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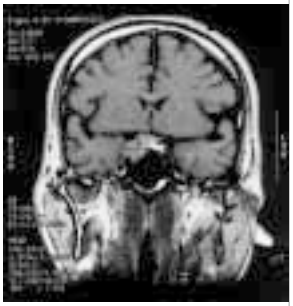

Cover Picture:
Coronal views of pituitary gland showing a large tumour (crosses) displacing the optic chiasm superiorly and partly encasing the carotid artery on the right side.
(Refer to page 433-437)

Editorial

Hyperprolactinaemia and its Clinical Significance

C Rajasoorya

Prolactin is unique amongst the pituitary hormones because it is under tonic inhibitory control. Pituitary stalk section causes a marked increase in prolactin secretion, dopamine being the major inhibitory factor. The only clearly established role for prolactin is in the initiation and maintenance of lactation. Some recent data suggests that prolactin may have an added immuno-modulatory role[1,2].

Hyperprolactinaemia is the most common hypothalamo-pituitary disorder encountered in clinical endocrinology and obstetrics and gynaecology. While the existence of the hormone has been suspected for many years, its measurement in human plasma was not accomplished until the early 70s – not many may be aware of this important international contribution by a local pioneer endocrinologist (Prof Peter Hwang) 30 years ago[3]. The introduction of the radioimmunoassay for the measurement of prolactin has tremendously helped our understanding of hyperprolactinaemia and prolactinomas.

Pathophysiologically, any process that interferes with dopamine synthesis, its transport to the pituitary gland, or its action on the lactotrophs can lead to hyperprolactinaemia. Practically this may be best remembered by the 3*P*s – *P*hysiological, *P*harmacological and *P*athological. Physiological elevations in prolactin may be resultant from pregnancy continuing into the immediate post partum and stress amongst others. Common pharmacologic agents that induce hyperprolactinaemia include neuroleptics, dopa blockers, antidepressants and oestrogens. Pathological causes include hypothalamo-pituitary disease, pituitary stalk injury, hypothyroidism, chronic renal failure and liver cirrhosis. The latter two conditions are often clinically obvious when hyperprolactinaemia coexists. Pregnancy must be excluded before any further evaluation for hyperprolactinaemia is undertaken. Hypothyroidism is best excluded by requesting for thyroxine and thyrotrophin levels.

The endocrine presentations of hyperprolactinaemia result from the hormonal influence on prolactin target tissue, which are predominantly the gonadal and reproductive systems, and breast tissue in both sexes. Galactorrhoea, diminished fertility, hypogonadism and secondary osteoporosis may result in both sexes, though it is more common in females. Galactorrhoea in either sex may be unilateral or bilateral, clinical or sub-clinical, spontaneous or expressed, and may be scanty or copious – it does not correlate with the level of hyperprolactinaemia. The presence of galactorrhoea does not equate with the demonstration of hyperprolactinaemia. Normoprolactinaemic galactorrhoea is a well-recognised entity and the reasons for its existence are not exactly clear[4]. Women with hyperprolactinaemia tend to show up earlier as they present with menstrual irregularities. Men tend to be diagnosed later

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when the effects of the pituitary tumour enlargement become manifest. Impotence is a common presentation in men. Rarely, hirsutism may result from prolactin-induced ACTH-dependent DHEA production[5].

The underlying tumour, if any, can cause compressive effects on the surrounding structures (e.g. visual field defects, cranial nerve deficits) as well as contribute to hypopituitarism. Hyperprolactinaemia occurring in a familial setting or with other associated endocrinopathy or its resultant manifestations should alert the consideration of Multiple Endocrine Neoplasia Type 1 (MEN-1). Approximately 30% of patients with MEN-1 have pituitary tumours of which the commonest is a prolactinoma (occurring in approximately 60% of those with pituitary tumours)[6]. Malignant or ectopic prolactin-secreting tumours are extremely rare.

Elevated prolactin levels should be confirmed on at least two occasions, as prolactin secretion may be labile and episodic in a given patient. It would be ideal that this is not done when the patient has had a recent breast examination. Prolactin values of more than 5000 mU/L (approx 250 ug/L) are usually indicative of a prolactinoma. Prolactin values of less than 5000 mU/L could be due to prolactinomas (micro- or macro-adenomas), pseudo-prolactinomas or to idiopathic causes[5]. Distinction between a prolactinoma and pseudo-prolactinoma is essential, although this is not always practicable at onset. A large number of sellar and parasellar lesions can cause hyperprolactinamia via compression of the stalk and/or hypothalamus, thereby interrupting dopamine inhibition of prolactin secretion. A large pituitary tumour with only marginally elevated prolactin levels would be extremely inconsistent with a prolactinoma. A misdiagnosis can result in a false sense of improvement, particularly where prolactin levels become normalised with dopamine agonist therapy – yet the tumour continues to grow. Occasionally patients with sub-clinical or early acromegaly may be misdiagnosed as prolactinomas. Pharmacological and dynamic tests cannot help to distinguish the various causes of hyperprolactinaemia[6,7]. Psychiatric patients on drugs causing hyperprolactinaemia may have a co-existent prolactinoma.

