Diagnosis and management of prolactinomas and non-functioning pituitary adenomas

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Pituitary tumours account for a major proportion of intracranial tumours; most are benign adenomas. The tumours present with a range of signs and symptoms. Although evidence suggests that they are diagnosed earlier than previously, some are still missed, often for years, with clues such as headache and visual problems not being picked up. Management by a multidisciplinary team improves outcomes and optimises resources. This article focuses on the diagnosis and management of prolactinomas and non-functioning pituitary adenomas, which are the commonest types of pituitary adenoma in clinical practice.

What are pituitary adenomas and how are they classified?

Pituitary adenomas are monoclonal benign tumours that arise from differentiated hormone expressing cells in the anterior pituitary. Five major cell types occur in the anterior pituitary: the lactotroph, producing prolactin; the somatotroph, producing growth hormone; the corticotroph, producing adrenocorticotropic hormone; the thyrotroph, producing thyroid stimulating hormone; and the gonadotroph, producing luteinising hormone and follicle stimulating hormone. Classification of pituitary adenomas is based in part on the cell type. Tumours that secrete hormones are called functioning adenomas and those that do not secrete hormones are called non-functioning adenomas. Pituitary adenomas are also classified anatomically, with microadenomas having a diameter of less than 10 mm (the maximum size of the normal pituitary gland) and larger tumours defined as macroadenomas.

How common are pituitary adenomas?

Pituitary tumours account for approximately 10% of clinically apparent intracranial neoplasms. In a recent UK population based study the prevalence of pituitary adenomas was 77.6 cases per 100 000 population, with prolactinomas accounting for 57% and lower rates for the other subtypes: non-functioning adenomas 28%, somatotrophinomas 11%, and adrenocorticotropic hormone secreting tumours 2%.1

What causes pituitary adenomas?

Knowledge of the genetic and epigenetic mechanisms underlying pituitary tumourigenesis has advanced considerably over recent years. More than 95% of pituitary adenomas are sporadic, the remainder being hereditary. The sporadic forms are associated with both genetic and epigenetic abnormalities. Several pituitary selective oncogenes, tumour suppressor genes, and mediators of the pituitary cell cycle are involved in pituitary tumourigenesis.2 Classic oncogene mutations are rarely encountered in pituitary tumours.2 Hereditary forms may be caused by multiple endocrine neoplasia (MEN). MEN is characterised by the occurrence of tumours involving two or more endocrine glands within a single patient.3 MEN type 1 is an autosomal dominant disorder due to mutations in the tumour suppressor gene MEN1, which encodes the 610 amino acid protein menin4 and is characterised by the predominant occurrence of tumours in the parathyroid glands, pancreatic islets, and anterior pituitary. MEN type 4, due to mutations in CDKN1B,5 can be found in approximately 3% of patients with a MEN1-like syndrome who do not have mutations of MEN1.6 Other inherited causes include the autosomal dominant condition Carney complex and familial isolated pituitary adenoma.7

What are the clinical features associated with pituitary adenomas?

Pituitary adenomas can present with a range of signs and symptoms related to a derangement in hormone production (overproduction or underproduction) or a mass effect caused by a space occupying lesion, or both. In general, patients with visual symptoms, headache, and gonadal dysfunction should be referred urgently for investigation. Often the clinical picture is more nuanced and a high index of suspicion is needed.

Prolactinomas

Prolactinomas are the most common of the pituitary adenomas,1 with a higher prevalence in women (78.2%).5 Microprolactinomas are more common than macroprolactinomas. Box 1 summarises the clinical features associated with prolactinomas. When prolactinomas occur in men, they tend to be larger than those in women, diagnosed on average 10 years later, and more likely to be associated with local pressure effects.7 This sex difference is partly
Incidentalomas
The incidental finding of a pituitary adenoma on an imaging study performed for an unrelated indication is an increasingly common mode of presentation for pituitary adenomas. These incidentalomas account for a major proportion of referrals from primary care and other specialties. Although pituitary incidentalomas are clinically unsuspected at diagnosis, many are finally associated with partial hypopituitarism and some with compression of the optic chiasm. Hence patients require referral to an endocrinologist for assessment.

Pituitary apoplexy
Presentation with pituitary apoplexy—haemorrhage into or infarction of the pituitary gland—is uncommon. It is characterised by severe headache, sudden onset of visual disturbance, meningism from blood in the cerebrospinal fluid, reduced consciousness, and hypotension. Although pituitary apoplexy is rare (0.2 per 100 patient years), it can be fatal as a result of sudden hypopituitarism and cortisol deficiency.

