Regular Review

Treatment of acromegaly

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Acromegaly is uncommon: a survey in the Newcastle region[1] found a prevalence of 40 cases per million population. The classical features are easy to recognise but, because patients may appear unchanged over long periods, acromegaly was assumed in the past to be a self-limiting disease. This is not so, except when a patient suffers pituitary apoplexy. Untreated, the prognosis is very poor, the mortality rate being twice that for controls matched for age and sex. Death is due to cerebrovascular disease or cardiac failure, and sometimes pulmonary disease.[2] Diabetes and hypertension may also occur. Over the past 20 years dramatic advances have been made in treatment so that it is now possible to achieve a remission in most patients. The object of this review is to put the various methods of treatment available into perspective.

Initial assessment must include hormone measurements and delineation of any tumour present. Plasma growth hormone assay introduced by Hunter and Greenwood in 1962[3] is the mainstay of diagnosis. Values fluctuate throughout the day in normal people and even more in patients with acromegaly. Ideally, repeated measurements made over 24 hours are desirable and can be obtained with a portable constant withdrawal pump.[4] The mean values of growth hormone obtained should accurately predict true production of hormone. Mean growth hormone values are higher in premenopausal women than in men but below 6·0 mU/l (SD $\pm$3·2). In practice, acromegaly is confirmed when the fasting growth hormone is greater than 10 mU/l with failure to suppress below 5 mU/l during an oral glucose tolerance test. Values are high in some patients but this may not necessarily be associated with biological activity of the hormone. In these circumstances growth hormone concentrations are usually higher when measured by radioimmunoassay than by receptor assay.[5] In about 8% of patients,[6] the measured growth hormone activity is low despite obviously active disease. Most show abnormalities of response of growth hormone to hyperglycaemia or hypoglycaemia and to other tests.[6] An alternative index of growth hormone activity has been sought by measurement of the somatomedins. Evidence has been presented, both in favour[7] and against[8] diagnostic use of measurement of these substances but until more information is available it would be unwise to interpret high somatomedin values as diagnostic of acromegaly.[9]

Abnormalities of the response of growth hormone to various dynamic stimuli may also be present in acromegaly.[10] There may be a paradoxical rise of growth hormone during a glucose load, an absence of the normal increase of growth hormone induced by hypoglycaemia or arginine, a rise after injection of thyrotrophin releasing hormone and sometimes luteinising hormone releasing hormone, and a decrease of growth hormone after oral administration of levodopa. This last, reported by Liuzzi and his associates in 1972,[11] is the basis for treatment of acromegaly with bromocriptine (2-bromo-alpha-ergocriptine), a long acting dopamine agonist. The cause of these dynamic disturbances is not known. Abnormal receptor sites have been shown on tumour cells in vitro[12] but it may be that they are due to aberrations in the normal hypothalamic control of secretion of growth hormone. When present these dynamic defects help in the initial diagnosis, and if they are corrected by surgery this may imply successful removal of autonomous tumour cells.[13]

The patient is admitted to hospital to obtain a growth hormone profile and to measure the response to a glucose load, insulin hypoglycaemia, and stimulation with thyrotrophin releasing hormone and luteinising hormone releasing hormone. The concentrations of other hormones may be measured where appropriate, including prolactin, whose concentration is raised in about one third of patients. Preferably, each test should be performed on a separate day. Initial investigation is completed by plotting the visual fields and radiography. A microadenoma, or tumour of less than 10 mm diameter, may be associated with a normal pituitary fossa on skull radiography, or produce unilateral expansion of the floor giving the appearance of a double contour. It may remain enclosed within the dura or invade this structure to cause cortical thinning or erosion. Such changes are best seen on thin section lateral tomography. Radiological abnormalities of the sella are found in almost all patients with acromegaly,[14] but these should be interpreted with caution, for minor duplication of the floor with or without thinning or erosion may be found in normal people.[14 15] Raji and others[16] reported a substantial discrepancy between the tomographic and surgical findings in 14 of 55 patients with microadenomas. Tomography may, however, help in delineating larger tumours. Of 24 patients with normal fossae on plain radiography, nine were shown by tomography to have major expansion into the sphenoid sinus.[14]

