Management of pituitary incidentalomas

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ABSTRACT

Pituitary incidentalomas are common findings with increasing use of modern neuroradiological imaging undertaken for symptoms unrelated to pituitary disease. The prevalence of these lesions is ~10% in autopsy studies and the incidence varies from 10% to 38% on magnetic resonance imaging in the published literature. They are almost always benign in nature and most are non-functioning (non-secreting) adenomas. Although many individuals are asymptomatic at diagnosis, some with functioning (secreting) pituitary adenomas or larger non-functioning adenomas have symptoms. All identified cases should have a thorough clinical and endocrinological evaluation to help with precise management, which depends on the size of the lesion, hormonal status (functioning versus non-functioning adenoma) and the presence of visual deficits resulting from optic nerve compression by the pituitary adenoma. Here, we provide an overview of the initial assessment and management of pituitary incidentalomas for clinicians not routinely involved in the management of pituitary disease.

Introduction

Pituitary incidentalomas are clinically unsuspected pituitary lesions discovered usually on radiological imaging during investigation of unrelated medical presentations, such as headaches, neurological insults or trauma. The literature on the definition of a pituitary incidentaloma varies.[1–6] Here, we include in the definition of pituitary incidentalomas lesions radiologically compatible with an adenoma and cystic lesions of the pituitary gland and surrounding structures. Pituitary adenomas, commonly referred to as pituitary tumours, are classified based on their size and hormone-producing status (functioning and non-functioning tumours). Lesion size is historically used to classify adenomas into microadenomas (<10 mm) and macroadenomas (≥10 mm) (Fig 1).

Pituitary incidentalomas are relatively common, with imaging studies reporting a prevalence of 10% on contrast-enhanced magnetic resonance imaging (MRI) within the normal adult population.[7] The incidence on MR imaging in unselected populations is 10–38% for microadenomas and 0.16–0.3% for macroadenomas.[7,8] Prevalence is similar in males and females. Most pituitary incidentalomas are non-functioning adenomas with minimal or no symptoms at diagnosis and do not usually require immediate surgical treatment. Evidence for the prevalence of functioning pituitary incidentalomas is limited, with estimates

Key points

Pituitary incidentalomas are a common finding on neuroimaging. Many will be non-functioning benign adenomas and most patients will be asymptomatic at diagnosis. However, all cases require a full endocrine evaluation.

Endocrine evaluation to distinguish functioning from non-functioning incidentalomas is vital because management of these two conditions differs.

Formal testing of visual fields is warranted in individuals with visual symptoms and evidence of the pituitary incidentaloma compressing or indenting on the optic chiasm on neuroimaging. The extent of visual deficit caused by the pituitary tumour determines the urgency of pituitary surgery to decompress the optic chiasm.

All patients with larger tumours (macroadenomas) should be evaluated for hypopituitarism. In the presence of hypopituitarism with multiple hormone deficiencies, sequential glucocorticoid replacement before thyroid hormone replacement should be undertaken to avoid precipitation of an adrenal crisis.

Pituitary apoplexy should be considered as a differential diagnosis in patients presenting with acute headache and/or neuro-ophthalmological deficits with evidence of a macroadenoma (incidentaloma) and features of a bleed within the tumour on radiological imaging. Such presentation is a medical emergency, and immediate administration of intravenous hydrocortisone is lifesaving in patients with hypocortisolaemia.

KEY WORDS: Pituitary incidentalomas, pituitary adenomas, pituitary tumours, pituitary lesions

