REVIEW: NEUROLOGY AND MEDICINE

Neurology of the pituitary gland

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This review will focus on those aspects of pituitary disease immediately relevant to neurologists and neurosurgeons when assessing and counselling patients. It is essential to adopt a multidisciplinary approach to the diagnosis and management of pituitary disease as emphasised by the recently published guidelines from the Royal College of Physicians of London.¹⁻⁴

Range of pathology presenting in the sellar region

The commonest lesions presenting in this region are pituitary tumours (incidence of 15-20/million/year), including adenomas and craniopharyngiomas, aneurysms, and meningiomas, but many other diseases need to be considered (table 1).

Neurological presentations of pituitary disease

"Pituitary incidentalomas" may be disclosed when investigating unrelated disease (fig 1). Although figures from 5% to 27% have been quoted for the incidence of subclinical adenomas at postmortem, far fewer are of significant size—that is, over 5 mm in diameter with deviation of the stalk and unilateral enlargement of the gland. Careful endocrine and visual assessments are required and, where no abnormalities are found, most can be managed conservatively with follow up MRI.⁵⁻⁸

Differential diagnosis of neoplasms and "tumour-like" lesions of the sellar region²

Tumours of adenohypophyseal origin	Cysts, hamartomas, and malformations
Pituitary adenoma	Rathke's cleft cyst
Pituitary carcinoma	Arachnoid cyst
Tumours of neurohypophyseal origin	Epidermoid cyst
Granular cell tumour	Dermoid cyst
Astrocytoma of posterior lobe and/or stalk (rare)	Gangliocytoma
Tumours of non-pituitary origin	Empty sella syndrome
Craniopharyngioma	Metastatic tumours
Germ cell tumours	Carcinoma
Glioma (hypothalamic, optic nerve/chiasm, infundibulum)	Plasmacytoma
Meningioma	Lymphoma
Haemangiopericytoma	Leukaemia
Chordoma	Inflammatory conditions
Haemangioblastoma	Infection/abscess
Lipoma	Mucocoele
Giant cell tumour of bone	Lymphocytic hypophysitis
Chondroma	Sarcoidosis
Fibrous dysplasia	Langerhans' cell histiocytosis
Sarcoma (chondrosarcoma, osteosarcoma, fibrosarcoma)	Giant cell granuloma
Postirradiation sarcomas	Vascular lesions
Paraganglioma	Internal carotid artery aneurysms
Schwannoma	Cavernous angioma
Glomangioma	
Esthesioneuroblastoma	
Primary lymphoma	
Melanoma	

Pituitary disease often presents insidiously and in retrospect might have been detected earlier. The symptoms of hormonal hypersecretion in endocrinologically active tumours will obviously present before evidence of suprasellar or parasellar extension. Although somatic changes usually bring the growth hormone secreting adenoma to medical attention first, the neurologist may encounter nerve entrapment (particularly the carpal tunnel syndrome), proximal myopathy (weakness disproportionate to the increased body mass), peripheral neuropathy (muscle atrophy, distal sensory loss, and neuropathic joints) and the psychological and emotional sequelae of the disease.⁹ It has been debated whether the emotional sequelae reflect a specific interaction between growth hormone and the limbic system.¹⁰ The headaches are often bitemporal, periorbital, or referred to the vertex, and do not seem to correlate with the size of the mass.¹¹ Fronto-occipital headaches have also been described that may be exacerbated by coughing. More remotely, acromegaly may present with the neurological complications of diabetes mellitus and hypertension. Some patients may present with symptoms drawn from more than one endocrinopathy when there is dual secretion by the pituitary adenoma—for example, of growth hormone and prolactin. Finally, not all growth hormone hypersecretion is the product of a pituitary adenoma—a rapidly progressive

Figure 1 (A) Normal appearance of pituitary gland. Sagittal T1 weighted image. Note the bright signal from the posterior lobe of the pituitary. More posteriorly the dorsum sella (arrow head) is shown as linear high signal (marrow) surrounded by low signal (dense cortex). (B) Microadenoma on the left side. This has a lower signal than normal pituitary. The normal pituitary and cavernous sinus show enhancement after gadolinium injection.

history over a few months suggests an ectopic tumour.