A pituitary Magnetic Resonance Imaging (MRI) is ideally indicated in patients with confirmed hyperprolactinaemia not due to physiological causes, pregnancy, drugs or hypothyroidism. A Computed Tomography (CT) scan, if substituted, can exclude macroadenomas but not microadenomas, although the newer generation CT scanners are able to identify small tumours. A very recent meta-analysis of 12 published studies on the prevalence of pituitary tumours suggested that where sensitive radiographic techniques are employed, the prevalence of small pituitary adenomas appears to be approximately 20%[10]. Thus the presence of a pituitary adenoma with hyperprolactinaemia does not necessarily equate to the diagnosis of a prolactinomas. Assessment of visual fields would be useful if a macroadenoma is present or hypopituitarism suspected.

Where hyperprolactinaemia exists management strategy should be directed towards revelation of the aetiology and treating the underlying cause, if any. The therapeutic strategy differs markedly in the way a prolactinoma and pseudo-prolactinoma is managed. Prolactinomas are usually responsive to dopamine agonists both in terms of prolactin level reduction and tumour shrinkage. Those intolerant or unresponsive to bromocriptine have the option of newer dopamine agonists like cabergoline. Experience with the use of cabergoline in pregnancy has been much more limited than that of bromocriptine. Patients unsuitable (poor response, non-compliance or intolerant) for long term dopamine agonist therapy may be

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candidates for surgery as would those with large macro-prolactinomas that cause significantly rapid visual field compromise or cranial nerve palsies. Women with macro-prolactinomas should be strongly advised against pregnancy till significant tumour shrinkage has been verified. If despite the advice, the patients get pregnant, it would merit very close monitoring during pregnancy. Patients with micro-prolactinomas without any menstrual disturbances or significant symptoms may be observed without therapy, provided they are monitored.

The clinical effects of hyperprolactinaemia should guide the decision to treat an individual patient, where no specific cause for the hyperprolactinaemia exists. Indications for treatment would include the presence of symptomatic and troublesome galactorrhoea, menstrual disturbance, infertility, impotence, hypogonadism or its sequelae, and hyperandrogenic states. Dopamine agonists are the first line therapy in such patients. Where no such indications exist it would seem reasonable to observe such patients with serial clinical evaluation and prolactin measurements.

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This issue of the journal[11] reports on an MRI study of the pituitary and the para-pituitary region of 24 patients with hyperprolactinaemia following radiation therapy for nasopharyngeal carcinoma. This paper reports on negative findings of structural defects/tumours as a cause of hyperprolactinaemia. As the authors rightfully point out, there are some limitations to this negative study. Among these, are the non-uniformity of the study protocol in MRI, problems in identifying small lesions beyond the resolution of MRI and lastly radiation-induced damage which could have been at the cellular level, evading MRI detection. The authors have taken precautions to avoid some common pitfalls in the evaluation of the secondary causes of hyperprolactinaemia, such as tumours causing pituitary erosions, primary hypothyroidism, and drug use amongst others. Presumably they had excluded conditions like cirrhosis and renal failure as well as pregnancy amongst their younger female patients. No clear details are provided in the paper on the methodology of identification of the 24 patients with hyperprolactinaemia amongst the 330 patients treated over nearly four years. This paper does not provide details on the method and the timings in which the prolactin levels were sampled and if these were singleton samples. This would be particularly relevant in those with borderline elevations of prolactin. The range of prolactin levels in the remaining non-hyperprolactinaemic patients (if assessed) would be of interest. The diagnostic utility of the "spot" cortisol levels in the evaluation for the hypothalmo-adrenal axis are points of contention. This does not, however, influence the conclusions of the paper. It would also have been interesting to see the interaction of prolactin on the gonadotrophin levels in this cohort of patients as well as the responsiveness to treatment, if any. Nonetheless, this study adds important information in the light of MRI being the choice evaluation modality for hyperprolactinaemia in recent years. Previous studies tended to look at such lesions on CT imaging only and this study is the first using MRI as an imaging modality in such group of patients. SMJ

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