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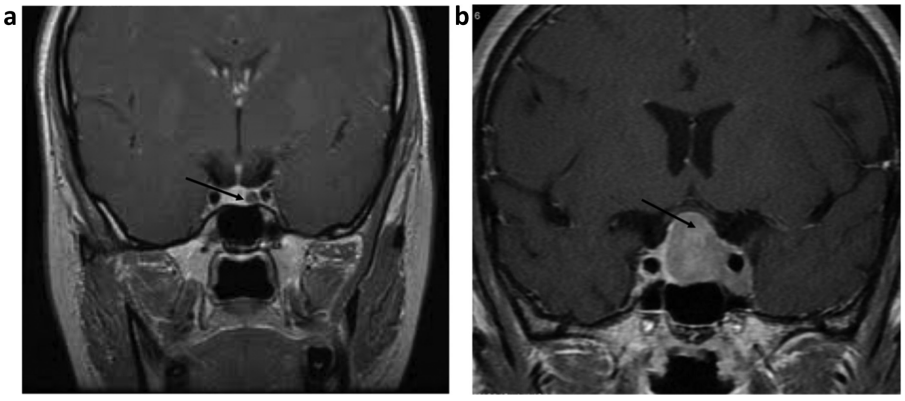

Fig 1. Magnetic resonance images with gadolinium contrast. (a) Pituitary microadenoma on the left side of pituitary shown as a hypoenhancing lesion (arrow). (b) Pituitary macroadenoma with suprasellar extension causing mild compression to the optic chiasm above (arrow). The adenoma also extends into the left cavernous sinus.

between 1.8% and 39.5% depending on the size of the adenoma and the hormone considered.[9] Here, we describe the evaluation and management of incidentalomas in adult patients.

Evaluation

All patients with a pituitary incidentaloma should have an assessment with detailed history, physical examination, relevant hormonal measurements and radiological imaging (Table 1). Symptoms such as visual disturbances and symptoms suggestive of pituitary hormone hypersecretion or hypopituitarism should be actively sought. Clinical signs suggestive of hormone hypersecretion, such as cushingoid or acromegaly features, might be detected on physical examination. Irrespective of the presence of signs and symptoms of hypopituitarism or hormone hypersecretion, individuals should have laboratory evaluation of their baseline pituitary function.[9]

Such laboratory evaluation should include a baseline pituitary profile with measurement of 09:00 h cortisol, thyroid-stimulating hormone (TSH), free thyroxine (FT4), prolactin, morning testosterone, luteinising hormone (LH), follicle-stimulating hormone (FSH), oestradiol, growth hormone (GH) and insulin-like growth factor 1 (IGF1).[9] Hypopituitarism refers to partial or complete deficiency of pituitary hormones. The size of pituitary incidentaloma is relevant in assessing for hypopituitarism because the latter is more likely with larger tumours. Microadenomas can be hormonally active with hypersecretion, but hypopituitarism is less likely in these lesions, particularly when they are <5 mm.

Prolactinomas are the second most-common incidentalomas after non-functioning adenomas. Prolactin is usually >5,000 mIU/L in macroprolactinomas (>10 mm) and lower in microprolactinomas. For patients with large adenomas, prolactin levels should be measured in diluted serum to ensure that levels are not falsely lowered by a hook effect.[10] Symptoms of hyperprolactinaemia are more evident in women, who usually present with secondary amenorrhoea or galactorrhoea. In men, symptoms of sexual dysfunction might not be that evident unless hypogonadism is severe. Therefore, large prolactinomas can be found as incidental findings in men on brain imaging performed for other reasons. When other hormone hypersecretion is suspected with incidentalomas, further specialist diagnostic evaluation is required, which is best done through endocrine outpatient services (Table 1).

Some pituitary lesions result from inflammation and infiltration of the pituitary gland and/or the pituitary stalk, referred to as hypophysitis. Patients with this condition can present with both anterior and posterior pituitary hormone deficiencies. Arginine vasopressin (AVP), also known as antidiuretic hormone, is produced in the hypothalamus, traverses through the pituitary stalk and is released from the posterior pituitary gland. Individuals with AVP deficiency have severe polyuria and polydipsia (also known as cranial diabetes insipidus).

Alongside laboratory hormonal evaluation, all individuals with visual symptoms or radiological evidence of the pituitary incidentaloma abutting or compressing the optic chiasm should undergo formal evaluation of visual fields.[9] Visual symptoms and the extent of visual field defects caused by the pituitary tumour determine the urgency of pituitary surgery to decompress the optic chiasm.