The clinical manifestations of Cushing's syndrome are well known. The patient usually presents at the microadenoma stage with remarkably little if any abnormality on MRI. Symptoms can fluctuate, particularly in teenagers. Weakness from proximal myopathy, psychiatric disturbances including anxiety and panic attacks, the neurological consequences of obesity and hypertension, and benign intracranial hypertension¹² may bring the patient to a neurologist.

A neurologist will usually see prolactinomas and endocrinologically inactive tumours when they have already reached a size sufficient to impinge on the normal pituitary and extrasellar structures (visual failure, ophthalmoplegia, trigeminal sensory loss, and hydrocephalus). Hypogonadal symptoms, weakness, fatigue, or

Figure 2 (A) Pituitary haemorrhage which presented with apoplexy. Coronal T1 weighted image. High signal blood within an enlarged sella. Infundibulum deviated to the left. (B) Infarction of macroadenoma. Postgadolinium coronal T1 weighted image. The optic chiasm is stretched and displaced superiorly (arrow head). Enhancement in residual viable adenoma superiorly and to the left. The very bright signal represents small areas of haemorrhage

headache may be the presenting feature. Hypogonadism may be compounded by mild hyperprolactinaemia resulting from the effect of raised intrasellar pressure on the normal pituitary gland (see later). The neurological manifestations of hypothyroidism include carpal tunnel syndrome, slowing of cerebration, and, less commonly, myotonia and myopathy.

The neurological consequences of hyperthyroidism including exophthalmos may herald a thyrotrophinoma, the great majority of which are macroadenomas and hence may be accompanied by headache, visual field defect, and galactorrhoea. However, other conditions may be associated with hyperthyroidism plus a detectable concentration of serum thyrotrophin and specialist expertise is required to differentiate them.¹³

Children with pituitary and third ventricular lesions may present with precocious puberty, growth retardation, diabetes insipidus, denial of visual failure, and the symptoms and signs of either high or low pressure hydrocephalus.

Some diagnostic pitfalls

Although most patients with a pituitary problem fall within well defined categories, a minority present with manifestations of one of the myriad of small print diagnoses. Ectopic tumours may cause not only Cushing's syndrome but also acromegaly. Primary hypothyroidism may be accompanied by pituitary gland swelling^{3 14} as the result of overstimulation from the hypothalamus leading to visual symptoms, hypopituitarism, headache, and less commonly, diabetes insipidus, syndrome of

inappropriate antidiuretic hormone secretion (SIADH), and precocious puberty. To add to the confusion, one third of such female patients may have menstrual irregularities as a reflection of modest hyperprolactinaemia leading to a misdiagnosis of prolactinoma. The pituitary swelling resolves with thyroxine and surgery is unnecessary.

The stalk compression syndrome refers to the symptoms and signs of hyperprolactinaemia in the presence of moderately raised prolactin concentrations and a sellar or suprasellar mass but distortion of the pituitary stalk alone does not correlate with prolactin concentrations.^{2 3 15} It is not clear why it is the prolactin inhibitory system alone of the hypothalamo-anterior pituitary control systems that is predominantly affected. Direct measurements of intrasellar pressure made during trans-sphenoidal surgery have shown that the intrasellar pressure may be raised above the presumed perfusion pressure of the anterior pituitary gland.¹⁶ The anterior pituitary is only supplied by thin walled portal vessels (derived from the superior and inferior hypophyseal arteries) that can easily be obstructed by CSF/intrasellar pressures above about 20 mm Hg. Dynamic CT after contrast injection discloses rapid enhancement of the posterior pituitary (direct arterial supply from the inferior hypophyseal arteries) followed by progressive enhancement of the anterior pituitary as the contrast supplied through the portal circulation extravasates through the defective blood-brain barrier in the anterior pituitary gland.¹⁷ There is no specific concentration of prolactin that distinguishes stalk compression from a true prolactinoma but values of 2500–5000 mU/l are often quoted despite many exceptions in the literature. It is more important to take the concentration in the context of the imaging.¹⁸ If the macroadenoma is a prolactinoma, the prolactin concentration should be much greater than 2500 mU/l. If there is no significant intrasellar or suprasellar mass and the concentration is less than 2500, this cannot be the result of stalk compression or raised intrasellar pressure. In addition there are many other causes of hyperprolactinaemia to be considered. Hopefully, the days are gone when patients with symptomatic hyperprolactinaemia were treated with dopamine agonists without any radiological imaging—bromocriptine will suppress the galactorrhoea of stalk compression hyperprolactinaemia whereas the craniopharyngioma gets bigger! Immunocytochemistry on the excised tumour is the final arbiter.