Computed tomography, preferably with 5 mm overlapping cuts, is particularly useful for detecting suprasellar adenomas, most of which are dense and enhance well with contrast. An "empty sella" is best detected on coronal cuts, but a high sphenoidal air cell can look very similar. Air studies will provide better definition but may miss lateral extensions above the fossa.[17] Angiography may be needed to show an aneurysm or to define the carotid vessels before ^{90}Y implantation or cryosurgery.

Cure of acromegaly depends on growth hormone values being consistently below 10 mU/l over an extended period (not documented as a percentage fall) and pre-existing dynamic abnormalities being correct. This implies clinical remission and shrinkage of any tumour present or its complete removal. Early signs of clinical remission are disappearance of

sweating and decrease of soft tissue thickening, manifest by loosening of finger rings and resolution of median nerve compression. Thereafter diabetes and hypertension may improve and skeletal overgrowth regress. The latter is best judged by changes in dentition and in shoe size.

The choice of treatment lies between surgery and external or internal irradiation. (Bromocriptine is best regarded as adjuvant.) Supervoltage external radiation, applied in 15-20 fractions to a total of 4000-5000 rads over four weeks, will achieve remission in most patients but has the disadvantage of attaining this objective slowly and with progressive loss of pituitary function. Eastman and his colleagues[18] reported growth hormone values below 10 mU/l in 42% of patients at five years and in 69% at 10 years. There was no immediate mortality and morbidity is low.[19] Nevertheless, a recent report records progressive visual failure in four of 25 acromegalic patients given conventional radiotherapy.[20] The cyclotron, available only in the United States, delivers higher radiation doses (up to 15 000 rads) in the form of alpha particles or a proton beam aimed directly at the fossa. A rapid response would be expected from such a powerful source. Surprisingly, any substantial reduction of growth hormone occurs only after six months and the final result is little better than with supervoltage treatment. After treatment with alpha particles growth hormone concentration was less than 10 mU/l in 51% of patients at five years and 78% at 10 years.[21] Similar results were obtained with the proton beam,[22] but precise figures were not given. These high energy systems carry increased risk of damage to surrounding structures causing ocular palsies, visual defect, and seizures,[23] as well as hypopituitarism.

Direct implantation of ^{90}Y into the fossa produces a more rapid result. Wright and his colleagues[24] quote mean growth hormone values during a glucose load of less than 10 mU/l in 15 of 50 patients one year after implantation of 50 to 150 thousand rads. Replacement hormone treatment for hypopituitarism was required in 11. In its most recent report this same group[25] refer to 53 patients, 22 of whom were treated by ^{90}Y implantation. When assessed by the same criteria a year or so later remission was recorded in 11 patients. There were few complications but seven needed replacement treatment. Implantation was not possible in 29 patients because of the size of the tumour or a partially empty sella; most were referred for surgery or radiotherapy.

Cryosurgery has been performed on patients selected by the same criteria as for ^{90}Y implantation.[26] Again the response is rapid, but in the two studies which compared cryosurgery and surgical hypophysectomy, surgical excision was more effective in producing remission and fewer patients required replacement treatment.[27 28]

Transfrontal surgery, which carries a high morbidity,[29] is now reserved for those few patients with large tumours extending well above the fossa or laterally. The transsphenoidal approach introduced by Cushing[30] was revived by Guiot and his associates,[31] who, with Hardy and Wigser,[32] adopted the image intensifier and operative microscope to allow selective removal of microadenomas. This route is also ideal for large tumours extending down into the sphenoidal sinus and for those which extend upwards but prolapse into the fossa at operation. Since 1975 results of transsphenoidal surgery in 547 patients have shown a reduction of growth hormone concentration to less than 10 mU/l in 348 (64%). The largest series[33] refers to 152 patients, gathered from several centres in the Federal Republic of Germany, in whom normal growth hormone values were recorded six months after operation in 82. There were no deaths and few complications—leak of cerebrospinal fluid in four, meningitis in four, and partial visual field defect in one. Twenty four patients developed hypopituitarism.

