The Ulster Medical Journal, Volume 59, No. 1, pp. 55 – 62, April 1990.

Ascertainment and natural history of treated acromegaly in Northern Ireland

Catherine M Ritchie, A B Atkinson, A L Kennedy, A R Lyons, D S Gordon, T Fannin, D R Hadden

Accepted 5 January 1990.

SUMMARY

The prevalence of known cases of acromegaly in Northern Ireland in 1984 was 6·3 per 100,000 population. The incidence of newly-diagnosed cases over the preceding 25 years was 5·5 patients per year, or 0·4 patients per 100,000 population per year. This rate would be equivalent to about 200 new cases per year in the United Kingdom.

Four options have been available to most of these patients — surgical hypophysectomy (transfrontal or transsphenoidal), pituitary radiotherapy (usually external cobalt beam), drug treatment with bromocriptine, or no treatment. Choice of treatment has been mainly influenced by tumour size, with the larger pituitary adenomas having surgery initially. No single form of treatment has been successful in achieving a clinical remission or cure in more than a minority of cases. The most successful outcome has been where total pituitary ablation has been achieved.

Life-table analysis for the whole group shows life expectancy which is not markedly different for that of an age-matched population from Northern Ireland. Morbidity related to long term osteoarthritis and treatment complications remain a major problem. The incidence of malignant tumours is higher than would be expected.

INTRODUCTION

The natural history of a chronic endocrine condition can be measured both by morbidity and mortality. While there have been several reviews of the experience of the management of acromegaly in patients referred to large endocrine units serving widely scattered and mobile populations, only the series from Newcastle-upon-Tyne[1] approaches a complete ascertainment of acromegaly in a community.

Royal Victoria Hospital, Belfast BT12 6BA.

Catherine M Ritchie, MD, MRCP, Senior Registrar in Endocrinology.
A B Atkinson, BSc, MD, FRCPGlas, Consultant Physician.
A L Kennedy, MD, FRCPEd, Consultant Physician.
A R Lyons, OBE, MD, FRCP, FFARCSI, Consultant Radiotherapist.
D S Gordon, OBE, MB, FRCS, Consultant Neurosurgeon.
D R Hadden, MD, FRCPEd, Consultant Physician.

Dr Ritchie is now Consultant Physician at the Craigavon Area Hospital.

Correspondence to Dr Hadden.

Treatment for acromegaly in different centres in the past 25 years has included direct surgical approach to the pituitary by the transfrontal or transsphenoidal route, radiotherapy using a standard cobalt unit or linear accelerator, and more recently drug therapy with bromocriptine or somatostatin. Some patients have had no pituitary-directed treatment. The choice of treatment has depended as much on available local expertise and facilities as on any defined protocol, and many recorded series are based on one particular treatment.[2] In Belfast we have been able to study all patients diagnosed to have acromegaly in Northern Ireland (population 1·5 million) during a 25 year period and to achieve 100% review. All treatment options have been equally available (except for a linear accelerator) and there has been close co-operation between the endocrine, the neurosurgical and the radiotherapy clinics. The long term review of all patients has been at the endocrine clinic.

METHODS

Records for 131 acromegalic patients were available for study. Since 1959 virtually all patients diagnosed to have clinical acromegaly in Northern Ireland have been seen by DRH. In the early years some of these patients had already been treated by radiotherapy or transfrontal hypohysectomy.

In 1984, 86 patients (65·6%) were still attending the endocrine review clinic. Nine (6·9%) had lapsed for a number of years but were ascertained to be alive, and up-to-date morbidity data was obtained from the family doctor. Only two had left Northern Ireland. Thirty-six (27·0%) had died — 17 died outside hospital and information was by death certification only; 19 (14·5%) died in hospital and in 12 of these an autopsy was carried out. Analysis of coded data sheets for each patient was carried out by computer using the SPSS system.

The diagnosis of acromegaly was reached in all cases on clinical grounds. All patients had a standard lateral skull X-ray. Radioimmunoassay for serum human growth hormone became available after 1967 and has been carried out in the endocrine laboratory at the Royal Victoria Hospital since that time.

RESULTS

Prevalence and incidence

Prevalence is the number of people in the community who have the condition. In 1984 there were 95 people alive and known to have acromegaly out of the 1,490,000 population of Northern Ireland (prevalence 6·3 per 100,000 population).