MRI provides more-detailed information on pituitary lesions. Where lesions are picked up incidentally on computed tomography (CT) imaging of the brain, further evaluation using pituitary-specific MRI protocols with gadolinium contrast should be undertaken unless contra-indicated.[11]

Finally, in patients presenting with acute-onset severe headache and/or neuro-ophthalmological deficits, with a newly diagnosed or pre-existing pituitary tumour on brain imaging, physicians should consider pituitary apoplexy as a differential diagnosis. The clinical features of pituitary apoplexy are indicated in Box 1.[12] In most patients, there is evidence of haemorrhage into the pituitary tumour on radiological imaging. There are several precipitating factors for pituitary apoplexy (Box 1) causing infarction or haemorrhage of the pituitary gland and resulting in sudden pituitary gland failure. Pituitary apoplexy is a medical emergency because patients might have severe cortisol deficiency. Immediate replacement with intravenous hydrocortisone can be lifesaving. Urgent endocrine opinion and neurosurgical evaluation should be sought for these cases.

Table 1. Initial evaluation of pituitary incidentalomas

	Type of tumour				
Evaulation	**Prolactin secreting adenoma**	**GH-secreting adenoma**	**ACTH secreting adenoma**	**Other (rare) TSHoma, FSHoma**	**Non-functioning adenoma**
Common clinical features	Galactorrhoea Oligo/amenorrhoea in women Infertility Erectile dysfunction in men Gynaecomastia	Coarse facial features Enlargement of jaw, hands and feet Deepening of voice Macroglossia Sleep apnoea Insulin resistance and diabetes	Round plethoric face, excess acne Rapid weight gain, truncal obesity, buffalo hump, supraclavicular fat pads, violaceous striae Easy bruising Proximal myopathy Hypertension Impaired glucose regulation and diabetes	TSHoma: symptoms suggestive of hyperthyroidism: heat intolerance, weight loss, irritability, anxiety, palpitations, tremors, diarrhoea FHSoma: rarely results in a clinical syndrome; can cause macro-orchidism	Can be associated with hypopituitarism Cortisol deficiency: lethargy, vomiting, hypotension, hyponatraemia, hyperkalaemia Thyroid hormone deficiency: as in hypothyroidism FSH/LH deficiency: oligo/amenorrhoea, infertility, reduced libido and erectile dysfunction in men GH deficiency: reduced energy level, bone mineral density and lean body mass
Expected abnormalities on baseline pituitary profile	Raised prolactin	Raised GH and IGF1	Loss of cortisol diurnal rhythm. Random cortisol might be normal or raised	Raised FT4 and FT3 and inappropriately normal or raised TSH	If hypopituitarism is present, any of the hormones (cortisol/TSH/FT4/FSH/LH/testosterone/GH/IGF1) could be low Prolactin might be mildly elevated because of pituitary stalk compression
Specialist dynamic pituitary tests to assess pituitary hormone production	Not required	Glucose tolerance test (OGTT) with GH levels	Dexamethasone suppression tests 24-h urinary free cortisol excretion Late-night salivary cortisol	Thyrotropin-releasing hormone (TRH) test	Insulin tolerance test (ITT) or glucagon stimulation test to assess cortisol and growth hormone deficiency Short Synacthen® test also used to assess for cortisol deficiency

ACTH = adrenocorticotropic hormone; FSH = follicle-stimulating hormone; FT3 = free triiodothyronine; FT4 = free thyroxine; GH = growth hormone; LH = luteinising hormone; IGF1 = insulin-like growth factor 1; ITT = insulin tolerance test; OGTT = oral glucose tolerance test; TSH = thyroid-stimulating hormone.

