Subclinical endocrinological disease

Series editor: Dr JWF Elte, Department of Internal Medicine, Sint Franciscus Gasthuis, Rotterdam, The Netherlands

Summary

The advent of sophisticated and sensitive radiologic techniques has undoubtedly improved the evaluation of patients with established endocrine disease. An inevitable consequence of the increased sensitivity and widespread availability of modern imaging is, however, the discovery of apparently asymptomatic mass lesions in endocrine tissues. The clinician is then required to determine the appropriate degree of often uncomfortable and costly investigation in a patient with no overt disease. This article attempts to provide guidelines for the management of the ‘pituitary incidentaloma’, a pituitary mass lesion evident on a computed tomography or magnetic resonance imaging scan performed for a reason other than the evaluation of the pituitary gland.

Keywords: pituitary adenoma, pituitary incidentaloma

Asymptomatic pituitary adenomas: prevalence

- autopsy 1.5–26.7%
- CT scan 3.7–20%
- MRI 10%

Box 1

Endocrine Unit, Department of Medicine, University College London Medical School, The Middlesex Hospital, London W1N 8AA, UK
SG Soule
HS Jacobs

Accepted 27 September 1995

The evaluation and management of subclinical pituitary disease

Steven G Soule, Howard S Jacobs

Prevalence of pituitary mass lesions

The frequency of detection of mass lesions in the pituitary depends on the sensitivity of the relevant imaging technique (box 1). Autopsy studies of almost 10 000 subjects not suspected of having pituitary disease whilst alive revealed a startling 11% prevalence of pituitary adenomas less than 10 mm in diameter (microadenomas).¹ Interestingly, only three macroadenomas (more than 10 mm diameter) were uncovered in this large group of subjects. The inevitable conclusions are that microadenomas are common in asymptomatic subjects and that they rarely progress to macroadenomas, which presumably declare their presence with symptoms of hypopituitarism or those of a pituitary mass lesion. Initial computed tomography (CT) studies of asymptomatic subjects supported the *post-mortem* findings as discrete areas of low density were found in 3.7–20% of ‘normal’ pituitaries.¹ The most sensitive pituitary imaging technique available, magnetic resonance imaging (MRI), has recently been subjected to the same scrutiny. Review of pituitary MRI scans of 100 adults with normal baseline endocrine parameters revealed that 10% have 3–6 mm areas of decreased signal intensity following contrast administration, compatible with pituitary microadenomas.² The ‘pituitary incidentaloma’, the offspring of modern imaging technology, has thus come of age and requires rational and reasoned evaluation by clinicians.³

Diagnostic considerations

The differential diagnosis of a mass lesion in the pituitary region is extensive (box 2) and although many of the entities listed are distinctly uncommon, they may require specific therapy. A patient harbouring a germinoma, for instance, would benefit from pituitary radiation as primary therapy, while a patient with a carotid siphon aneurysm in the pituitary region would be placed at substantial risk by pituitary exploration. An incidental lesion in the pituitary area thus requires specialist evaluation by an endocrinologist, neuroradiologist, and neurosurgeon if unusual conditions are to be detected and potentially dangerous management errors avoided. The vast majority of patients will, however, have a pituitary adenoma as the cause of the radiologic abnormality and the remainder of the discussion refers to these patients. Pathologic studies of patients with symptomatic pituitary tumours reveal that approximately 30–40% are prolactinomas and a similar proportion are clinically nonfunctional tumours. The latter do not usually present with a clear syndrome of hormone excess, although the majority produce or secrete varying combinations of gonadotropin α - and β -subunits *in vivo* or *in vitro*.⁵ Adenocorticotropin (ACTH)- and growth hormone (GH)-secreting tumours each comprise 2–10% of pituitary adenomas, whilst thyroid-stimulating hormone (TSH)-secreting adenomas are rare.⁶ In the asymptomatic patient with a pituitary incidentaloma the balance will be shifted toward nonfunctional tumours in both sexes and prolactinomas in men, as deterioration in sexual function occurring as a consequence of prolactin-induced hypogonadism frequently presents late in males (figure 1).

