Modern management of acromegaly

Acromegaly is a rare disease, about 5 new patients/million population being diagnosed each year. The cause is almost always a benign adenoma of the somatotroph cells of the pituitary, exceptionally the ectopic production of growth hormone releasing factor or growth hormone itself being implicated. Rarely, acromegaly is familial, with or without other endocrine tumours (e.g. parathyroid and pancreatic islets), as in multiple endocrine neoplasia Type 1.

The characteristic signs of acral expansion in acromegaly are easily recognized by the trained observer, but because of their insidious onset and gradual progression may go unrecognized for many years by patients and their close relatives. Herein lies one of the major unknowns; what damage, particularly to the cardiovascular system, has already been done by the time of diagnosis and can this be reversed by elimination of growth hormone hypersecretion? It might be argued that those who present with marked hyperhidrosis, headache, visual impairment, or hypopituitarism as early symptoms may be diagnosed earlier and fare better.

It has long been recognized that acromegals have a 2- to 3-fold greater mortality than age- and sex-matched cohorts and this still appears true in the 90s, as the paper by Bates et al. reminds us. The excess mortality is largely from cardiovascular and respiratory causes, although in some, though not all, there is an increased prevalence of deaths from malignancy, particularly colonic neoplasms. The predilection for the colon is not immediately obvious and probably is not simplistically explained by chronically elevated circulating growth factors, especially insulin-like growth factor I (IGF-I). Can anything be done to alter this adverse long-term outlook, which is still evident in spite of currently acceptable treatments?

Before attempting to provide answers to this question it is necessary to examine several inter-related management issues. Firstly, what are the objectives of treatment? These can be broadly grouped into three: (1) relief of symptoms directly caused by growth hormone hypersecretion, viz: hyperhidrosis, soft tissue swelling, headache, and compression symptoms from tumour expansion (visual impairment and hypopituitarism); (2) prevention of progressive disfigurement, bone expansion, and osteoarthritis which are frequent disabling long-term consequences of acromegaly, and prevention of hypertension, insulin resistance, diabetes mellitus, and lipid abnormalities, all of which are risk factors for the macrovascular damage commonly encountered; (3) reversing the poor long-term outcome by reducing the mortality from the disease.

Secondly, we need to know to what level treatment needs to reduce growth hormone and IGF-I levels in order to achieve these objectives, especially the second two.

Thirdly, what is the most effective treatment modality and its cost in respect of complications or side effects relative to the benefit in terms of lowering growth hormone levels? From studies of fairly large groups (50–250) some answers to these questions are emerging, but the problem faced by the clinician is how aggressively should any individual patient be treated?

Dealing with the symptoms directly caused by growth hormone hypersecretion is most rapidly achieved by hypophysectomy. In most patients, even the majority with macroadenomas and suprasellar extension, this is best done by the trans-sphenoidal or transethmoidal approach which provides good direct vision of the fossa contents and the best opportunity for visualization of the abnormal tissue in smaller adenomas. These latter can usually be entirely removed with preservation of normal pituitary function. Unfortunately, small (< 1 cm) adenomas are the exception though adenomectomy in this group produces a higher ‘cure’ rate than for those with macroadenomas, in whom it is often impossible to remove all tumour tissue and hypopituitarism is much more common. With successful adenomectomy/hypophysectomy growth hormone levels plummet and symptomatic relief may be evident within 24 h. Soft tissue swelling is due to increased intercellular fluid due to the sodium and water retaining properties of growth hormone (intravascular volume expansion contributes to the hypertension of acromegaly). A rapid naturiesis accompanies reduction in growth hormone levels; this may explain the rapid clinical
benefits observed after total/near total tumour removal. Very large tumours with 2–3 cm of suprasellar extension causing visual field defects can also be removed by the trans-sphenoidal approach, the suprasellar component dropping down into the fossa when its contents are removed. This approach has dramatically reduced the number of transfrontal craniotomies performed and the attendant increased morbidity. With modern trans-sphenoidal surgery patients are usually discharged within 6–7 days of surgery, and wound healing is rapid. There is no requirement for the prophylactic anticonvulsants often used by neurosurgeons after craniotomy, and life-style restrictions are minimized. The major complications of trans-sphenoidal surgery are CSF rhinorrhoea and meningitis but these are fortunately rare (around 1–2% in most series). Diabetes insipidus occurs in about 20% of patients, predominantly those with large tumours, and is usually transient. Hypopituitarism, when present, is usually permanent; it is also more common in those undergoing extensive resection of large tumours. In some series up to 30% of patients develop some evidence of pituitary hypofunction.