Where the report gives specific surgical details the results of selective and total hypophysectomy may be compared. One group recorded growth hormone values of less than 10 mU/l in 47 of 53 patients directly after selective adenectomy with no change in pituitary function in 37, improvement in 14, and partial deficit in two,[34] and another claimed similar success in 63 of 67 patients with preservation of pituitary function in 57 of them.[35] Where the deliberate policy was total hypophysectomy for all patients suitable for surgery, one report quoted growth hormone values below 10 mU/l in 39 of 59 patients with complete hypopituitarism in 13 patients,[36] and another group found the same result in 27 of 35 patients with hypopituitarism in 13 patients.[37]

Restoration of growth hormone values to normal is less common after total hypophysectomy because of inclusion of larger tumours (greater than 10 mm diameter), for which surgery is generally less successful.[35] Surgeons who advocate total hypophysectomy maintain that, even with modern equipment, all tumour tissue cannot be removed with certainty by conservative excision. This view is shared by several authors.[28 36–38] In a detailed report by Wrightson,[39] tumour tissue was found to be soft because of its high cellular content but areas indistinguishable by their consistency from normal gland might contain tumour. He also found that no recognisable border might exist between normal and tumour tissue or that tumour cells might be present beyond any apparent plane of cleavage. The dura mater from the tumour bed was invaded in more than half of the cases examined. Similar microscopic features were reported by Giovanelli and his colleagues, who performed total hypophysectomy on most of their patients.[38]

Pituitary tumours grow slowly, so that the incidence of recurrence after selective adenectomy will not be known for years. One of the authors quoted here[35] found recurrence within one and a half to four years in four of 46 patients, all of whom had normal growth hormone values after operation. Also Arafah and his coworkers[40] identified and removed an adenoma in 27 of 28 patients with acromegaly, and three to six months later growth hormone values were normal in 20; but three out of seven patients with normal growth hormone concentrations but persistently abnormal dynamic responses relapsed within one year. Our own experience is that there has been no recurrence in 27 patients followed up for four to 15 years after total hypophysectomy.[37] We therefore favour this radical approach to surgical treatment of acromegaly and consider radiotherapy to be essential if growth hormone activities remain high after hypophysectomy or when the growth hormone concentration is normal but abnormal dynamic responses persist.

Bromocriptine given alone restores the growth hormone value to normal in relatively few patients. Wass and his colleagues reported growth hormone of less than 10 mU/l in only 15 of 73 patients (20%) despite objective improvement in most.[41] The basis of this discrepancy is not known, but interestingly patients who do respond to this drug are more likely to have simultaneous increase of both growth hormone and serum prolactin concentrations before treatment is given.[42] In two patients with acromegaly in whom there was *x* ray evidence of shrinkage of pituitary tumour hyperprolactinaemia was present.[43] Patients who respond are obliged to take frequent daily doses of this expensive drug indefinitely, but possibly more potent dopamine agonists will soon replace it. Bromocriptine is used to complement radiotherapy, taking

advantage of its rapid action, and for patients in whom surgery has either failed or is refused. It is probably the treatment of choice for mild acromegaly, particularly when the patient is old or otherwise unwell.

For most patients, however, surgery is the treatment of choice for acromegaly and should be performed early to ensure the best chance of success. Future generations of computed tomography scanners will improve precision in locating tumours,[44] but continued documentation of the experience of those who manage patients with this lethal disease is still required to determine optimal treatment.

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