Incidence is the number of new cases per unit of population per year. One hundred and thirty-one patients in 25 years represents 5·5 patients per year for Northern Ireland, or 0·38 patients per 100,000 population per year. It may be that not all patients identified in Northern Ireland were referred to the Royal Victoria Hospital in the early part of this time, but we can be sure from 1970 onwards of complete notification: over this 13 year period there were 81 patients, representing 6·4 new cases of acromegaly per year, or 0·41 patients diagnosed per 100,000 population per year.

Clinical features at diagnosis

The presenting features did not differ from those found in other larger series.[2] There were 66 females and 65 males. We have excluded from this review some

patients who were referred because of clinical resemblance to acromegaly (large hands or prognathic jaw) in whom serum growth hormone levels were normal and no radiological evidence compatible with acromegaly was found. The median age at diagnosis was 40–49 years, the youngest was 11 and the oldest 71. The clinical estimate of the mean duration of symptoms prior to diagnosis was about 10 years. Six patients were noted to have acromegalic clinical features during treatment for a non-pituitary malignancy.

Cardiovascular disease at diagnosis

Forty-two patients (33%) were hypertensive at diagnosis (blood pressure >160/95 mmHg), or already on antihypertensive treatment. An abnormal electrocardiograph (any reported abnormality) was found in 23 (25%) of 93 patients. Cardiomegaly on routine chest X-ray was found in 18 (19%) of 95 patients.

Carbohydrate metabolism at diagnosis

Sixteen of 116 patients (14%) were diagnosed to be diabetic by oral glucose tolerance test using the criteria in use at the time of the test. None of the other 15 patients had glycosuria at the time of diagnosis. Two others (1·7%) fell into the impaired glucose tolerance category used since 1980.[3] Of these 16 diabetic patients, eight required insulin treatment to control hyperglycaemia, six were on oral hypoglycaemic agents and two on diet only.

Other endocrine disorders at diagnosis

Only one patient had a close relative (sister) also known to be acromegalic. She had been diagnosed and treated by surgical hypophysectomy in Glasgow, where she had been living for some time and she has not been included in this analysis.

Using standard thyroid function tests available at the time, two of the 114 patients (2%) were shown to be hyperthyroid and two others were euthyroid having previously been treated for hyperthyroidism; seven (6%) had secondary hypothyroidism (absence of serum TSH rise or other evidence of panhypopituitarism) and five (4%) had primary hypothyroidism (elevated serum TSH at the time of diagnosis). Four patients were hypercalcaemic, of whom three were shown to have primary hyperparathyroidism which was subsequently cured by parathyroidectomy.

Detailed studies on hypothalamic/pituitary function have only been carried out in recent years and in younger patients. Thirteen of 72 patients (18%) had secondary hypogonadism at diagnosis, and six of 84 patients (7%) had secondary hypoadrenalism. Serum prolactin measurements were only available at diagnosis in 34 patients. Nine of these (27%) had a serum prolactin greater than 360 mU/l.

Radiography

Ninety-three of 127 patients (73%) had an abnormality of the pituitary fossa on lateral skull X-ray. Detailed measurements of pituitary size were not made, but the radiological opinion was reached at weekly ward meetings with the same radiologist (Dr J O Y Cole) for the major period of this review. Computerised tomographic scanning of the pituitary fossa was available from 1980 and with more precision from 1983: of 21 cases examined at diagnosis, three were judged entirely normal, 10 were consistent with an intrasellar adenoma and eight had an extrasellar extension of an adenoma (seven suprasellar, one into the sphenoidal sinus).

Ophthalmology

A formal ophthalmic record of visual acuity at diagnosis was available in 97 patients; 89 (92%) were normal. In eight, visual acuity was abnormal, and was less than 6/60 in one eye or worse in five patients. Perimetry was carried out on 115 patients (initially with a simple confrontation perimeter, after 1972 with a Tubingen static perimeter). Visual fields were normal in 94 patients (82%). Unilateral field loss was found in seven (6%) and bilateral loss in 14 patients (12%).

TREATMENT

Twelve patients (9·2%) have had no treatment diercted toward the pituitary. Sixty-two have had only one single form of treatment (10 hypophysectomy, 34 radiotherapy and 18 bromocriptine only), 37 have had two separate episodes of treatment, 17 have had three, and three have had four different treatment episodes. In all, 199 treatments have been given to 119 patients.

Fifty-one patients (39%) have had external cobalt irradiation (usually 4,500 rads); 12 of these also had pituitary surgery and five received bromocriptine later. Eleven patients (8%) had internal irradiation by Yttrium-90 implantation at the time of hypophysectomy.[4] Sixty patients had 78 hypophysectomy operations, 45 by the transfrontal route and 33 transsphenoidal. Repeat surgery was carried out in 15 patients and three had a third exploration.

