GIGANTISM AND ACROMEGALY IN SINGAPORE

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SYNOPSIS

Acromegaly and gigantism are both uncommon endocrine disorders. This paper describes the clinical presentation and endocrine abnormalities in 2 giants and 17 acromegalics from Singapore over a 23 year period in the University Department of Medicine. The mean age at diagnosis is 42.5 years (range 12 - 67 years) with an unusual male preponderance (M : F ratio 4.7 : 1) and the disease is confined to Chinese in Singapore. The most common symptom was headache (57.8%) followed by excessive sweating (42.2%), polyuria and polydipsia (15.7%). All patients had acromegalic features, fourteen (73%) had hypertension, eight (42.2%) had goitres and five (29.4%) patients suffered from temporal field defects. Besides elevated growth hormone levels, 50% of patients had impaired glucose tolerance. Serum calcium was marginally elevated in 1 patient and 2 patients had serum phosphate above 4.5 mg%. Prolactin levels were normal in 6 out of 8 patients. Thyroid function test in 14 patients were all normal. A significant proportion (52%) refused definitive therapy. This is reflected in the high incidence of hypertension (73%) and symptomatic diabetes mellitus (37.9%). The only mortality occurred in an untreated acromegalic at the age of 70 years. The high incidence of hypertension and diabetes mellitus in our series confirms the importance of starting early and effective treatment in acromegaly.

INTRODUCTION

Gigantism is characterised by excessive height and body proportions and acromegaly by disproportional enlargement of the face and acral parts, hands and feet (1). Both are uncommon endocrine disorders but gigantism is even rarer. This paper describes the clinical presentation and endocrine abnormalities in 2 giants and 17 acromegalics from Singapore over a 23-year period in the National University Department of Medicine. A significant proportion (52%) refused definitive therapy. This is reflected in the high incidence of hypertension (73%) and symptomatic diabetes mellitus (37.9%). The only mortality occurred in an untreated acromegalic at the age of 70 years. There is an unusual male preponderance (4.7 : 1 M : F ratio) of acromegalics and the disease is confined to Chinese in Singapore.

PATIENTS AND METHODS

All cases of acromegaly and gigantism seen in the Department of Medicine, National University of Singapore were studied. There were 15 males and 4 females and the duration of followup ranged from 6 months to 23 years (mean 6 years). One of the giants has been reported previously (2). All patients were photographed and relevant clinical data noted. Growth hormone excess was confirmed by non-suppression of serum growth hormone to glucose[3]. Additional investigations included pituitary radiology, computerised axial tomography (recent cases), visual field charting, heel-pad measurements and hand volume estimations. Serum growth hormone, prolactin, thyroid stimulating hormone were measured by radio-immunoassay. Serum thyroxine was measured by competitive protein binding method. Protein bound iodine was used as an index of thyroid function in the earlier cases.

RESULTS

1. **Age :** Figure 1

   During the period of follow-up 19 cases of growth hormone excess were seen. Their ages at the time of diagnosis ranged from 12 years to 67 years with a mean age of 42.5 years. The age distribution is shown in Figure 1. The commonest age group was 40 - 49 years (6 cases or 32%).

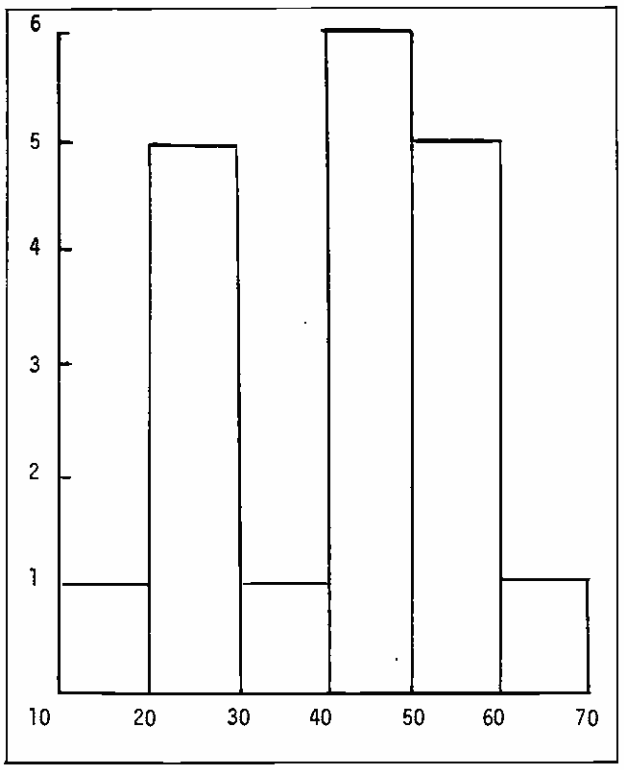

Figure 1

2. **Sex :**

   Acromegaly occurred predominantly in males. There were 14 males (82%) and 3 females (18%). In contrast during the same period of follow-up there was 1 elderly male giant and 1 young female giant.