Box 1. Clinical features and precipitating factors of pituitary apoplexy

Clinical features of pituitary apoplexy[12]

Sudden-onset headache

Vomiting

Meningism

Reduced visual acuity

Ophthalmoplegia

Reduced consciousness

Precipitating factors for pituitary apoplexy[12]

Hypertension

Major surgery

Coronary artery bypass grafting

Dynamic testing of pituitary

Anticoagulation therapy

Pregnancy

Head trauma

Initiation of oestrogen therapy

Management

The management of pituitary incidentalomas depends on the presence of hormone hypersecretion (functioning adenomas), size of the adenoma and presence of visual field deficits resulting from tumour compression on the optic chiasm or optic nerves. We provide a simple flow diagram outlining the initial assessment and management of pituitary incidentalomas based on the Endocrine Society guidelines (Fig 2).[9]

Medical therapy

Non-functioning pituitary adenomas do not respond to medical therapy. Prolactin-secreting pituitary adenomas (prolactinomas) respond to dopamine agonists (eg cabergoline or bromocriptine) and this is usually the preferred first-line treatment independent of size of the prolactinoma. Dopamine agonists reduce prolactin levels and can also cause tumour shrinkage. These drugs can be used effectively even in tumours causing mild compression of the optic chiasm because reduction in tumour volume can be expected in most patients within weeks of treatment. Surgery can be considered in patients with large prolactinomas resistant to dopamine agonist treatment.

Hypopituitarism might be seen in patients with larger pituitary adenomas and is less likely to be present in patients with microadenomas. If present, hormone replacement therapy should be guided by the endocrine team as appropriate. Cortisol is the most important hormone because failure to replace this in a patient who is cortisol deficient can be life-threatening. Hydrocortisone is the most commonly used form of glucocorticoid replacement. The usual dose is 15–20 mg per day in two or three divided doses.[13] Patients taking glucocorticoid replacement therapy should be educated about sick day rules in which double doses of glucocorticoid are required for the periods of illness. Education about the use of emergency hydrocortisone injections and steroid alert cards should also be offered to such patients to support early recognition and treatment of adrenal crises in adults, in line with NHS England's National Patient Safety Alert (NPSA) guidance.[14] Emergency hydrocortisone injections are particularly important if there is an acute malabsorptive state (eg vomiting or diarrhoea).

Levothyroxine is used to replace thyroid hormone deficiency. Care should be taken not to replace thyroid hormone before glucocorticoid replacement because this can precipitate adrenal crisis. Serum FT4 instead of TSH should be used to adjust thyroid hormone replacement in central hypothyroidism resulting from pituitary tumours because TSH no longer displays normal feedback responses to thyroid hormone levels.[13,15] Testosterone, GH and AVP replacement should be initiated on advice from local endocrine teams.

Indications for surgery

Surgical resection is the preferred first-line treatment for all functioning pituitary adenomas except prolactinomas. The aim is to achieve remission from hormone hypersecretion and to reduce the tumour burden in patients in whom the tumour is not completely resectable. For non-functioning pituitary adenomas, urgent pituitary surgery is indicated in patients with visual field deficits resulting from compression of optic nerves by the pituitary adenoma. Urgent neurosurgical evaluation is also recommended in patients with pituitary apoplexy and persistent visual disturbance.[9] Additionally, neurosurgical referral should be considered in patients with clinically significant growth of the pituitary incidentaloma noted on serial imaging, and in those with adenomas close to the optic chiasm.[9]

Radiological monitoring

Macro-incidentalomas require long-term radiological surveillance because they have greater tendency for growth compared with micro-incidentalomas. The growth is usually slow and up a few millimetres in a year except in a few aggressive tumours. The evidence for how often to undertake radiological surveillance remains unclear. This depends on the size of the lesion, its proximity to the optic chiasm and surrounding brain structures, age of the patient and the changes in size of the tumour that may have occurred in the preceding years. Guidelines recommend repeating the MRI scan for macroadenomas 6 months after the initial diagnosis and repeating the scan every year for the next 3 years.[9] If there is no change in the size of the adenoma on serial imaging, the interval between the scans can be prolonged in the later years. In patients who have had surgery, histological subtyping and tumour proliferative markers (eg Ki-67 index) can be used as prognostic markers for regrowth to help determine the frequency of imaging. Non-functioning micro-incidentalomas are less likely to grow. A follow-up MRI scan is recommended a year after diagnosis. Subsequent imaging should be less frequent in lesions that have not changed. In asymptomatic patients with unchanged lesions <5 mm, further imaging might not be necessary.[9] ■