Ten of the 39 patients who received a single treatment with external radiation became panhypopituitary during follow-up. The onset of hypopituitarism ranged from 1–17 years after irradiation. Five patients who received only pituitary-directed radiotherapy developed visual complications which were shown to be due to the radiation rather than to local pressure from further pituitary enlargement.[5] Temporary diabetes insipidus developed postoperatively after hypophysectomy on 22 occasions — nine following transsphenoidal surgery (27%) and 13 following transfrontal surgery (29%). Severe haemorrhage causing abandonment of operation occurred in two attempted hypophysectomies, one patient developing a subdural haematoma. Other operative complications were infection of wound or bone flap in seven, deterioration in visual fields in two, and single cases of aphasia and mild hemiplegia, loss of taste and smell, and third nerve palsy. No patient received treatment for meningitis but one patient who died suddenly of respiratory arrest associated with severe headache and pyrexia one day postoperatively was suspected to have had overwhelming meningitis despite lack of post-mortem confirmation of this diagnosis. Another patient developed self-limiting CSF rhinorrhoea.

After brief experience with chlorpromazine (four patients),[6] 63 patients since 1972 have been treated with bromocriptine, usually as an adjunct to other definitive therapy. Eighteen have been treated with bromocriptine only. Drug intolerance occurred in seven patients; treatment was continued in three of these. One patient developed acute gastrointestinal symptoms and died of a perforated duodenal ulcer shortly after starting bromocriptine as adjunctive therapy.

MORBIDITY AND MORTALITY

Morbidity at six months

In the first six months after treatment (or after diagnosis in those who were not treated) six patients died. There were two peri-operative deaths (one on the

first day from possible overwhelming meningitis and one on the seventh day from pulmonary embolus and cerebral infarction). Three untreated patients died rapidly of malignancy (carcinoma of lung) and one died of a cerebrovascular accident three months after pituitary radiotherapy. In three cases no data on six-month review was recorded. None of the other nine untreated patients had any appreciable morbidity at six months. Full assessment of residual pituitary function was not in general carried out on the earlier patients, and replacement therapy with cortisone acetate or hydrocortisone was generally started postoperatively. Fifty-three of the 116 patients were taking adrenal steroids and 55 were taking thyroxine at six months. Of the 21 patients operated on transfrontally as an initial treatment, all were on replacement treatment, compared with 13 of the 15 operated on transsphenoidally. Only 19 (16%) were receiving androgen or oestrogen replacement therapy. Blood pressure was elevated in 31 of the 125 patients alive at six months (25%).

Morbidity at last review

The case notes of all 125 patients who survived six months from diagnosis, including those who had no treatment, were studied to ascertain morbidity at last attendance or prior to death. Eighty-six patients were still under review and had been seen within the last year. Nine patients, including two who had left Northern Ireland, had lapsed from the clinic; information concerning their state of health was obtained from their general practitioners. Morbidity prior to terminal illness was ascertained from the case notes in the 30 patients who died. Twenty-one of the 125 patients were judged still to have active acromegaly on the evidence of persistently elevated serum GH.[7] Sixty-three (50%) were either demonstrably panhypopituitary or were established on replacement therapy. Forty-eight (38%) had arthritis, predominantly destructive osteoarthritis of the large joints, especially hips, knees and lumbar spine. There were two cases with rheumatoid arthritis which produced widespread and particularly crippling disability. Forty-three patients (34%) had ischaemic heart disease based on documented myocardial infarction, or a history of angina and electrocardiographic changes. Forty-two patients (33%) were hypertensive. Nineteen (15%) were diabetic. Nine had had a cerebrovascular accident. Other medical problems, mostly not of major significance, occurred in 28% of these patients. Nine patients (7%) admitted to no symptoms or disabilities of any sort.

Mortality

By December 1984, 36 of the 131 patients had died. There were 12 deaths from cardiovascular disease (five from acute myocardial infarction, three with an episode of congestive cardiac failure, and four sudden deaths outside hospital had been certified as due to myocardial infarction) and five deaths from cerebrovascular disease. Eleven patients died from a malignancy (see below). The two early post-craniotomy deaths were due to pulmonary embolus and possible overwhelming meningitis. Two older patients died of bronchopneumonia, tuberculous in one case. One young patient died in an orthopaedic hospital from pulmonary embolus after tibial osteotomy to reduce excessive height. One patient committed suicide 22 years after treatment. One died of acute adrenal insufficiency having survived two years without taking replacement therapy following treatment by radiotherapy and then transfrontal craniotomy in 1961. One patient died of peritonitis after perforation of a duodenal ulcer while taking bromocriptine.