3. **Race :**

   Although the Singapore population consist of Chinese (76.2%), Malays (15%), Indians (7%) and others (1.8%) in this study 18 (94.7%) patients were Chinese and 1 was a caucasian.

4. **Symptoms :** Table 1

   The most common symptom was headache occurring in 11 (57.8%) patients. Characteristically the patient complains of a dull annoying-type of pain which does not respond to the usual analgesics.

   Excessive sweating was noted in 8 (42.2%) patients, polyuria and polydipsia in 3 (15.7%) of patients. Of the four females, the young giant had primary amenorrhoea, one was post menopausal, the third presented with irregular menstruation while the last patient had regular periods. Among the fifteen males only two had diminished libido. Two patients complained of parasthesiae and one had severe right shoulder and left knee pain.

TABLE 1
SYMPTOMS

	No. Cases	%
Headache	11	57.8
Hyperhydriosis	8	42.2
Polyuria, polydipsia	3	15.7
Blurring of vision	3	15.7
Diminished libido	2	10.5
Parasthesiae	2	10.5
Joint pains	1	5.3
Amenorrhoea	1	5.3
Menstrual irregularity	1	5.3

5. **Signs :** Table 2

   Acromegalic features were present in all 19 patients although the majority 13 (63.1%) were unaware of any change in physical appearances. The male giant had marked thoraco-lumbar kyphoscoliosis. His height inspite of kyphosis was 6 ft. 9 in. and the estimated true height was 7 ft. 1 in. Our young female giant was 6 ft. 5 in. tall when she was 14 years of age.

   Goitre of varying degree was found in 8 (42.2%) patients. All patients were clinically and biochemically euthyroid. A 63-year old female acromegalic was mistakenly diagnosed to have thyroid heart disease because she presented with a goitre and congestive cardiac failure.

   Fourteen patients (73%) had hypertension. The mean blood pressure was 150/94, range of 95/60 to 200/130. One patient died from congestive cardiac failure. Two patients had gross cardiomegaly. Bitemporal visual field defects were detected in 5/17 (29.4%) patients, although only three patients complained of blurring of vision. The pituitary fossa was abnormal in 16/17 (94.1%).

TABLE 2
SIGNS

	No.	Total	%
Acromegalic features	19	19	100.0
Pituitary fossae abnormal	16	17	94.1
Hypertension	14	19	73.0
Goitre	8	19	42.2
Visual field defect	5	17	29.4

Endocrine Function : Table 3

Growth hormone :

Basal growth hormone levels were elevated in 18 patients in whom growth hormone was estimated. Mean basal growth hormone was 69.3 ng/ml (range 1 to 380 ug/ml). In all 17 patients there was failure of suppression of growth hormone to less than 5 ug/ml following glucose tolerance test. A paradoxical rise of growth hormone to glucose challenge was noted in 7 patients.

TABLE 3
ENDOCRINE ABNORMALITY

	Abnormal	Total	%
Growth hormone	18	18	100.0
GTT	9	18	50.0
Symptomatic diabetes	7	18	37.9
Thyroid function	0	14	0
Se Calcium > 10.4 mg%	1	11	10.0
Se Phosphate > 4.5 mg%	3	11	27.2
Se Prolactin	2	8	26.0

Glucose tolerance test :

Nine (50%) out of eighteen patients had abnormal glucose tolerance test. Of these 7 were symptomatic. One patient was controlled with dietary restriction, another was on insulin and the rest were treated with sulphonylureas.

Thyroid function :

Serum thyroxine was normal in 12 patients and protein bound iodine was normal in 2 other patients.

Serum calcium and phosphate :

Serum calcium and phosphate were measured in 10 patients. Only one patient (10%) had a marginally raised serum calcium (10.7 mg%). Three patients had serum phosphate above 4.5 mg%.

Serum prolactin :

Basal prolactin levels were normal in 6 out of 8 patients.

Therapy : Table 4

Four patients were treated with hypophysectomy, one had hypophysectomy and external radiation, while another had only external radiation. Ten patients refused any form of therapy. Three recent cases were treated with bromocriptine while awaiting surgery.

TABLE 4
TREATMENT

Refused treatment	10
Hypophysectomy	4
Hypophysectomy + DXT	1
DXT	1
Bromocriptine	3

Results of hypophysectomy : Table 5

Transfrontal hypophysectomy resulted in complete cure (growth hormone suppressed by glucose) in 3 patients. Of these two developed panhypopituitism and required steroid, thyroid and gonadal replacement. The fourth patient developed recurrence of headache 6 years after hypophysectomy. Growth hormone studies revealed that he had recurrence of acromegaly but the patient refused further treatment. He also had panhypopituitism. Our young giant continued to grow in spite of two hypophysectomies and external radiation and was amenorrhoeic at the age of 21 years.