Clinical approach

There are two major issues which should prompt consideration of pituitary surgery in the patient with an incidentaloma. The first relates to the potential for compression of neighbouring structures by macroadenomas, which have already declared their growth potential (figure 2). These patients should have formal evaluation of visual fields by Goldmann perimetry if there is any evidence of

Diagnostic considerations for pituitary sellar or suprasellar mass lesions

- pituitary adenomas: prolactin-secreting, GH-secreting, ACTH-secreting, gonadotropin-secreting, TSH-secreting, nonsecreting
- germ cell tumours: germinoma/teratoma
- benign lesions: meningioma, enchondroma
- granulomatous/inflammatory: pituitary abscess, sarcoidosis, tuberculosis, histiocytosis X, lymphocytic hypophysitis
- cell rest tumours: craniopharyngioma, Rathke's cleft cyst, chordoma, lipoma, colloid cyst
- gliomas
- aneurysms
- metastatic tumours
- miscellaneous: arachnoid cyst, empty sella syndrome

Box 2

Figure 1 Relative frequency of various pituitary adenomas in symptomatic patients

Figure 2 MRI coronal view of the pituitary (without contrast) reveals a large left-sided pituitary macroadenoma with invasion of the left cavernous sinus, erosion of the floor of the pituitary fossa and deviation of the pituitary stalk to the right

Asymptomatic pituitary adenomas: evaluation

- micro: hormone excess (GH, prolactin, cortisol, TSH)
- macro: hormone excess, hypopituitarism (free thyroxine, cortisol, follicle-stimulating hormone/luteinising hormone), compression (optic chiasm), potential for infarction (apoplexy)

Box 3

encroachment on the visual pathways on MRI. Furthermore, evidence of hypopituitarism should be sought both clinically and biochemically ⁷ (box 3). A patient with a macroadenoma, other than a macroprolactinoma, producing a visual field deficit or hypopituitarism should be considered for pituitary surgery.

The second concern pertaining to both micro- and macroadenomas, is the possibility of hormone excess. Each patient should therefore be evaluated clinically for evidence of Cushing's syndrome, acromegaly and prolactinoma, as these conditions have been shown to be associated with substantial morbidity and, for the first two, increased mortality.⁸⁻¹⁰ A patient with biochemical evidence of GH, cortisol or rarely TSH hypersecretion should be offered pituitary surgery, although the patient's age and general condition will clearly affect the decision. Prolactinomas are, however, successfully treated medically with a dopamine agonist in the majority of patients.¹⁰

Natural history of untreated pituitary adenomas

If we accept the notion that most patients with a pituitary incidentaloma and evidence of hormone excess require definitive therapy, what are we to make of the majority of patients with a hormonally silent pituitary adenoma? Evidence of hypopituitarism or a reduction in vision constitute reasonable indications for pituitary surgery as the procedure may reverse or improve both abnormalities.¹¹ The approach to incidental pituitary adenomas without hormone excess, hypopituitarism or mass effects depends on the natural history of these lesions if left untreated. Several recent studies have addressed this important issue (box 4).^{12,13} The study by Reincke *et al* prospectively followed 14 patients with pituitary incidentalomas (seven micro- and seven macroadenomas) treated conservatively for a median of 22 months. Three patients had biochemical evidence of hypopituitarism at baseline assessment. In 13 patients there was no change in the endocrine status during follow-up, while a single subject had a further decrease in serum gonadotropin levels. Tumour volume remained unaltered in 10 patients, although three patients (two macro- and one micro-adenomas) had an increase in tumour diameter of between 3 and 6 mm without any deterioration in visual acuity, while one subject had a 4-mm reduction in diameter. The results of this small study suggest that conservative treatment of asymptomatic incidental pituitary micro- and even macroadenomas may be safely contemplated. A more recent series from Donovan *et al* provides further reassurance. After a median follow-up of approximately six years, none of 15 micro- and four of 16 macroadenomas enlarged, only two with any complications. The patient who developed visual impairment harboured a craniopharyngioma. The concept is thus evolving that micro-incidentalomas rarely enlarge, and that in a patient with a macro-incidentaloma a reasonable approach would be to repeat scans periodically, reserving surgery for patients manifesting tumour growth or hypopituitarism. This approach is based on preliminary data and may be modified as clinical experience accumulates.

