Neuro-endocrinology
17 BRIEFINGS

PITUITARY TUMOUR THERAPY: USING THE BIOLOGY

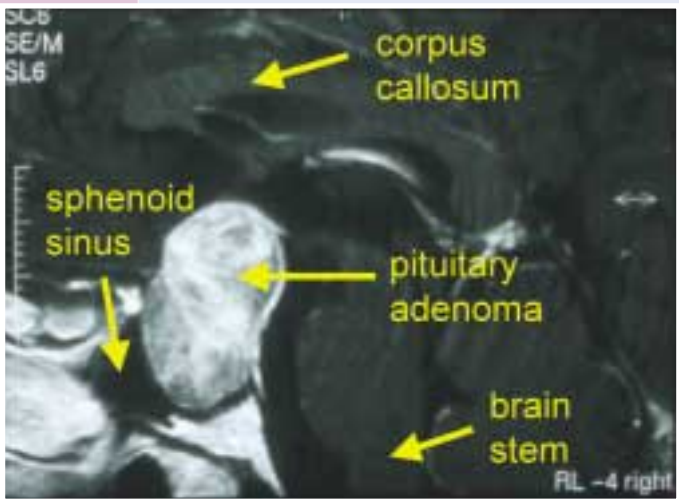
SUMMARY

Pituitary tumours are benign but cause significant problems, both because of their compressive effects on brain structures and also because of the syndromes of hormone excess or deficiency that they can cause. Endocrine therapy has become increasingly successful, with the development of dopamine agonists and somatostatin analogues. Recently growth hormone receptor antagonists have been developed by modification of the GH molecule. It is likely that further advances based on our understanding of the biology will dramatically improve the treatment of these tumours.

Small, benign, and sometimes trouble

Pituitary tumours are surprisingly common – about 20% of us will develop a small benign adenoma in the pituitary during our lifetime. In most of us these are never noticed, as they are usually small and do not secrete a significant excess of any pituitary hormone. These common micro-adenomas are increasingly noticed incidentally on brain scans. In a proportion of people, however, pituitary tumours secrete one of the six main pituitary hormones in large enough amounts to cause a clinical syndrome. Many tumours do not secrete much functional hormone, but some grow large enough to compress the optic nerves on their way from the eyes to the brain, erode the bone surrounding the gland, or compress the remaining normal pituitary tissue. These clinical problems – endocrine syndromes, visual loss, headache, and hypopituitarism – are quite unusual, but they cause serious difficulties to their owners, and can cause premature death.

Pituitary tumour biology has moved on greatly in the past 20 years and it is now normal to consider these tumours in terms of their cell type of origin. Measurements of circulating hormone levels and immunocytochemical analysis of tumour samples has given our current categories of 'non-functioning' tumours and of 'functioning' tumours that usually secrete prolactin, growth hormone (GH), or ACTH. The respective clinical syndromes of hormone excess seen with prolactinoma, acromegaly or Cushing's disease are well recognised, and diagnosis can be made fairly easily in most cases.



A magnetic resonance (MR) scan of a large pituitary adenoma.

Surgeons and X-rays

An obvious treatment for a benign troublesome tumour is just to remove it. Getting to the pituitary gland is not easy and the surgical techniques require access through the sphenoid sinus into the base of the pituitary gland. Success demands the removal of the entire tumour from a deep inaccessible recess, without damaging normal structures. 'Debulking' may be fine

for non-functioning lumps, but endocrine-active tumours need to be totally removed to achieve an adequate 'cure' of the clinical syndrome. It is not surprising that even in the most expert hands, endocrine cure rates are at best usually 80-90%, and may be as low as 40%. Pituitary tumours grow very slowly over many years, and external beam radiotherapy works just as slowly, killing cells as they occasionally try to divide. This means that it is very good at preventing growth of tumour remnants after partly successful surgery, but its effects are slow, and improvements in hormone hypersecretion may take as long as 12-15 years.

Using biology further

Endocrine therapy for pituitary tumours was discovered in the early 1970s, when scientists at Sandoz Pharmaceuticals (now Novartis) discovered that a new drug, CB154, inhibited prolactin secretion. The drug, now known as bromocriptine, acted on dopamine D2-receptors and was able to normalise prolactin levels in patients with prolactinomas. Even more striking, bromocriptine induced dramatic shrinkage of prolactinomas, even very large ones, completely avoiding the need for surgery. A series of further dopamine agonist drugs have been developed, including cabergoline and quinagolide, and these have remained the preferred treatment for patients with this type of tumour.

With the astonishing success of dopamine agonists, other candidate therapies were sought. Somatostatin is a peptide hormone found widely throughout the body and is involved in the regulation of secretion of many hormones. Its potential for the treatment of GH secreting tumours was recognised early, but its therapeutic efficacy was limited by its very short half-life and lack of specificity for GH. To overcome these problems, somatostatin analogues with much longer half-lives and greater specificity for the somatostatin receptors (types 2 and 5) relevant to GH secretion were synthesised. Somatostatin analogues are now the main medical treatment for GH-secreting tumours and are also used for the rare TSH-secreting pituitary tumours. Octreotide and lanreotide will control GH secretion in the majority of patients with acromegaly and in a minority cause some tumour shrinkage.

However, even with the best available of these treatments, GH secretion cannot be controlled in a significant minority of patients. To address this problem a new class of drug has been developed which does not attempt to lower GH levels but rather inhibits GH action. Pegvisomant is a recombinant protein GH analogue with amino acid substitutions in binding site regions such that receptor dimerization is prevented and function is blocked. The peptide has also been conjugated to polyethylene glycol to prolong its half-life to over 70 hours. Studies in patients with acromegaly suggest it is effective in virtually all patients and it is hoped that it will be granted a licence and become more widely available in 2003.

Gene therapy

Endocrine therapies are likely to be refined further over the coming years, but there has been some recent interest in the possibilities of using gene therapy to treat pituitary tumours. Gene therapy simply means gene transfer in vivo for therapeutic benefit, and has been used so far to attempt treatment of otherwise fatal diseases. Applications to date include replacement of missing or defective enzymes or other proteins, and delivery of 'suicide' genes, whose protein products kill the host cell. The latter approach may hold some promise for aggressive pituitary tumours that prove resistant to all standard therapies. Pituitary-specific gene promoters can target transgenes to the right cell types, and pre-clinical studies are currently evaluating different virus 'vectors' for efficacy and safety. These applications are rapidly becoming feasible, and the safety issues better understood, and may well alter therapeutic strategies for pituitary disease in the future.

" . . . receptor dimerization is prevented and function is blocked."

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