TABLE 5
RESULTS OF HYPOPHYSECTOMY

	No.	Panhypopituitism
Cured	3	2
No improvement	1	—
Relapse	1	1
Total	5	3

Natural History : Tables 6 & 7

In our series of 19 patients, one patient (untreated) died at the age of 70 years from congestive cardiac failure. He also had hypertension and diabetes. Six patients were given definitive treatment. Two (33%) subsequently developed diabetes mellitus compared with 7 (53.8%) who did not receive any form of therapy. Four (66%) of the treated group had hypertension compared with 10 (76.9%) who did not have any form of treatment.

DISCUSSION

Acromegaly is an uncommon disease occurring in about 1 in 3,000 to 1 in 10,000 hospital admissions (4). Our series of 17 acromegalics collected over 23 years confirms that acromegaly is an uncommon disease. It is said to affect both sexes equally (5) but our series

TABLE 6
NATURAL HISTORY IN ACROMEGALY AND GIGANTISM

Mortality	1	(CCF, Diabetes, hypertension)
Alive	16	
Lost to follow up	2	

TABLE 7
Comparison of Hypertension and Diabetes in Treated and Untreated Patients

	Treated	No Treatment
Hypertension	4	10
No hypertension	2	3

Chi x^2 0.5 (ns)

	Treated	No Treatment
Impaired GTT	2	7
Normal GTT	4	6

Chi x^2 0.5 (ns)

shows a marked male preponderance (M:F ratio 4.7:1). The reason for this discrepancy is not clear. Of the 17 acromegalics, 16 are Chinese. The remaining patient is a Caucasian acromegalic referred to us for followup because he is working in Singapore. When compared to the multiracial composition of the population acromegaly appears to have a racial predilection for Chinese in Singapore. We are unaware of any report of racial bias in acromegaly.

Gigantism, on the other hand, is even rarer. Sotos (1) estimated that there are probably not more than 200 cases reported in the literature and this condition occurs more frequently in boys. We have 1 elderly male giant and a young female giant in the present series.

Headache is the commonest symptom (58.8%) followed by hyperhydrosis (42.2%), polyuria and polydipsia. Other symptoms include loss of libido, parasthesia, joint pains and menstrual irregularities. These findings are similar to those reported in larger series (1, 6, 7).

Acral and soft tissue enlargement was present in all 19 patients. These include thick, redundant, greasy, sweaty skin, prognathism, a bulbous nose, large tongue, spatulate hands and feet. The majority of our patients were unaware of any change of physical appearance probably because the onset of the disease is so insiduous. Goitre occurred in 42% of our series and all were clinically and biochemically euthyroid.

Radioimmunoassay of growth hormone revealed that all 17 patients failed to suppress growth hormone to less than 5 ng/ml following a 50 gm glucose load. There was a paradoxical rise in seven patients. One patient (elderly giant) refused venesection despite persuasion while the remaining patients with gross acromegalic features had a mean basal growth hormone of 74 ng/ml. These results are compatible with those reported by Neelon (3).

Our series of 17 acromegalics is interesting because the majority refused any form of definitive therapy. This may explain the high incidence of hypertension (73%) and symptomatic diabetes mellitus (37.9%) when compared with the usual incidence of about 20% (hypertension) and 15% (diabetes mellitus) by Besser (6) and Sonksen (8). Supporting evidence for this postulation is seen in Table 7. The frequency of impaired glucose tolerance was higher in the untreated group (53%) than in the treated group (33%). Hypertension was present in 76.9% of the untreated and 66% of the treated group. Although the small number in series do not permit valid statistical tests of significance these observations appear to be in keeping with the finding that impaired glucose tolerance often improves with adequate therapy of acromegaly while hypertension does not reverse with treatment (6, 7). We are however unable to explain the high incidence of hypertension in our patients.

The five patients with visual field defects all had hypophysectomy with improvement of visual field in all patients. Hypophysectomy is an effective form of treatment (9, 10). It resulted in complete cure in 3 patients but at the expense of hypopituitism in 2 patients. The fourth patient had apparent remission of acromegaly following hypophysectomy but developed recurrence 7 years later. This illustrates the importance of including some radiotherapy to surgery to curb tumour seeding as suggested by Fraser (11).

In spite of modern therapy some invasive tumours remain problematic as illustrated by our young giant. She had total transfrontal hypophysectomy followed by external radiation of 6000 rads to the pituitary in 1971 at the age of 12 years but continued to grow at a rate of 2½ inches a year. A second hypophysectomy 2 years later failed to control excessive growth hormone secretion. When last seen she continues to grow in spite of therapy with bromocriptine. Without treatment, giants rarely survive past middle age; the giant reported by us was alive at the age of 51 years and is one of the longest surviving giant without treatment (2).

Acromegaly is associated with increased mortality and morbidity (12). Although we have only one mortality in a 70 year old untreated acromegalic male from congestive cardiac failure, hypertension and diabetes, the high incidence of hypertension and diabetes mellitus in our series confirms the importance of early and effective treatment once the diagnosis of acromegaly is made.

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