial features/prognathism; sweating/oily skin; headache; paraesthesia/numbness) can be easily overlooked by the patient or attributable to other common etiologies. Acne as a presenting feature of acromegaly is rarely included in reviews; however, the pathogenesis of increased sebum production is a commonly recognized feature of acromegaly. Case reports and comments on the association between acne and acromegaly have been made and in our study eight patients presented with acne [17]. All patients who presented with acne in this survey were female, with an average age of 37 years. Four patients presented with sweating/oily skin and one other presented with a concomitant menstrual disturbance. This association may be explained by the unusual presentation of acromegaly in younger women with features of polycystic ovarian syndrome or interference with LH/FSH secretion [18] (Table 5).

This study addressed the extent to which acromegaly was complicated by co-morbidity, which was recorded in medical records, if noted. As the onset of acromegaly is insidious: patients can have unrecognized GH over-secretion and can accumulate morbidity over time. Like the Belgian Acromegaly Survey [11], arthropathy, hypertension, diabetes mellitus and sleep apnea were the most commonly found morbidities; however, this study found significantly lower prevalence of cardiovascular disease, goiter, colonic polyps and visual field defects. This could be attributed to under-reporting, as data was not obtained via direct questioning of patients but were extracted

from medical records. What is clear from both studies is the multi-disciplinary nature of managing patients with acromegaly and the necessity for regular review not only of GH and IGF-1 levels but also of the investigations carried out by other specialties.

The sleep apnea syndrome was observed in 21.5% of our registry; however greater prevalence has been reported in other studies [19,20]. This could be due to both a low awareness of the problem and to under-reporting by many physicians.

Colonic polyps were present in 8.5% of patients. Other reports on different populations recorded a prevalence of between 9.5% and 45% [10,11,21,22]. This range of value is probably due to underutilization of colonoscopy or to under-reporting. The prevalence of gallstones in our registry was 6.2%. This is much lower than the prevalence observed in Belgian registry and Spanish database (23.4% and 9.5%, respectively) [10,11]. Further awareness of this problem is required, especially with increased use of somatostatin analogues - where treatment results in the development of asymptomatic gallstones in up to 30% of patients [20].

Surgery was the cornerstone of management for most patients (88.5%). Of the surgical patients, 21.5% went on to radiotherapy and 66.9% were subsequently treated medically. There was a marked reduction in the use of adjunctive radiotherapy after 1999, which could be, in part, due to the availability of somatostatin therapy as adjuvant therapy for incomplete surgical cure. Surgery was associated with complications in 26.3% of cases, including cerebrospinal fluid (CSF) leak (12.5%), temporary diabetes insipidus (10.0%), bleeding (3.8%) and SIADH (1.3%). Hypopituitarism was associated in 18.5 % of patients undergoing radiotherapy.

It has also been observed, over the last decade, that the use of somatostatin analogs has increased; however, there are no randomized controlled studies that compare primary medical therapy with initial surgery. Somatostatin analogs may be equally effective if used as adjuvant or initial therapy [23,24] and can be a good primary treatment option in carefully selected patients [24-26]. Among the active patients, two patients were on pegvisomant, with subsequent good control. Cost was a major barrier to use of this medication.

Stringent criteria were used to determine if a patient was cured based on their latest GH and IGF-1 results. Cure, after only surgery and/or radiotherapy, or control, on medical treatment, required GH < 2 µg/l and IGF-1 within normal limits. This is based on a consensus statement with a view to reducing mortality from acromegaly [27, 28]. Cure or control based on either GH or IGF-1 was found in 35.4% of patients while 30% still showed active disease. These results are probably

TABLE 5. Comparison of the prevalence of co-morbidities between the Vancouver and Belgium Acromegaly Studies

Morbidity	Prevalence (%)	
	Vancouver	Belgium (ACROBEL) [11]
Arthropathy	28	46.7
Carpel, Tunnel	18.5	28.1
Cardiovascular	6.2	18.0
Cerebrovascular	3.8	5.7
Colonic Polyps	8.5	27.2
Diabetes Mellitus	27.7	25.3
Goiter	7.7	24.2
Any Hormone Deficiency	13.1	39.7
Hypertension	31.5	39.4
Sleep Apnea	32.8	17.1
Visual Field Defect	4.6	15.4

closer to the outcomes encountered in clinical practice. In the Belgian registry, the cure or control rate was 49% [11] while in the Spanish database, cure was reported in 35% [10]. In accordance with previous reports, Biermasz *et al.* found 37% control rate 10 years after transsphenoidal microsurgery [29].

In the current study, results were unobtainable for some patients. There were a number of reasons for this: letters of referral were not included in patient's records; referral for follow-up with a detailed previous history were not included; or pathology reports were not included. Nevertheless, the majority of records were well kept and the relevant information easily extracted. Our registry of patients with acromegaly in Vancouver shows a relatively low cure rate following surgery but better results in controlling disease with medical treatment.

Patients tend to accumulate complications as time progresses, and further analysis of how patient morbidity relates to biochemical results will be important for managing and investigating patients within a multidisciplinary setting as well as in the endocrine clinic.

Our registry is small when compared to those of larger European countries. The lack of availability of centralized GH and IGF-I measurements, allowing a standardized evaluation of the outcome of different treatment strategies, also limits analysis. To improve GH and IGF-I measurements, the Acromegaly Consensus Group recommended that the World Health Organization (WHO) adopt international standards and the expression of GH results in mass units (micrograms per liter). Additionally, they address other issues with IGF-1 measurement, such as use of highly specific antibodies and the need to establish normative data [30].

Mortality data, which was not available, would also strengthen our assessment of different treatment outcomes; however, it should be highlighted that untreated acromegaly is associated with reduced life expectancy, with 2- to 3-fold increased mortality in acromegalic patients compared with the general population [31]. In a recent meta-analysis of 16 studies, the weighted mean of the SMR of 1.72 (95% CI, 1.62–1.83) that, reflects a 72% increase in mortality in patients with acromegaly [32]. Successful treatment to reduce GH level to < 2–2.5 g/liter can reduce the mortality associated with acromegaly [31].

Results of this study indicate that disease 'cure or control, based on either measurements of either GH or IGF-1, was found in 35.4% patients, whereas 30% still showed active disease. Cure rate was low following surgery but symptoms were at least partially controlled with adjuvant medical treatment. Our survey illustrates the changing pattern of therapy over the last decades in newly diagnosed acromegalic patients, with less reliance on radiotherapy and increased use of medical therapy.

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