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Acromegaly: treatment after 100 years

The aim should be symptomatic control and a growth hormone concentration <5 mU/l

One hundred years ago this month, the *BMJ* published a report of the first case of acromegaly to be treated.[1] A skull flap was raised to relieve intractable headache, which it did successfully, but the patient died three months later aged 35.

Subsequent studies have confirmed the substantially increased morbidity and mortality among patients with acromegaly.[2-4] It results from cardiovascular, cerebrovascular, respiratory, and possibly malignant disease[5] and is related to both the degree and the duration of the increased growth hormone concentration.[3]

Treatment has come a long way since 1893. We now understand the mechanism of tumorigenesis in two fifths of the pituitary tumours that secrete growth hormone.[6] The combination of different treatments alleviates symptoms and results in growth hormone concentrations that are near normal in most patients.[7] Two recent meetings this year, one in Los Angeles and the other at the Royal Society of Medicine in London, have resulted in a consensus about the treatment of most cases of acromegaly.

Although symptomatic control is important, it should not be the only aim, and biochemical acromegaly can persist despite symptomatic relief. At what concentrations of growth hormone and its dependent somatomedin, insulin-like growth factor 1, should we aim? Treatment rarely restores these concentrations to normal.

Many surgical series have used growth hormone concentrations of <10 mU/l (5 μg/l) to define a cure, but at this concentration some patients have raised concentrations of insulin-like growth factor 1. Evidence is now accumulating that growth hormone concentrations of <5 mU/l (2·5 μg/l) on multiple sampling through the day or throughout a glucose tolerance test are usually associated with a normal insulin-like growth factor 1 concentration,[8] and, although data are available on only a few patients assessed in this way, mortality is not significantly increased.

How can concentrations <5mU/l be achieved? Surgery, most commonly by the transsphenoidal route, is the mainstay of treatment.[9] Surgical removal of small tumours (<1 cm in diameter; microadenomas) is more likely to succeed, and postoperative concentrations of growth hormone <5 mU/l are achieved in most cases.[9,10] Surgery cures a smaller proportion of large intrasellar tumours and the chances of remission after the surgical removal of an extrasellar tumour are less than 20%. With large intrasellar and extrasellar tumours, surgery carries about a 30% risk of loss of pituitary function.[10] Major complications, including meningitis and cerebrospinal rhinorrhoea, are rare (around 1-2%).[10] Whether attempts should be made before operation to decrease the size of the tumour with drugs is not yet known.

External beam irradiation reduces growth hormone concentrations in some 90% of patients with acromegaly and prevents regrowth of the tumour in 99% of them,[11] but effects on growth hormone secretion are slow. Although the biggest fall in concentration occurs in the first two years after irradiation, the concentration continues to fall for at least 15 years—by then most patients have concentrations <10 mU/l.[11] Hypopituitarism is the commonest side effect of radiotherapy so patients need regular yearly or two yearly tests of pituitary function. Up to one half of patients may require replacement treatment for adrenocorticotrophic hormone, thyroid stimulating hormone, or gonadotrophin deficiency by 10 years. Other complications may supervene, including visual loss and brain necrosis, and tumorigenesis induced by radiation is theoretically possible. Visual loss and brain necrosis are extremely rare unless unnecessarily high doses of radiation have been used. Tumorigenesis induced by radiation has been suggested in one big series [12] but not another.[13]

The first effective pharmacological agent to be described was bromocriptine, a dopamine agonist, which paradoxically induces a fall in growth hormone concentrations.[14] Although it improves symptoms in many patients, growth hormone concentrations fall to <10 mU/l in only one in seven.[10] Octreotide, a long acting analogue of somatostatin, is currently the most effective medical treatment of acromegaly and reduces growth hormone concentrations in most cases (to below 5 mU/l in 30% of cases and below 10 mU/l in 50%).[15] In half the cases the tumour gets smaller.[16]. In comparative studies more patients respond to octreotide than to bromocriptine, and in the same patients octreotide suppresses growth hormone secretion more than bromocriptine does.[17] But side effects have caused some concern, particularly the development of gall stones in 14-60% of patients,[18] which have been symptomatic in some cases, particularly on drug withdrawal. Octreotide is expensive, costing £6000 for a year's treatment at conventional doses of 100 μg three times daily.