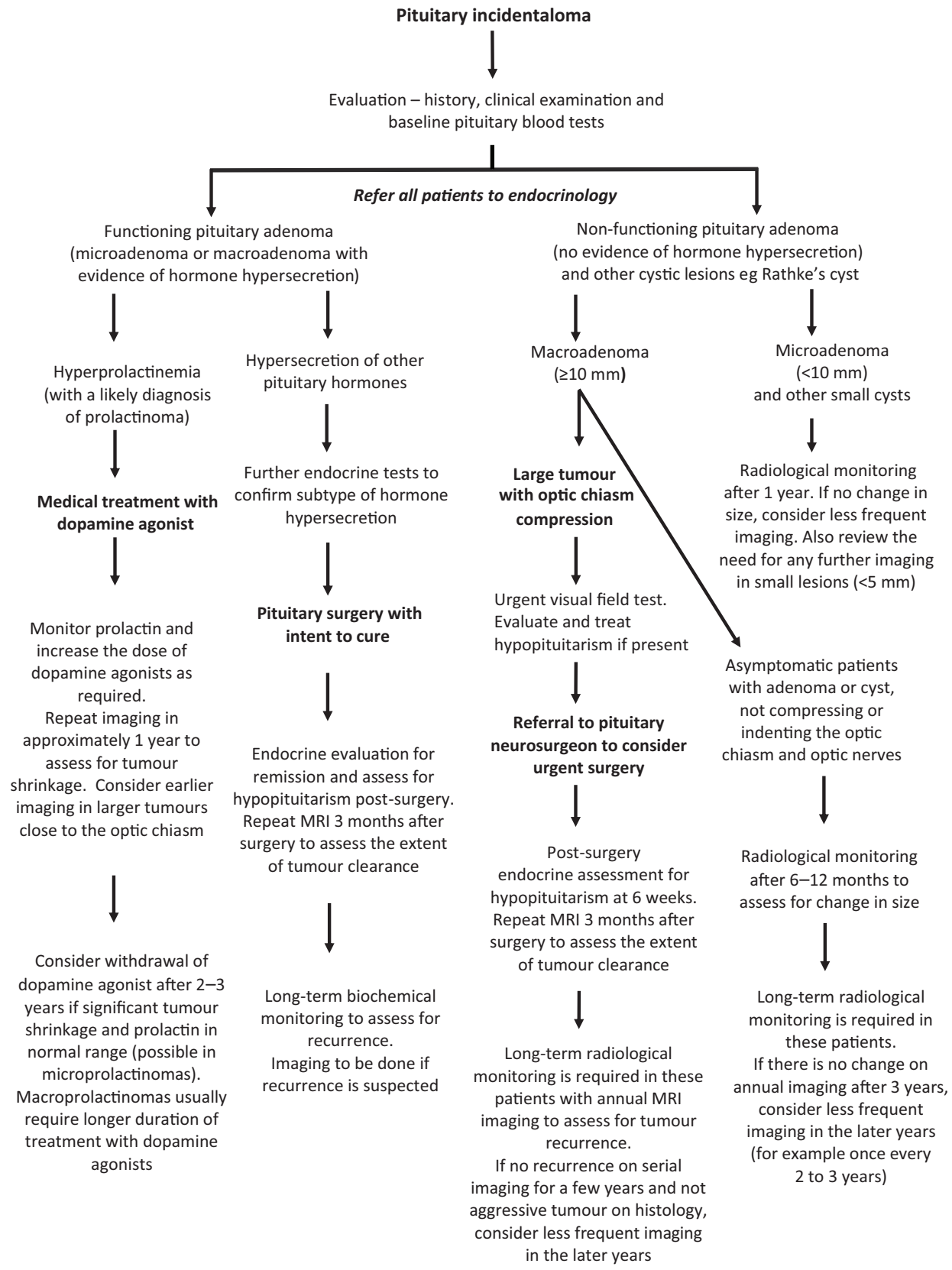

Fig 2. Evaluation and management of pituitary incidentalomas. MRI = magnetic resonance imaging.

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