Lymphocytic hypophysitis often presents at the end of pregnancy with visual failure and it has also been described in men. MRI shows an enlarged homogeneously enhancing pituitary gland but a specific diagnosis cannot be made by imaging alone. Management requires careful coordination between obstetrician, endocrinologist, ophthalmologist, and neurosurgeon—early delivery may lead to early shrinkage and avoid trans-sphenoidal decompression provided vision has not deteriorated too far. Lymphocytic hypophysitis represents

an autoimmune attack on the adenohypophysis and manifests histologically as diffuse lymphocytic infiltration effacing and destroying the normal glandular elements with progression to fibrotic scarring.¹⁹ The infiltrate is polyclonal, predominantly T cell, but often includes lymphoid germinal centres, plasma cells, and foamy macrophages. A similar lymphocytic inflammatory process may be confined to the neurohypophyseal system, sparing the anterior pituitary. By contrast, granulomatous hypophysitis is characterised by non-caseating epithelioid granulomata and multinucleate Langhans-type giant cells. When restricted to the anterior pituitary this pathology probably overlaps with lymphocytic hypophysitis²⁰ but in the posterior pituitary it is more often a manifestation of neurosarcoidosis and invariably associated with involvement of the hypothalamus and basal meninges. In any inflammatory process, unusual infections, particularly mycobacterial or fungal, must be excluded but in western countries these are unlikely except in the context of immunosuppression.

The symptoms and signs of extrasellar extension depend on its direction:

- Downwards—nasal obstruction or epistaxis; CSF leak
- Upwards—visual failure (see later); hypothalamic disturbance, third ventricular obstruction with acute hydrocephalus (symptoms and signs of raised intracranial pressure), or chronic hydrocephalus (gait apraxia, slowing of mentation, and incontinence)
- Laterally—cavernous sinus syndrome; complex partial seizures.

Pituitary apoplexy (fig 2)

As pituitary adenomas enlarge, they acquire a direct arterial blood supply in addition to the portal blood supply but their blood supply remains tenuous.^{3 21–23} There is a range of presentation of haemorrhagic infarction from subclinical infarction, noted at operation or on preoperative imaging (the prevalence of haemorrhage within adenomas is 9%–43% on MRI of which less than 30% are symptomatic), to full blown apoplexy that mimics subarachnoid haemorrhage. Indeed, the diagnosis may initially be missed. Many of these patients may not be aware of a pre-existing adenoma. In addition to abrupt headache with or without loss of consciousness, the clinical features include visual failure,²⁴ cavernous sinus syndrome, focal neurological signs, and acute panhypopituitarism, sometimes with low blood pressure. Pituitary apoplexy can occur with a relatively small adenoma and is often spontaneous but may be precipitated by endocrine stress tests, bromocriptine,^{25 26} and anticoagulants. The unenhanced emergency CT usually shows an enlarged pituitary fossa with some blood or speckled density within the mass. Magnetic resonance imaging will then confirm the diagnosis and angiography is rarely needed to exclude a vascular abnormality. Haemorrhage appears as high signal on both T1 and T2 weighted imaging, and can be confused with craniopharyngioma and Rathke's cleft cyst, especially as the signal changes can persist for

Figure 3 (A) Empty sella with normal residual pituitary tissue in the floor of the sella. (B) Enlarged partly empty sella after treatment of a macroadenoma. Note the prolapse into the sella of both the chiasm and more anteriorly, the posterior part of the gyrus rectus of the frontal lobe.