Endocrine evaluation

The decision to screen biochemically for pituitary hormone excess, even in the absence of clinical indicators, is supported by recent reviews of the topic.^{3,5} The argument advanced by the protagonists of biochemical screening is the detection of a single 'silent' case of acromegaly in a series of 18 patients with pituitary incidentalomas.¹² A recent study of 31 adults with pituitary incidentalomas suggests, however, that biochemical screening of subjects with no clinical evidence of an endocrine disorder may be fruitless.¹³ The subjects were followed for a mean of 6.4 years after an initial clinical evaluation excluded an endocrinopathy (no routine biochemical evaluation for Cushing's syndrome or acromegaly was performed) and no patient subsequently developed a syndrome of hormone excess. The available data relating to the necessity for routine biochemical screening for acromegaly and Cushing's syndrome are thus limited and contradictory. Our current approach is to exclude these two conditions definitively by means of simple screening tests, although we concede that evidence may accumulate in the future proving this to be over cautious.

PROLACTINOMAS

The mere presence of hyperprolactinaemia in a patient with a microprolactinoma does not necessarily demand definitive therapy (figure 3). Firstly, two or three measurements of prolactin are indicated to ensure the hyperprolactinaemia is sustained. Secondly, the common secondary causes of elevated prolactin concentrations should be considered (box 5) as a small lesion evident on pituitary imaging may be unrelated to the hyperprolactinaemia. If the hyperprolac-

Pituitary incidentalomas: natural history		
• No of patients:	<i>Reincke</i> ¹²	<i>Donovan</i> ¹³
micro	7	15
macro	7	16
• mean follow-up (months)	30	77
• size increase:		
micro (%)	1 (14)	0
macro (%)	2 (28)	4 (25)
• development of hormone excess	0	0
• complications due to tumour mass	nil	↓vision apoplexy

Box 4

Figure 3 MRI coronal view of the pituitary (without contrast) demonstrating a low density left-sided pituitary microadenoma with some convexity of the upper border of the gland and deviation of the pituitary stalk to the right

Evaluation of hyperprolactinaemia
<i>Microadenoma present</i> <ul style="list-style-type: none">• exclude transient hyperprolactinaemia• consider drugs, hypothyroidism and pregnancy• evaluate for hyperprolactinaemic syndrome
<i>Macroadenoma present</i> <ul style="list-style-type: none">• measure prolactin level (≤ 3000 mU/l = probable ‘stalk effect’, $3000\text{--}8000$ = stalk or macroprolactinoma, ≥ 8000 = macroprolactinoma)

Box 5

Screening for acromegaly
<ul style="list-style-type: none">• random GH, excludes acromegaly if <0.5 mU/l• glucose tolerance test, 75 g, failure of GH suppression to <1 mU/l• IGF-1, if normal, active acromegaly unlikely

Box 6

tinaemia is both sustained and primary, the female patient should be evaluated for features of the hyperprolactinaemic syndrome, comprising menstrual disturbance and a reduction in libido, with or without galactorrhoea.¹⁰ The necessity to treat patients with oligo- or amenorrhoea relates mainly to the risk of osteoporosis in patients with hypogonadism secondary to hyperprolactinaemia. Early studies noted a 25% reduction in mean spinal bone mineral content in hyperprolactinaemic women, and it appears that the deficit may not be entirely reversible despite restoration of physiological levels of oestrogen.^{14,15}

The patient with a macroadenoma and hyperprolactinaemia requires thoughtful evaluation. Synthesis and release of prolactin from anterior pituitary lactotrophs are under the inhibitory influence of dopamine, which is produced in the hypothalamus, released into the portal circulation and then interacts with a specific class of D₂ receptors on the lactotroph cell membrane. The clinical correlate of the physiology is the ‘stalk effect’ whereby any lesion that interferes with dopamine synthesis, release or passage to the anterior pituitary may produce hyperprolactinaemia. A large nonfunctional pituitary tumour may thus be mistaken for a macroprolactinoma by the unwary. The distinction is not merely academic as it may have a profound influence on the therapeutic approach.