Hypopituitarism
Partial or panhypopituitarism occurs commonly in patients with pituitary adenomas. According to a meta-analysis, gonadotrophin deficiency is the most typical pituitary hormone deficiency at presentation, leading to reduced libido, erectile dysfunction, and decreased sperm count in men, menstrual disturbance and infertility in women, and a reduction in pubic, axillary, and facial hair in both sexes. Hyponadism may cause anaemia because testosterone stimulates erythropoiesis. Growth hormone deficiency in adults results in impaired psychological wellbeing, increased abdominal adiposity, and reduced muscle strength. Thyroid stimulating hormone deficiency leads to pituitary hypothyroidism, which may be missed if just serum thyroid stimulating hormone is measured because although the thyroxine level will be low, thyroid stimulating hormone is most often inappropriately normal. Hyposecretion of adrenocorticotrophic hormone is associated with the features of corticosteroid deficiency, including lethargy, weakness, weight loss, hypotension, hynoponorrhea, and, in contrast with primary adrenal failure, pallor, not hyperpigmentation, of the skin. Deficiency of antidiuretic hormone released from the posterior pituitary results in diabetes insipidus, which is rarely seen at presentation of a non-functioning adenoma. Diabetes insipidus is more commonly seen at the presentation of suprasellar lesions such as craniopharyngiomas. This can be instructive when considering the differential diagnosis of hypopituitarism (box 3).

How are patients with suspected pituitary adenoma investigated?
The aims of investigation are to identify a suspected pituitary adenoma and assess pituitary function to identify hormonal excess or deficiency.

Box 2 | Early symptoms of non-functioning pituitary adenomas

<table>
<thead>
<tr>
<th>Effects of hormone underproduction</th>
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<tr>
<td>• Fatigue</td>
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<td>• Low libido or erectile dysfunction</td>
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<td>• Oligomenorrhea or amenorrhea</td>
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<th>Mass or associated effects</th>
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<tr>
<td>• Headache</td>
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<td>• Visual problems</td>
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Assessment of pituitary function

If a pituitary adenoma is suspected, the essential biochemical tests to request before referral are early morning (9 am) basal serum cortisol and prolactin levels. Patients with serum cortisol levels of less than 100 nmol/L require hydrocortisone replacement. A typical prescription for hydrocortisone replacement therapy would be 20 mg hydrocortisone orally daily in divided doses: 10 mg on waking, 5 mg at lunchtime, and 5 mg at 6 pm (no later as it can cause insomnia). Patients should be advised to double the normal daily dose of steroids for a febrile illness or after one vomit; administer a steroid emergency injection if more than one vomit occurs or they are seriously ill or injured and call a duty doctor or the emergency services; and wear a steroid medical alert bracelet or pendant and carry a card stating that steroids are required at all times.

Macroprolactinomas are usually associated with prolactin levels greater than 3000 mU/L. If the prolactin is mildly increased, a repeat test should be done before referral. In the normal state, dopamine from the hypothalamus inhibits prolactin release from the anterior pituitary. Non-functioning macroadenomas can compress the pituitary stalk and interfere with the passage of dopamine, resulting in “disconnection hyperprolactinaemia.” A study of 226 clinically and histologically confirmed cases of non-functioning macroadenomas found that disconnection hyperprolactinaemia rarely exceeded 2000 mU/L. A proportion of prolactin secreting adenomas can co-secrete growth hormone, and in these the levels of insulin-like growth factor 1 will be increased.

Other tests are carried out to assess pituitary function. To fully assess anterior pituitary function, early morning (9 am) basal serum levels of insulin-like growth factor 1, thyroid stimulating hormone, free thyroxine, cortisol, prolactin, luteinising hormone, follicle stimulating hormone, and testosterone or oestradiol should be measured. It is helpful for the pituitary multidisciplinary team to have these results at the time of referral. Thyroxine and cortisol deficiency should be tested for and corrected before investigating for diabetes insipidus as they may mask the symptoms of the diabetes by reducing the glomerular filtration rate.

The insulin hypoglycaemia tolerance test is the gold standard method for assessing adrenocorticotrophic hormone and growth hormone reserves. Trained staff in a specialist unit should perform the test, intravenous glucose and hydrocortisone should be available, and it should not be performed in patients with ischaemic heart disease or epilepsy. The short Synacthen test is an alternative means of checking the adrenocorticotrophic hormone reserve and nowadays is the preferred test in many centres. However, the results are not reliable if performed within six weeks of an insult (for example, surgery). We therefore recommend referral to an endocrinologist before dynamic testing.

Posterior pituitary function is tested with a water deprivation test. It is essential that other causes of polyuria, including diabetes mellitus, chronic renal failure, hypercalcaemia, and hypokalaemia, have been considered and excluded before carrying out the test.