3–12 months, to be replaced by an area of hypointensity in the chronic phase. Management includes resuscitation, steroid replacement, and early transphenoidal decompression with craniotomy reserved for the very small minority of patients with a dumb-bell tumour.²⁷

Empty sella syndrome (fig 3)

Empty or partial empty sella are terms used when the pituitary gland does not fully occupy the sella, and this is found in 6% of routine postmortems and MRI examinations when a midline sagittal image is obtained. It is more common in multiparous women, presumably due to repeated enlargement and involution of the gland with each pregnancy. Empty sella is a radiological diagnosis based on CT or MRI performed for headache, CSF leak, or late visual deterioration after surgery or radiation therapy for a pituitary lesion. The radiological diagnosis of an empty sella should be made with care—a cystic craniopharyngioma or Rathke's cleft cyst may sometimes mimic the normal anatomical contours both within and above the sella. This distinction is particularly important in those 18% of children with neuroendocrinological abnormalities who could have an empty sella, cyst, or craniopharyngioma.^{28–29} This should be less of a problem with MRI than it was with CT. Primary empty sella conventionally is not associated with significant endocrine or visual abnor-

malities. Sensitive dynamic endocrine testing may disclose abnormalities but hormone replacement is seldom indicated.³⁰ An empty sella is commonly seen in patients with benign intracranial hypertension³¹ and may be the sequel to pituitary apoplexy. About 50% of adult patients with a primary empty sella have antipituitary antibodies that indicate previous autoimmune hypophysitis.³² Postpartum necrosis of the pituitary gland may be followed by an empty fossa. Spontaneous CSF rhinorrhoea may be associated with an empty sella with or without raised intracranial pressure.³³ When there has been a previous cause for the empty sella, then there may be an associated endocrine abnormality (either hypopituitarism or hormone hypersecretion) if there is an accompanying pituitary adenoma, particularly when shrunk either by bromocriptine or somatostatin. Prior intrasellar surgery and radiotherapy may lead to an empty sella.

The optic chiasm may herniate down into the empty fossa but there is considerable debate as to whether such herniation itself can be responsible for visual field defects.³⁴ Radiation necrosis and arachnoiditis are more likely to be the cause of visual failure in such circumstances. Although some good results from chiasmectomy have been reported,³⁵ both for the relief of intractable headache and for visual failure, there have certainly been disasters, which inevitably go underreported.

Diabetes insipidus and SIADH

Neither of these fluid balance disturbances are common presentations of anterior pituitary pathology—they usually indicate hypothalamic or pituitary stalk pathology. The posterior pituitary gland and stalk are supplied by an arterial circulation and the rise in intrasellar pressure produced by a pituitary adenoma is insufficient to compromise such an arterial circulation except possibly after pituitary apoplexy. Vasopressin and oxytocin are produced in hypothalamic nuclei and are transported by their axons to be stored as neurosecretory granules in the posterior pituitary which appear as a high signal intensity on MRI. The normal high signal (see fig 1A) is absent in almost all patients with central and nephrogenic diabetes insipidus.³⁶ This, however, should be interpreted with caution as the bright signal is also absent in 15%–20% of the normal population, albeit usually in the elderly age group who, although asymptomatic, have a high circulating plasma osmolality.³⁷ The presence of the bright signal indicates normal vasopressin stores, implying an intact neurohypophyseal system, which eliminates central diabetes insipidus as a diagnostic possibility. Ectopic location of the posterior lobe is very rare as an isolated finding with normal pituitary function. Any process, however, that disturbs transport of hormones from the hypothalamus to the neurohypophysis as in transection of the stalk, after head injury or surgery, or destruction of the posterior lobe, can result in the accumulation of the high signal material proximal to the site of obstruction.³⁸ In idiopathic

Figure 4 (A, B) Chiasm/hypothalamic glioma. Sagittal and coronal T1 weighted image (postgadolinium). (C, D) Astrocytoma (suprasellar/sellar); coronal T1 weighted image before and after contrast medium injection

growth hormone deficiency, there is a high incidence (43%) of ectopic posterior pituitary.³⁹

Diabetes insipidus is more common with metastases (33%) compared with adenomas (1%) (see fig 7F).⁴⁰ Neoplasms of the posterior pituitary are rare. Low grade gliomas that closely resemble astrocytomas may occur in the posterior lobe or stalk (fig 4). Benign, granular tumours, also called choristomas, contain large PAS positive granules which are solely due to abundant large lysosomes.

