▪ SINGAPORE MEDICAL JOURNAL ▪

SMJ

ISSN 0037 - 5675
Permit No MITA (P) 261/01/98
PP (S) No 580/12/95
ISSN 0037 - 5675

JOURNAL OF THE
SINGAPORE MEDICAL ASSOCIATION

Editorial Address
Prof Kua Ee Heok, Editor
Singapore Medical Journal
Singapore Medical Association
2 College Road
Singapore 169850

For advertising placement, please call Ms Ng Mei San
Printed by Tri-Art Printers Pte Ltd

Editorial

Pituitary Tumours – A New Look at an Old Problem

C Rajasoorya

Patients with pituitary tumours are uncommon, with an estimated incidence of 20 – 30 per million per year[1]. Manifestations of pituitary tumours are dependent on the cell line involved, age of onset and the rapidity and extent of expansion. They manifest as functional disorders or as an expansive lesion arising within the confines of the sella, if not incidental. Functionally, pituitary tumours can present as hormonally - excess or -deficient syndromes; these may be multi-hormonal or multi-syndromic. A pituitary tumour may precede or accompany the diagnosis of Multiple Endocrine Neoplasia Type I. Rarely, an ectopic hormone-producing tumour can mimic a pituitary syndrome and tumours in structures adjacent to the pituitary may be misdiagnosed radiologically as pituitary tumours. Malignant pituitary tumours are extremely rare.

Evaluation must involve both anatomic and functional considerations. The laboratory serves as a crucial aid in diagnosis, treatment and follow-up. Laboratory data must be interpreted by applying physiological principles with special consideration to diurnal, age and sex related variations, and to the concept of relativity in interpreting "normal" ranges. The functional posterior pituitary gland must not be ignored in assessment. Hormone measurements only attempt to assess function. However, receptor insensitivity or disordered anatomy may also be responsible for clinical manifestations. The utilisation of dynamic stimulation and suppression tests has now shifted from being one of a routine in the past, to its selective use in non-interpretable baseline hormone levels or in equivocal cases, where management is influenced. Increasingly, magnetic resonance imaging (MRI) has been used for visualisation of the pituitary gland and adjacent structures rather than computed tomography (CT).

Surgical, medical and radiation therapies have remained the mainstay therapy for pituitary tumours. The widespread utility of CT and MRI has led to the increasing recognition of incidental pituitary tumours. These "incidentalomas" and the recently recognised entity of lymphocytic hypophysitis have heightened the need to consider non-intervention and observation in selected instances.

Deficiencies, whether at diagnosis or after therapeutic intervention must be corrected. Adequate steroid replacement would prevent a potential fatality and may unmask an unsuspected diabetes insipidus. The recent availability of oral vasopressin tablets has been an added convenience to patients. While the cost-benefits of replacement of steroids, thyroxine, sex hormones and vasopressin have never been called into question, the issue of growth hormone (GH) replacement in those with its deficiency had been controversial. Newer evidence suggests that GH replacement may have benefits in reducing both morbidity and mortality[2].

Prolactinomas are usually responsive to dopamine agonists both in terms of prolactin level reduction and tumour shrinkage. Those intolerant or unresponsive to bromocriptine, now have the option of the newer dopamine agonists like cabergoline and quinagolide. The non-responsive tumour should raise the possibility of a masquerading pseudoprolactinoma ie. a non-functioning tumour causing stalk compression and hence hyperprolactinaemia. Patients intolerant/unresponsive to long

term dopamine agonist therapy may be candidates for surgery as would those with large macroprolactinomas that cause significantly rapid visual field compromise or cranial nerve palsies. Female patients with microprolactinomas without any menstrual disturbances or significant symptoms may be observed without therapy, provided they are closely monitored.

Acromegaly is best managed surgically. It can achieve a rapid cure and studies have demonstrated that morbidity and mortality are strongly influenced by the achieved GH level[3]. The availability of long-and supra- long-acting somatostatin analogues like octreotide, octreotide-LAR and lanreotide has been an option for selected cases. The prohibitive cost aside, these have been shown to reduce tumour size in about a third of patients by up to 30% and significantly reduce GH levels. It has been suggested as a tool to promote tumour shrinkage pre-operatively as well as to rectify incomplete surgical cure. Dopamine agonists suppress GH levels but studies show rather incomplete suppression in the majority. Radiation therapy has been used more often as an adjunct or in those deemed unsuitable for surgery.

The limitations of radiation however are mainly that of delayed effectiveness (with the concomitant effects of GH excess) and the risk of hypopituitarism and its associated morbidity and mortality. Currently, the gamma knife has been used mainly to treat residual or recurrent small tumours, no large scale studies comparing it with conventional radiation therapy exist.