Malignant diseases

Fifteen of the 131 patients have been diagnosed to have a malignant tumour. Four of these are still under surgical review, one having been treated for breast carcinoma, one for renal cell carcinoma and two for transitional cell bladder carcinoma. Four patients have died of carcinoma of the colon, three from carcinoma of the bronchus and one each from carcinoma of breast, pancreas, oesophagus and bile ducts.

Squamous cell skin carcinomas were successfully treated in two patients. Benign epithelial tumours were found in six patients (four nasal polyps, one benign tumour of the gum and one benign vocal cord polyp). Two patients had large benign subcutaneous lipomas.

DISCUSSION

The epidemiology of acromegaly has not been easy to study as patients are often referred long distances for consultation and management and many less severely affected patients do not remain under long term review by the treatment centre. In Newcastle-upon-Tyne a retrospective survey of all known cases in the region suggested an annual incidence of close to three new cases per million population and a prevalence of diagnosed cases of up to 40 cases per million.[1] The Northern Ireland experience is likely to be even more complete due to the geographical isolation and the clinical referral of all patients to the regional endocrine, radiotherapy and neurosurgical centres in Belfast. In addition, a central register of acromegalic patients has been maintained for the past 28 years with the aim of producing long term data. The overall annual incidence of newly-diagnosed cases of about four per million population is somewhat higher than in Newcastle, perhaps because that study was less successful in maintaining contact with the more peripheral parts of their region. This figure would be equivalent to 200 new cases per year in the United Kingdom (population about 50 million) or 1000 per year in the USA (population 250 million).

Cause of death

The London five-hospital review (1937–1967) of 55 deaths in 194 patients showed a mortality almost twice that expected from the general population,[8] with increased deaths from cardiovascular and respiratory disease in males and cerebrovascular and respiratory disease in females. There was also an excess mortality from malignant neoplasms in females aged 65–74 years. The Newcastle study[1] also showed a significantly higher mortality in males from cardiovascular, cerebrovascular, respiratory and malignant diseases but in females only from cerebrovascular causes. Both of these studies have suggestive evidence of lower mortality in treated patients, but neither was able to produce incontrovertible data. Even in a single centre in Northern Ireland there has not been a consistent therapeutic policy, due to the gradual introduction of new options such as bromocriptine and transsphenoidal microsurgery.

A life-table analysis of the 131 patients shows that 80·7% survived to 10 years, 63·2% to 20 years and 37% to 30 years, which is similar to the life expectancy for age- and sex-matched groups from the general population of Northern Ireland.

An aetiological association between excessive growth hormone secretion and malignant colonic tumours has been suggested by some authors,[9] but Wright et al[8] and Mustacchi and Shimken[10] found no increased morbidity from, or risk

of, cancer in acromegalic patients. Alexander et al[1] found an excess of malignancy death in men only. We found a higher than expected mortality from malignant tumours, but the numbers are too small for detailed statistical analysis.

Treatment options

The problem in assessing response to treatment with a very long term disorder such as acromegaly is that the patient often survives for a longer time than the clinical interest of the doctor who made the treatment decision. Both surgical hypophysectomy and pituitary radiotherapy have been available at most centres for the past 40 years, so that a truly "untreated" series for comparison does not exist. Most analyses have been carried out to try to assess the effectiveness of one or other newly-introduced technique or drug, such as 'conventional' radiotherapy,[11] bromocriptine[12] or transsphenoidal microsurgery.[13] The Acromegaly Study Group in Germany have made the best attempt to compare primary treatment with transsphenoidal surgery (with or without cryotherapy), Yttrium-90 implantation or bromocriptine, but their results are short term and based largely on a single endocrinological evaluation six months after the treatment.[14]

The short term complications of surgical treatment are well-documented and probably depend both on the experience at the centre and the severity of the disease process. Analysis of the morbidity at last review may be a more useful indicator of the patient's health than short term post-treatment assessment of growth hormone levels. This would be particularly valid if the long term morbidity of the treated patient depended more on the degree and duration of the excess growth hormone secretion prior to treatment than on the post-treatment growth hormone value. The Northern Ireland experience would support this view; although 21 patients (more than six months after treatment) were judged still to have active acromegaly with excess growth hormone secretion, compared to 63 where pituitary function was effectively ablated, the prevalence of osteoarthritis (50% vs 38%) and hypertension (33% vs 33%) was not noticeably different in the two groups. Only 7% of patients had no symptoms or disabilities of any sort, although the great majority had been able to continue their normal occupation in spite of acromegaly and its treatment.