Visual failure

ANATOMY OF THE CHIASM

The chiasm (4 mm thick, 12 mm wide, and 8 mm long) lies about 1 cm above the pituitary fossa, inclining as much as 45° from the horizontal.⁴¹ In humans, about 53% of fibres decussate and there are about 2 million axons for both nerves.⁴² Because of the normal variation in the length of the optic nerves, the chiasm may be prefixed (overlying the tuberculum sella anteriorly) or postfixed (overlying the tuberculum sella posteriorly).⁴³ Small tumours in this region or ophthalmic artery aneurysms may cause unilateral blindness by pressure on one intracranial optic nerve. A space of about 1 cm between the dorsum sella and the chiasm will accommodate a reasonably large tumour arising above the dorsum sella before it compresses the chiasm. Fibres from the macula comprise most of the fibres of the optic nerve, chiasm and optic tract. As a consequence, pituitary tumours compressing these structures will have field defects that affect the central 30° and so may be detected using the tangent screen and automated perimeters which test out to 24° or 30°.

The inferior nasal fibres which cross within the chiasm sweep forward into the opposite optic nerve and thence into the opposite optic tract, forming Wilbrand's knee.⁴⁴ Recent anatomical studies of the chiasm have emphasised that the exaggerated bulge of crossing fibres, which seems to involve the contralateral optic nerve, is partly an artefact caused by enucleation.⁴⁵

VISUAL SYMPTOMS OF PITUITARY TUMOUR

Some patients may be unaware of their field defects. The most frequent complaints of patients with chiasmal compression from pituitary tumours are progressive loss of central acuity and dimming of the visual field, especially in its temporal portion. However, the lack of a binocular temporal field may also cause difficulties with depth perception for near vision and diplopia. Convergence for near vision results in crossing of the two blind hemifields so that an object posterior to fixation apparently disappears—so called postfixation blindness. Patients often complain of difficulty with fine tasks such as threading a needle and cutting fingernails.⁴⁶ Diplopia without an ocular motor paresis results from “vertical slip”. Patients with a bitemporal hemianopia do not have a link between the remaining hemifields so that vertical or horizontal separation occurs between the two intact nasal hemifields and visual sensory difficulties result. Diplopia may also result from involvement of the third, fourth, and sixth cranial nerves in the cavernous sinus causing a disturbance of ocular motility.

FIELD DEFECTS IN CHIASMAL LESIONS

The classic pattern of a chiasmal visual field defect is a bitemporal depression and greater

near fixation, but the effects may be peripheral, central, or a combination. The defects may be absolute or relative.⁴⁷ Patients with chiasmal disease may have normal or reduced acuity and colour vision. The initial field defect usually occurs in the superior temporal quadrants and then to the inferior nasal and superior nasal quadrants.

The types of field defect with chiasmal lesions may be classified as:

(1) anterior angle of the chiasm

When only a small lesion involves the crossing fibres of the ipsilateral eye, the field defect is temporal with a midline hemianopic character; if only the macular crossed fibres are affected the field defect is paracentral and temporal. When both the crossed and ventral fibres from the contralateral eye are affected, there is a defect in the temporal field of that eye. If there is extensive involvement of one optic nerve, an extensive field defect or even blindness of that eye may result; when such a lesion extends to involve the chiasm, the earliest indication is a temporal defect in the contralateral eye.

(2) Lesions involving the body of the chiasm

These characteristically produce a bitemporal hemianopia that may be peripheral, central, or a combination of both with or without splitting of the macula. Usually the visual acuity is normal. In the field of the right eye, the defect progresses in a clockwise direction and, in the left eye, a counterclockwise direction. A complete bitemporal hemianopia is rarely seen except after trauma to the chiasm. Most compressive lesions cause relative bitemporal hemianopias.

(3) Lesions at the posterior angle of the chiasm

These lesions characteristically produce bitemporal homonymous scotomas often associated with peripheral bitemporal defects as well. Lesions affecting this area often also compress the ipsilateral optic tract.

(4) The lateral aspect of the chiasm

Compression of the lateral aspect of the chiasm affects both the uncrossed temporal fibres and the crossed nasal fibres causing a contralateral homonymous hemianopia.