Bevan *et al* correlated the serum prolactin concentration with the histological diagnosis in a series of 128 patients with sellar enlargement who were referred for excision of a presumed pituitary adenoma.¹⁶ A prolactin concentration of more than 8000 mU/l was always caused by a macroprolactinoma. All but three patients with ‘stalk effect’ and none with a large prolactinoma had a prolactin concentration less than 3000 mU/l. A prolactin of between 3000 and 8000 mU/l could be caused by either lesion. These results suggest that a pituitary macroadenoma with hyperprolactinaemia less than 3000 mU/l should be regarded as a nonfunctional tumour and be considered for surgery if there is evidence of hypopituitarism or compromise of visual fields. Conversely, if the prolactin concentration is greater than 8000 mU/l, the lesion is likely to be a true prolactinoma and should respond to dopamine agonist therapy with a reduction in tumour volume. Patients with prolactin concentrations in the 3000 to 8000 mU/l range and a macroadenoma may reasonably be given a trial of dopamine agonist therapy with the proviso that lack of tumour shrinkage at follow-up MRI or CT scan should prompt consideration of surgery.

In summary, all patients with incidental pituitary microadenomas with hyperprolactinaemia syndrome (galactorrhoea, reduction in libido, hypogonadism) should receive dopamine agonist therapy. Patients with incidental macroadenomas and hyperprolactinaemia should be evaluated according to the scheme outlined above and treated either with dopamine agonists (macroprolactinomas), pituitary surgery (nonfunctional tumours with hypopituitarism or visual deficits) or conservatively (nonfunctional tumours with intact pituitary function and vision).

ACROMEGALY

Acromegaly, in addition to producing disfigurement, reduces life expectancy. A variety of studies reveal a substantial increase in mortality amongst acromegalics in general, with observed:expected mortality ratios of between 1.9 and 3.3. Furthermore, recent retrospective studies suggest that a mean postoperative GH concentration of less than 5 mU/l is associated with normal life expectancy.⁹ Patients with a pituitary ‘incidentaloma’ who are demonstrated to have acromegaly thus warrant definitive therapy to reduce their increased mortality.¹⁷

The optimal method of screening for acromegaly remains somewhat controversial.¹⁸ The estimation of a random GH is generally unhelpful unless undetectable (less than 0.5 mU/l), in which case acromegaly is reliably excluded.¹⁹ Moreover, it is important to appreciate that normal individuals may have GH concentrations above 40 mU/l during a secretory episode. A GH suppressive test namely a 75 g oral glucose load, is thus required to diagnose acromegaly definitively: the acromegalic fails to suppress plasma GH concentrations below 1 mU/l in response to the glucose challenge. The major mediator of GH bioactivity in the tissues, insulin-like growth factor 1 (IGF-1), is produced principally in the liver and may now be measured in serum. The utility of an IGF-1 measurement as a screening test for acromegaly remains contentious,^{18,20} a reflection of variations in assay sensitivity and the presence of an array of IGF-binding proteins.²¹ Doubtless, improvements in IGF-1 assays over the next few years will see the emergence of IGF-1 measurement as a reliable screening test for acromegaly (box 6).

CUSHING’S DISEASE

The simplest test for exclusion of hypercortisolism is the measurement of plasma cortisol at 09.00 h following ingestion of 1 mg dexamethasone at midnight the

Screening for hypercortisolism
Overnight 1 mg dexamethasone
• failure to suppress 09.00 h plasma cortisol (false + ve = 12.5%, false – ve = 2.0%)
24-h urine free cortisol
• greater than 275 nmol/day
• check adequacy of collection (urinary creatinine)
• several collections if clinically suspicious

Box 7

previous evening. Failure of suppression of cortisol below approximately 100 nmol/l (the precise degree of suppression depends on the cortisol assay used) would be compatible with Cushing’s syndrome, although up to 12.5% of normal subjects may not suppress.²² The test is fairly sensitive (false negative rate only 2.5%) and therefore adequate suppression effectively excludes hypercortisolism. Alternatively, an integrated measure of cortisol secretion may be obtained by estimation of a 24-hour urinary free cortisol. This is a useful complementary test to overnight dexamethasone as the false positive rate is only 1%. Significant elevation of urinary cortisol in a patient who fails to suppress following overnight dexamethasone is thus virtually diagnostic of hypercortisolism (box 7).²³ The entity of cyclical Cushing’s syndrome is liable to cause diagnostic confusion. These patients have episodic hypercortisolism with a periodicity ranging from less than one day to one year.²⁴ The biochemistry may be entirely normal during the nadir of the periodic hypercortisolism, and repeated biochemical evaluation is therefore appropriate if there is a high clinical index of suspicion of Cushing’s syndrome.