This approach is not to argue against the most effective treatment possible to reduce inappropriate growth hormone secretion, but rather to concentrate on the disability caused by the pre-treatment phase of the disease. Relevant to this aspect is whether the natural history of distinct forms of inappropriate growth hormone secretion is different. Analogy with the problems of hyperprolactinaemia would suggest that some acromegalic patients with large, predominantly chromophobe adenomas would have a more protracted disease which was more resistant to any form of intervention than other patients with smaller, more discrete pituitary lesions. It has been suggested that these two histological forms of the disorder may represent different aetiological entities[15] rather than the larger adenoma merely being a later stage in the evolution of the smaller lesion. If that is so, the neurosurgical practice of considering the larger pituitary lesion as necessitating as extensive a hypophysectomy as possible, employing additional cryotherapy or local irradiation to achieve a panhypopituitary state may well be correct at the present time. The smaller, more discrete eosinophilic 'adenoma' in the pituitary may in some cases be removed while leaving normal residual pituitary tissue, but this form of the disease may in any case be less aggressive.

Whatever endocrine treatment option is undertaken, the natural history of the treated patient who avoids acute peri-operative problems is probably more

dependent on the pre-treatment severity and underlying pathophysiology of the disease, than on the immediate post-treatment assessment. It is now 100 years since the initial recognition of acromegaly by Pierre Marie,[16] but the neuro-endocrine basis of this particular disorder is still elusive and present-day treatment remains less than ideal.

REFERENCES

1. Alexander L, Appleton D, Hall R, Ross WM, Wilkinson R. Epidemiology of acromegaly in the Newcastle region. *Clin Endocrinol* 1980; **12**: 71-9.
2. Jadresic A, Banks LM, Child DF et al. The acromegaly syndrome. Relation between clinical features, growth hormone values and radiological characteristics of the pituitary tumours. *Quart J Med* 1982; **51**: 189-204.
3. WHO Technical Report Series No 646, 1980 (WHO Expert Committee on Diabetes Mellitus: Second Report).
4. Edelstyn GA, Gleadhill CA, Lyons AR, Rodgers HW, Taylor AR, Wellbourn RB. Hypophysectomy combined with intrasellar irradiation with Yttrium-90. *Lancet* 1958; **1**: 462-3.
5. Atkinson AB, Allen IV, Gordon DS et al. Progressive visual failure in acromegaly following external pituitary irradiation. *Clin Endocrinol* 1979; **10**: 469-79.
6. Singh P, McDevitt DG, Mackay J, Hadden DR. Effects of L-dopa and chlorpromazine on human growth hormone and TSH secretion in normal subjects and acromegalics. *Horm Res* 1973; **4**: 293-301.
7. Lindholm J, Giwercman B, Giwercman A, Astrup J, Bjerre P, Skakkebaek NE. Investigation of the criteria for assessing the outcome of treatment in acromegaly. *Clin Endocrinol* 1987; **27**: 553-62.
8. Wright AD, Hill DM, Lowy C, Fraser TR. Mortality in acromegaly. *Quart J Med* 1970; **39**: 1-16.
9. Ituarte EA, Petrini J, Hershman JM. Acromegaly and colon cancer. *Ann Int Med* 1982; **101**: 627-8.
10. Mustacchi P, Shimken MB. Occurrence of cancer in acromegaly and in hypopituitarism. *Cancer* 1957; **10**: 100-4.
11. Eastman RC, Gordon P, Rath J. Conventional supervoltage irradiation is an effective treatment for acromegaly. *J Clin Endocrinol Metab* 1979; **48**: 931-40.
12. Bell PM, Atkinson AB, Hadden DR et al. Bromocriptine reduces growth hormone in acromegaly. *Arch Int Med* 1986; **146**: 1145-9.
13. Roelfsema F, Van Dulken H, Frolich M. Long-term results of transsphenoidal pituitary micro-surgery in 60 acromegalic patients. *Clin Endocrinol* 1985; **23**: 555-65.
14. Quabbe H-J. Treatment of acromegaly by transsphenoidal operation, Yttrium-90 implantation and bromocriptine: results in 230 patients. *Clin Endocrinol* 1982; **16**: 107-19.
15. Cryer PE, Daughaday WH. Growth hormone. In: Clinical neuroendocrinology. Martini L, Besser GM (eds). New York: Academic Press, 1982: 243-77.
16. Marie P. Sur deux cas d'acromegalie: hypertrophie singulière non-congénitale des extrémitiés superieures, inferieures et cephalique. *Review Médicale* (Paris) 1886; **6**: 297-333.