Where a tumour is clearly identified and the diagnosis unequivocal, surgery is the ideal option for Cushing's disease. Not infrequently, the biggest dilemma has been in the accurate localisation of the tumour. The more widespread use of inferior petrosal sinus sampling would no doubt help improve the success rate. There is still a place to utilise medical therapy with ketoconazole and aminoglutethimide as temporising measures pending localisation or bilateral adrenalectomy (with prior pituitary radiation to avoid Nelson's syndrome) where tumour localisation or removal proves difficult in a deteriorating patient.

Rarer tumours like thyrotrophinomas and gonadotrophinomas are best managed surgically, although sometimes they do respond to dopamine agonists and somatostatin analogues. Clinically non-functioning pituitary macroadenomas, which present with visual or neurological symptoms, should have treatment directed at reducing the tumour mass and correcting visual loss, if present. Radiation therapy has been used to treat residual or inoperable tumours. Dopamine agonists and somatostatin analogues occasionally reduce tumour size and therefore represent a potential form of adjunct therapy. Clinically non-functioning pituitary microadenoamas have a prevalence of up to 11% in some autopsy series[4]. As the risk for microadenomas to enlarge is low, the decision to operate may be confidently postponed with guidance from sequential imaging studies to establish the growth rate and the need for intervention.

Where surgery is a considered option for pituitary tumours, an experienced pituitary neurosurgeon would seem to have an advantage in the final outcome analysis[5,6]. All patients who had surgical cure should be adequately monitored for recurrence. One therapeutic modality alone may be insufficient to achieve cure or control of the hyper-secretory state. Alternate adjunct therapy should be considered in such instances.

Hormone-secreting pituitary adenomas are associated with a high frequency of local and/or systemic complications at diagnosis. Although treatment reduces the prevalence of these complications, this is often at the price of increased rates of hypopituitarism[7]. The use of adjunct radiation therapy must also be carefully weighed against the concerns raised about the risk of a second cerebral malignancy[8].

Management is straightforward and unequivocal in most instances. But controversies exist. The tripartite collaboration amongst the endocrinologist, neurosurgeon and the radiation oncologist would help to minimise these. The choice of therapeutic option depends on what tumour we are dealing with and in which patient, and what expertise is available. Cost considerations may be an influencing factor. Like choosing a lane on the highway, it depends on how much time and experience we have, what perils exists and what risks we accept. Along the journey we may still change our routes but whichever route we choose to take our patients through, the ultimate aim is to bring them to the destination of cure, or at least good control.

REFERENCES

1. Pituitary Tumours: recommendations for service provision and guidelines for management of patients - Consensus statements of a working party. London: Royal College of Physicians of London, 1997.
2. Consensus Guidelines for the Diagnosis and Treatment of Adults with Growth Hormone Deficiency: Summary Statement of the Growth Hormone Research Society Workshop on Adult Growth Hormone Deficiency. J Clin Endocrinol Metab 1998; 83(2):379-82.
3. Rajasoorya C, Holdaway IM, Wrightson P, Scott DJ, Ibbertson HK. Determinants of clinical outcome and survival in acromegaly. Clin Endocrinol (Oxf) 1994; 41:95-102.
4. Molitch ME. Pituitary incidentalomas. Endocrinol Metab Clin North Am. 1997; 26:702-40.
5. Burke CW, Adams CBT, Esiri MM, Morris C, Bevan JS. Transphenoidal surgery for Cushing's disease: does what is removed determine the endocrine outcome? Clin Endocrinol (Oxf) 1990; 33:525-37.
6. Lisset CA, Pearcey SR, Laing I, Tetlow L, Davis JRE, Shalet SM. The outcome of surgery for acromegaly: the need for a specialist pituitary surgeon for all types of growth hormone secreting adenoma. Clin Endocrinol (Oxf) 1998; 49:653-7.
7. Holdaway IM, Rajasoorya C, Wong J, Orr-Walker B, Gamble G. The natural history of treated functional pituitary adenomas. In Webb S, Ed. The Management of Pituitary Tumours. Bristol: BioScientifica Ltd 1998: 31-42.
8. Jones A. Radiation oncogenesis in relation to the treatment of pituitary tumours. Clinical Endocrinol (Oxf) 1991; 35:379-98.

Department of Medicine, Alexandra Hospital, 378 Alexandra Road, Singapore 159964
C Rajasoorya, MBBS, MMed, FAMS, FRCP (Edin), FACE, Consultant Endocrinologist

Cover picture:
"Fishing" *Acrylic on canvas 47 cm x 61 cm 1996* by Prof Arthur Lim