GONADOTROPH ADENOMAS

Advances in immunocytochemistry and molecular biology have revealed that the majority of pituitary adenomas previously classified as ‘nonfunctional’ chromophobe adenomas synthesise either intact glycoprotein hormones or their free α or β subunits *in vivo* or *in vitro*.⁵ Studies of clinically nonfunctional tumours using immunocytochemical techniques show that up to 86% stain positively for at least one glycoprotein hormone subunit, although the proportion of hormone excess measurable *in vivo* is substantially lower – 15% for follicle-stimulating hormone, 48% for α -subunit and less than 5% for intact luteinising hormone.²⁵ These tumours are thus inefficient hormone secretors and most of the adenomas which do secrete *in vivo* do not manifest a recognisable syndrome of hormone excess (other than the occasional patient who produces substantial amounts of bioactive intact luteinising hormone and hence has a supranormal serum testosterone concentration). The corollary of the endocrine inactivity of these adenomas is their long latency, generally large size at diagnosis and ultimate presentation with mass effects (hypopituitarism and visual deterioration), rather than evidence of hormone excess. Unfortunately there is currently no consistently effective medical therapy for these lesions.

What then are the potential benefits of diagnosing these lesions pre-operatively? Firstly, a secure diagnosis of a gonadotroph adenoma in a patient with a pituitary mass lesion would reassure both clinician and patient that they are not dealing with a more sinister pituitary problem (box 2). Conservative therapy may then be a reasonable option in the absence of hypopituitarism or visual compromise. Secondly, finding a ‘tumour marker’ of a gonadotroph adenoma may assist follow-up in those patients who do require surgery.²⁶ The problem facing the clinician is that few gonadotroph adenomas secrete a measurable hormone (see figures above). A thyrotropin-releasing hormone stimulation test may be diagnostically useful, as in perhaps 50–75% of patients, serum levels of gonadotropins or their subunits increase in response to thyrotropin-releasing hormone.²⁷ In summary, gonadotroph adenomas are the most common form of nonfunctional pituitary adenomas, rarely present with hormone excess and require consideration for surgery only if they are associated with hypopituitarism, visual impairment, or progressive enlargement during radiologic review.

THYROTROPH ADENOMAS

A small percentage of glycoprotein hormone-producing tumours synthesise and secrete excess bioactive TSH, usually with excess α -subunit. These patients present with the clinical and biochemical consequences of autonomous TSH production, namely variable degrees of thyrotoxicosis and a syndrome of ‘inappropriate TSH secretion’ – elevated concentrations of free thyroxine and failure of suppression of TSH. There is currently no reliably effective medical therapy and transsphenoidal surgery is indicated in the majority of patients.²⁸

Concluding remarks

Our current recommendations for the management of the patient with a pituitary incidentaloma are outlined in figure 4. The suggested approach is of necessity preliminary and may be modified by two major advances. First, the accumulation of more data concerning the natural history of the untreated pituitary incidentaloma may allow patients with hypopituitarism at presentation to be safely treated with hormone replacement rather than transsphenoidal surgery. With the limited information available at present, however, we feel pituitary surgery

Figure 4 Suggested approach to the patient presenting with an incidental pituitary mass lesion

should be considered in the majority of these patients. Second, the rapid advances in the understanding of the molecular biological abnormalities underlying the pathogenesis of pituitary adenomas should provide clinicians with effective medical therapies for many of these tumours within the next decade.²⁹