Neuro-ophthalmological investigation

Thorough neuro-ophthalmological examination, including visual acuity, formal assessment of visual fields using Goldman perimetry, optic disc examination for optic atrophy, eye movements, and pupillary responses should be undertaken at diagnosis, and before and after surgery as needed. The results aid diagnosis and timing of treatment, and serial examinations can be used for monitoring progress. Most endocrine units will arrange neuro-ophthalmological assessments after referral of a new patient and therefore a separate ophthalmological referral by the general practitioner is often not required. The assessment of visual fields at the bedside is useful in the initial assessment of patients with suspected pituitary tumours to identify gross defects but will fail to find subtle defects even when performed correctly, hence the necessity for formal testing of visual fields.

Radiological investigation

All patients with a suspected pituitary adenoma require imaging. Because of its superior contrast resolution, magnetic resonance imaging using the pituitary sellar protocol is the imaging modality of choice. The differential diagnosis of a sellar mass lesion is long and mainly includes pituitary adenomas, which can be hormone secreting or non-secreting, craniopharyngioma, Rathke’s cleft cyst, epidermoid cyst, chordoma, meningioma, metastatic tumour, lymphoma, aneurysm, lymphocytic hypophysitis, arachnoid cyst, mucocele, pituitary abscess, or sarcoidosis. As the list of differential diagnoses is extensive, imaging should be reviewed by a neuroradiologist and discussed with the pituitary multidisciplinary team. Notably, pituitary lesions are found incidentally in 10-38% of patients undergoing magnetic resonance imaging for an unrelated reason, thus increasing the number of relevant referrals to specialist centres.

How are pituitary adenomas managed?

The role of the pituitary multidisciplinary team

The pituitary multidisciplinary team comprises an endocrinologist, pituitary neurosurgeon, neuroradiologist, neuropathologist, and oncologist. In the United Kingdom, guidance from the National Institute for Health and Care Excellence on central nervous system tumours recommends standardisation of multidisciplinary teams. Despite the rarity of pituitary carcinomas or metastases, pituitary multidisciplinary teams aim to work to the standards of cancer related multidisciplinary teams. Most tertiary endocrine units hold monthly meetings.

Differential diagnosis of hypopituitarism

- Neoplastic—meningioma, craniopharyngioma, lymphoma, pituitary metastasis
- Pituitary surgery
- Infiltrative—sarcoidosis, hereditary haemochromatosis
- Infection—basal meningitis (for example, tuberculosis), pituitary abscess
- Vascular—Sheehan’s syndrome (post-partum pituitary necrosis), carotid artery aneurysm
- Others—radiation therapy involving the pituitary gland

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- Others—radiation therapy involving the pituitary gland
Prompt referral of patients with a new diagnosis to the multidisciplinary team enables rapid access to appropriate expertise, optimising patient care and the work of the multidisciplinary team and thus more efficient use of time and resources.

**Prolactinomas**

The treatment of prolactinomas aims to remove the local mass effects by reducing tumour size, achieving normal prolactin levels, and preserving or restoring anterior pituitary function.

**Medical treatment**

Medical treatment with a dopamine agonist, such as cabergoline, bromocriptine, or quinagolide, is the preferred treatment according to consensus guidelines. Normoprolactinaemia is achieved in 85-90% of patients using cabergoline and 75% using bromocriptine. These drugs suppress prolactin by stimulating G-protein coupled dopaminergic type 2 receptors expressed on prolactinomas, resulting in tumour shrinkage.Cabergoline is superior to bromocriptine for the frequency with which prolactin levels return to normal and the incidence of side effects. In a retrospective study of 455 participants, cabergoline resulted in normoprolactinaemia in 92% of 244 patients with idiopathic hyperprolactinaemia or a microprolactinoma and in 77% of 181 patients with macroprolactinomas. In this study 8.5% of the participants experienced the side effects of headache, postural hypotension, nausea, and sleepiness and 3.5% stopped treatment because of intolerance to cabergoline. Quinagolide, a non-ergot dopamine agonist, is used in patients who are intolerant to cabergoline or bromocriptine. Occasionally, dopamine agonist treatment of an invasive prolactinoma that is eroding the skull base can result in leakage of cerebrospinal fluid, manifesting as cerebrospinal rhinorrhoea. General practitioners and emergency care clinicians should be aware of this complication as these patients are at risk of meningitis from the breach in the dura and require urgent neurosurgical review.

As prolactin levels normalise, fertility should improve and advice on contraception given. Women who want to conceive should be advised to discontinue dopamine agonists as soon as they discover that they are pregnant, and their endocrinologist should be made aware of the pregnancy. Worsening headache or deteriorating vision during pregnancy are causes for concern and should prompt magnetic resonance imaging of the pituitary. Measuring serum prolactin levels during pregnancy are unhelpful.