What is the definition of 'cure' and how is this determined? For this a brief discussion of normal growth hormone secretion is required. Using conventional radioimmunoassays (limits of detection around 0.5–1 mU/l), growth hormone secretion in adults is largely undetectable throughout the waking hours with only occasional secretory bursts (every 6–8 h). In acromegalis the whole growth hormone baseline is raised and peaks become more discernible. Moreover, 20–30% of acromegals have a paradoxical rise of growth hormone secretion in response to thyrotrophin releasing hormone and gonadotrophin releasing hormone. A good long-term marker of growth hormone hypersecretion (which does not exhibit rapid oscillations) is the liver growth hormone-dependent protein, IGF-I, whose levels correlate well with mean growth hormone levels. Levels of IGF-I are almost always elevated prior to treatment. The ideal biochemical cure should be the return to the normal dynamic daytime pattern of growth hormone secretion and IGF-I levels and the abolition of paradoxical responses. Assessment of mean daytime growth hormone levels by averaging values from 4–6 samples taken at 2- to 3-h intervals, or averaging levels obtained during an oral glucose tolerance test, are currently acceptable methods, although there is interest in using single random growth hormone measurements and overnight urinary growth hormone excretion as simpler, less time consuming methods for assessment. Currently accepted criteria of 'cure' are mean growth hormone level below 5 mU/l and normal IGF-I levels, although recently a leader article from USA was citing less than 10 mU/l as an acceptable criterion of 'cure'. It is certainly well accepted among endocrinologists that active acromegaly and raised IGF-I levels can be seen with mean daytime growth hormone levels between 5 and 10 mU/l. Thus, in the UK at least, 10 mU/l is no longer acceptable. Is 5 mU/l low enough or should we be aiming for between 0–2 mU/l? In a small series clinical cure was reported with mean levels below 5 mU/l, but not above this level. No data are available for levels below 2 mU/l. We do not know the mean growth hormone levels needed to reduce the long-term complication rate and excess mortality associated with acromegaly. The small study by Bates et al. addresses that question, using epidemiological methodology identical to that of earlier studies comparing mortality with that of the general population, in a retrospective analysis of hospital records and death certificates. The authors report that in 39% of their acromegals (n = 79) with lowest mean growth hormone level below 5 mU/l over an average of 9 years, the survival was the same as for the general population. However, if the growth hormone 'cure' level was taken as less than 10 mU/l mortality was still significantly worse than for the general population. These are the first data to provide an answer to this important question, but they clearly need to be confirmed in a much larger sample, and several important questions remain unanswered. Nevertheless, they provide objective support for the currently accepted target of mean daytime growth hormone levels of 5 mU/l or less. The above result is somewhat surprising since 50% of patients with growth hormone levels below 5 mU/l had some evidence of pituitary hypofunction, and it has been previously reported that hypopituitarism is associated with a 2- to 3-fold increased mortality. Questions remain, including what is the contribution, if any, of hypopituitarism to mortality in acromegals? Do patients with GH levels below 5 mU/l and no pituitary hypofunction do better in the long term than those with GH below 5 mU/l and some or complete pituitary hypofunction?

The next issue is how best to achieve mean daytime growth hormone levels below 5 mU/l. Most authorities agree that where feasible this should be by hypophysectomy, as discussed earlier. The main advantage is the rapid relief of symptoms and lowering of growth hormone levels, based on the belief (unsubstantiated by evidence) that the sooner tissue exposure to excess growth hormone is abolished the better. Are there other primary treatment options and what should be done if hypophysectomy fails to achieve target growth hormone levels? External radiotherapy has been
used for many years, but as primary treatment it is slow to work and after 10 years the hypopituitarism rate is high and progressively increases. It does, however, have the advantage of probably preventing tumour regrowth.

Adjunctive medical treatment with bromocriptine while awaiting the full effects of radiotherapy and after failed hypophysectomy has been available for 20 years. However, this only lowers growth hormone levels in about 20–30% of patients, and few reach the target of less than 5 mU/l. Nevertheless, clinical benefit is achievable in some, the drug is usually well tolerated for many years, it is cheap and easy to administer, and benefit in terms of growth hormone suppression can be assessed after 1–2 months of therapy, making a therapeutic trial justified in most patients.

There is, however, the prospect of a much more effective medical treatment with the long-acting somatostatin analogue, octreotide. This lowers growth hormone levels in 70–80% of patients;8,12,13 up to 50% achieve levels of less than 10 mU/l, and 20–30% achieve levels below 5 mU/l. Symptomatic relief occurs in most patients and, more significantly, up to 50% show up to 50% reduction in tumour size after 6 months. This may prove useful prior to hypophysectomy in those with large suprasellar extensions. Although large doses of this peptide hormone are sometimes required it seems that long-term growth hormone control can be achieved with little evidence of ‘escape’ due to desensitization. This is clearly a very promising addition to the therapeutic armoury but there are still significant problems to be overcome: (1) 3–4 times daily subcutaneous injections are required, and this is inconvenient for the patient; (2) owing to suppression of cholecystokinin release, gallbladder contraction is reduced and development of gallstones may be a real problem.14 Fortunately there is no precipitation of diabetes mellitus and no deterioration in glycæmic control in the long term; (3) it is very costly (up to £12,000/year if high doses are required). More long-term data need to be collected to evaluate the place of octreotide in the hierarchy of management.

The final question is who should we treat and how aggressively? The young and middle-aged (< 50) should be treated aggressively and the elderly (> 70) should be treated more conservatively, if at all. Difficult decisions involve those between 50 and 70, who may have more than 20 years life expectancy. Perhaps some endocrinologists have erred on the conservative side in this group, but this approach may need to be reconsidered if lowering GH to < 5 mU/l really improves survival, despite having had the disease for several years before treatment. We certainly have the means now whereby this can be achieved with minimal risk to patients.

More long-term follow-up data are urgently required, with large enough numbers of patients in the various age and treatment subgroups for reliable conclusions to be reached. This could be achieved if we all pooled our data in a multicentre national register.

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References