Experience with these treatments has allowed us to formulate a policy for treating most patients with acromegaly. In a patient with a microadenoma, transsphenoidal surgical exploration is the best treatment. If symptoms improve, the insulin-like growth factor 1 concentration is normal, and growth hormone concentrations are <5 mU/l, leaving the

patient without further treatment of his or her acromegaly is safe. If the concentration of growth hormone is >5 mU/l and symptoms remain, with an increased concentration of insulin-like growth factor 1, external beam irradiation should be considered. Until growth hormone concentrations fall to ≤5 mU/l either bromocriptine or octreotide can be given and withdrawn at yearly intervals to assess the effects of radiotherapy on growth hormone secretion.

Symptomatic elderly patients, particularly those in whom surgery is contraindicated, are more susceptible to the beneficial effects of octreotide than younger patients.[19] In patients with macroadenomas (>1 cm in diameter) transsphenoidal surgery is the best treatment. Again, external beam radiotherapy and bromocriptine or octreotide may be used until growth hormone concentrations fall below 5 mU/l.

We need further large scale studies to decide whether reducing growth hormone concentrations to <5 mU/l is safe; a nationwide register of patients with acromegaly would help. We need too to ascertain the effects of abnormally low growth hormone concentrations after treatment—hypopituitarism has been associated with an increased mortality and the development of premature arterial degeneration.[20]

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Genetic testing and insurance

Emphasises the irreconcilable dilemma in underwriting

The question of whether companies that issue policies for health insurance, disability insurance, and life insurance should have access to the results of genetic tests should be addressed as part of a more fundamental issue: the irreconcilable dilemma in underwriting. Traditionally, an insurance policy affords protection against very large costs resulting from the occurrence of an undesirable event whose probability is small. If the probability of loss is the same for each person then each will pay the same premium. But if the insurance company has information about the relative risk to each person it might charge premiums proportional to the risk. In the extreme case that there is sufficient knowledge to predict definitively to whom events will occur, the traditional concept of insurance breaks down as the person's premium minus his or her share of the company's expenses and profits will exactly equal his or her loss.

No solution to this dilemma exists. If insurance premiums are set to be equal for all people then the phenomenon of adverse selection may arise. Those people with a high risk may tend to purchase a great deal of insurance; those with a low risk may tend to purchase less. A vicious circle ensues as insurance companies are forced to raise their premiums to cover their expenses. On the other hand, if a company charges rates that depend on the risk those at high risk, who often form a small proportion of the total population and are most in need of insurance, will not be able to afford policies.

This discussion raises two questions. Firstly, should information be used in setting insurance rates, and, secondly, is genetic information any different from any other medical information? To answer these questions some people argue that it is useful to separate health insurance from disability insurance and life insurance. To an increasing extent, health insurance is considered to be a necessity that should be available to all. Even in the United States, the last Western country not to have universal health care, there is a consensus that a system guaranteeing a basic level of health care to all is essential.

Although it can be argued strongly that disability insurance and life insurance are also necessities and that such cover should be universal, this position is controversial. Consequently, companies offering these types of insurance will continue to engage in underwriting. Whether these companies should have access to the results of genetic tests depends on whether genetic tests are different from other types of medical tests.

Genetic tests for single gene disorders that manifest in all environments are most easily distinguished from non-genetic medical tests. Unlike tests for most non-genetic conditions, genetic tests for such monogenic conditions as Huntington's disease, cystic fibrosis, and haemochromatosis can be used to diagnose a disease before clinical symptoms appear. On the basis of information obtained from these types of genetic tests insurance companies and employers have discriminated against asymptomatic carriers and presymptomatic people.[1,2] We believe that discrimination against these classes of people is unjustified as the asymptomatic carriers will never become ill and some of the presymptomatic people may develop only mild symptoms of their disease.

In addition, genetic information is different from other medical information in that it can often provide information about the health of other members of the family of the person tested. These people, too, can be victims of unfair discrimina-