**Surgery**

The indications for pituitary surgery in prolactinoma are pituitary apoplexy with persistent, severe neurological signs; failure of medical treatment, defined as failure to achieve normoprolactinaemia or important reduction in tumour size, despite a maximal tolerable dose of dopamine agonist; and increasing tumour size associated with neurological and ophthalmological deficits unresponsive to dopamine agonists. A retrospective study of 120 patients with microprolactinomas and macroprolactinomas who underwent pituitary surgery identified 77 patients whose prolactin levels normalised postoperatively. Recurrence of hyperprolactinaemia occurred in 16.9% during a mean follow-up of 50.2 (standard deviation 3.0) months. Mortality associated with endoscopic endonasal trans-sphenoidal pituitary surgery performed by an experienced pituitary neurosurgeon is low (<1%) and complications such as haemorrhage, cerebrospinal fluid leak, and meningitis are rare (about 1% each). Hypopituitarism is seen after trans-sphenoidal surgery and its frequency depends on tumour size.

**Radiotherapy**

Consensus guidelines recommend radiotherapy for patients with residual tumour after surgery or those who have aggressive or malignant prolactinomas. Patients are at risk of hypopituitarism when the hypothalamic-pituitary axis falls within the field of irradiation and require assessment of anterior pituitary function annually for 10 years or if relevant symptoms develop.

**Non-functioning pituitary adenomas**

The treatment of non-functioning pituitary adenomas aims to remove the pressure effects by reducing tumour size and to preserve or restore anterior pituitary function. A watch and wait policy can be adopted for some patients with non-functioning adenomas that do not compress the optic chiasm. A retrospective study of 40 patients with presumed non-functioning adenomas who were not offered surgery at presentation found radiographic evidence of enlargement in 12.5% of the microadenomas and 50% of the macroadenomas. No microadenoma enlarged sufficiently to result in a visual field defect over 42 months of follow-up.

**INDICATIONS FOR REFERRAL TO SPECIALIST ENDOCRINOLOGY DEPARTMENT**

- Manifestations of hypopituitarism—for example, hypogonadism (infertility, oligomenorrhea or amenorrhea, reduced libido, erectile dysfunction)
- Chronic headaches
- Visual field defects
- Hyperprolactinaemia
- Pituitary incidentaloma

**ESSENTIAL GUIDE TO MANAGING PATIENTS PRESENTING WITH A PITUITARY MACROADENOMA**

- Ensure that early morning blood samples (9 am) are measured for cortisol and prolactin levels
- Administer hydrocortisone (do not wait for cortisol result) if there is clinical suspicion of adrenocorticotrophic hormone deficiency
- Carry out a bedside neuro-ophthalmological assessment
- Refer to local endocrinology team or pituitary neurosurgeon immediately
- Arrange for pituitary magnetic resonance imaging of the pituitary.
- Communicate with the pituitary multidisciplinary team and thus more efficient use of time and resources.
Surgery
Pituitary surgery is the treatment for patients with non-functioning adenomas and visual field defects. A retrospective study of 102 patients aged more than 70 years and presenting to a single neurological centre undergoing trans-sphenoidal surgery for a variety of diagnoses (>80% non-functioning adenomas) over 106 months reported intraoperative complications of hypotension (1.9%) and blood loss requiring transfusion (2.9%). Complications at 30 days included transient diabetes insipidus (9.6%), syndrome of inappropriate antidiuretic hormone secretion (8.7%), and delayed cerebrospinal fluid leak requiring lumbar drainage (0.9%) with no patient needing formal repair. Thus older patients can undergo surgery by experienced neurosurgeons without major long term sequelae.

Radiotherapy
Conventional external beam radiotherapy is reserved for patients with non-functioning adenomas that have the potential to behave more aggressively, major postoperative residual tumour, or tumour recurrence not amenable to further surgery. A retrospective study of 126 patients with non-functioning adenomas showed that progression-free survival at 10 years was 94% in the radiotherapy group compared with 59% in the non-irradiated group.28

Pituitary apoplexy
UK guidelines for the management of pituitary apoplexy have been developed to optimise treatment.13 These are the only available guidelines on pituitary apoplexy. To ensure haemodynamic stability, patients require careful assessment of fluid and electrolyte status, hydrocortisone replacement, and supportive measures.19 Hydrocortisone should be given intravenously as a 100 mg bolus dose followed by a continuous intravenous infusion of 200 mg per 24 hours or 50-100 mg six hourly by intramuscular injection. Indications for empirical steroid therapy are haemodynamic instability, altered level of consciousness, reduced visual acuity, and severe visual field defects.18 Patients should be managed jointly by the specialist neurosurgical and endocrine teams with a multidisciplinary decision about conservative or surgical management, as currently no evidence based criteria exist.19

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