- Molitch ME, Russell EJ. The pituitary 'incidentaloma'. *Ann Intern Med* 1990; 112: 925–31.
- Hall WA, Luciano MG, Doppman JL, Patronas NJ, Oldfield EH. Pituitary magnetic resonance imaging in normal human volunteers: occult adenomas in the general population. *Ann Intern Med* 1994; 120: 817–20.
- Molitch ME. Evaluation and treatment of the patient with a pituitary incidentaloma. *J Clin Endocrinol Metab* 1995; 80: 3–6.
- Post KD, McCormick PC, Bello JA. Differential diagnosis of pituitary tumours. *Endocrinol Metab Clin North Am* 1987; 16: 609–45.
- Katznelson L, Alexander JA, Kibanski A. Clinically nonfunctioning pituitary adenomas. *J Clin Endocrinol Metab* 1993; 76: 1089–94.
- Kovacs K, Horvath E. Pathology of pituitary tumours. *Endocrinol Metab Clin North Am* 1987; 16: 529–51.
- Burke CW. The pituitary megatest: outdated? *Clin Endocrinol* 1992; 36: 133–4.
- Plotz CM, Knowlton AI, Ragan C. The natural history of Cushing's syndrome. *Am J Med* 1952; 13: 597–614.
- Bates AS, Van't Hoff W, Jones JM, Clayton RM. An audit of outcome in acromegaly. *Q J Med* 1993; 86: 293–9.
- Soule SG, Jacobs HS. Prolactinomas: present day management. *Br J Obstet Gynaecol* 1995; 102: 178–81.
- Arafah BM. Reversible hypopituitarism in patients with large nonfunctioning pituitary adenomas. *J Clin Endocrinol Metab* 1986; 62: 1173–9.
- Reincke M, Allolio B, Saeger W, Menzel J, Winkelmann W. The 'incidentaloma' of the pituitary gland – is neurosurgery required? *JAMA* 1990; 263: 2772–6.
- Donovan LE, Corenblum B. The natural history of the pituitary incidentaloma. *Arch Intern Med* 1995; 155: 181–3.
- Schlechte J, El-Khoury G, Kathol M, Walkner L. Forearm and vertebral bone mineral in treated and untreated hyperprolactinaemic amenorrhoea. *J Clin Endocrinol Metab* 1987; 64: 1021–6.
- Schlechte J, Walkner L, Kathol M. A longitudinal analysis of premenopausal bone loss in healthy women and women with hyperprolactinaemia. *J Clin Endocrinol Metab* 1992; 75: 698–703.
- Bevan JS, Burke CW, Esiri MM, Adams CBT. Misinterpretation of prolactin levels leading to management errors in patients with sellar enlargement. *Am J Med* 1987; 82: 29–32.
- Acromegaly therapy consensus development panel. Consensus statement: benefits versus risks of medical therapy for acromegaly. *Am J Med* 1994; 97: 468–73.
- Chang-DeMoranville BM, Jackson IMD. Diagnosis and endocrine testing in acromegaly. *Endocrinol Metab Clin North Am* 1992; 21: 649–67.
- Van den Berg G, Frolich M, Veldhuis JD, Roelfsema F. Growth hormone secretion in recently operated acromegalic patients. *J Clin Endocrinol Metab* 1994; 79: 1706–15.
- Melmed S. Acromegaly. *N Engl J Med* 1990; 322: 966–75.
- Jones JJ, Clemmons DR. Insulin-like growth factors and their binding proteins: biological actions. *Endocr Rev* 1995; 16: 3–34.
- Cronin C, Igoe D, Duffy MJ, Cunningham SK, McKenna TJ. The overnight dexamethasone test is a worthwhile screening procedure. *Clin Endocrinol* 1990; 33: 27–33.
- Orth DN. Cushing's syndrome. *N Engl J Med* 1995; 332: 791–803.
- Atkinson AB, Kennedy AL, Carson DJ, Haden DR, Weaver JA, Sheridan B. Five cases of cyclical Cushing's syndrome. *BMJ* 1985; 291: 1453–7.
- Snyder PJ. Gonadotroph cell adenomas of the pituitary. *Endocr Rev* 1985; 80: 1059–61.
- Snyder PJ. Gonadotroph adenomas. *J Clin Endocrinol Metab* 1995; 80: 1059–61.
- Daneshdoost L, Genarelli TA, Bashey HM, et al. Recognition of gonadotroph adenomas in women. *N Engl J Med* 1991; 324: 589–94.
- Smallridge RC. Thyrotropin-secreting pituitary tumours. *Endocrinol Metab Clin North Am* 1987; 16: 765–92.
- Spada A, Vallar L, Faglia G. Cellular alterations in pituitary tumours. *Eur J Endocrinol* 1994; 130: 43–52.