PSYCHOPHYSICAL ABNORMALITIES IN CHIASMAL LESIONS

Recent investigation with contrast sensitivity techniques has attempted to characterise changes in visual function resulting from chiasmal compression before visual acuity and visual field are affected. Studies of temporal contrast sensitivity have shown both uniform and low temporal frequency loss of contrast sensitivity in patients with chiasmal compression.⁴⁸ Studies assessing spatial frequency sensitivity in lesions affecting the suprasellar region have found alterations either to be total or limited to low to medium spatial frequencies only.⁴⁹ A recent study of psychophysical losses in foveal sensitivity found significant losses in chromatic, luminance, and temporal sensitivities in patients with suprasellar lesions without field defects.⁵⁰

FUNDAL SIGNS

Optic atrophy is a late sign of chiasmal compression from pituitary tumour; usually the optic discs are normal. Optic atrophy is weakly correlated with the duration of visual symptoms and strongly correlated with persistent postoperative decreased visual acuity.⁵¹ There is a characteristic optic atrophy found in advanced chiasmal compression—"bow tie" or "band" atrophy. The optic disc shows atrophy of the nasal and temporal margins with relative sparing of the superior and inferior portions where most spared temporal fibres (serving the nasal field) enter.⁴⁷ A relative afferent pupillary defect may be detected when there is asymmetric compression of the optic nerves.

THE MECHANISM OF CHIASMAL COMPRESSION

The mechanism by which pituitary adenomas and other lesions damage selectively the decussating nasal fibres remains uncertain. Because the axons for the entire superior visual field are in the inferior portion of the chiasm, compression from below would be expected to produce a defect in the entire upper field; yet an altitudinal hemianopia is extremely rare. Thus, unless the decussating fibres are more vulnerable to compression than the uncrossed fibres, simple compression does not provide a complete explanation for bitemporal field defects.

There is evidence from animal studies of the effect of direct compression on the anterior visual system. In a macaque monkey a suprasellar meningioma compressed the optic nerves, chiasm, and tracts dorsally causing a selective loss of small diameter fibres.⁵² In cats, optic nerve pressure obstruction has been shown to disrupt large diameter fibres selectively.⁵³ The vulnerability of the crossing fibres to compression from below may be related to the vascular supply; in humans, the central chiasm derives its blood supply from the inferior vessels.⁴³ Alternatively, the attachments of the optic chiasm are such that expanding tumours produce tension on the crossing fibres only.⁵⁴

THE PROGNOSIS FOR VISUAL FUNCTION AFTER TRANS-SPHENOIDAL HYPOPHYSECTOMY

After uncomplicated surgical decompression of the chiasm and optic nerves, visual acuity and visual fields usually improve rapidly over a few days. There may also be a slower improvement occurring over weeks and months. Visual recovery is usually complete by 4 months.^{55 56} Visual outcome is favourable in most patients; in a recent report of 67 patients, the vision was improved in 88%, the same in 7%, and worse in 4%.⁵⁵ The extent of improvement depends on whether permanent damage to the optic nerve and chiasm has occurred. The extent of preoperative damage may be judged from a loss of arcuate nerve fibres surrounding the optic disc (the nerve fibre layer) and the degree of atrophy and pallor of the disc itself. The duration of visual loss and the degree of chiasm and optic nerve compression are the chief influences on the preoperative visual status. In cases of advanced visual failure and severe optic atrophy, it is wise to caution the patient that

Figure 5 Acromegaly. Adenoma secreting growth hormone. The injection of gadolinium allows the clear distinction between the normal displaced enhancing gland (small arrow head) and the tumour.

decompression may prevent further visual deterioration but may not improve visual function.

Rarely, visual function may deteriorate after trans-sphenoidal hypophysectomy particularly with second operations or after radiotherapy and all patients should be warned of this possibility before surgery. Visual deterioration after surgery is usually related to an intracapsular haematoma, possibly as the result of infarction of a tumour remnant, or direct surgical manipulation of the optic nerve or chiasm and its blood supply. Visual deterioration is more likely after craniotomy, particularly when radical removal of a capsule from the chiasm has been attempted.

The other important concern in follow up is whether patients with persistent bitemporal field defects should be allowed to drive. According to the current criteria of the United Kingdom Driver and Vehicle Licensing Authority, if there is a bitemporal field defect affecting the central 20°, patients should be advised that they will not be permitted to drive.

Investigations

ENDOCRINOLOGY

Patients with pituitary tumours should be assessed by a multidisciplinary team.¹ They often require long term supervision, and early referral to the appropriate endocrinologist is sensible. The only urgent endocrine test required in a patient with visual failure and a large suprasellar mass is a basal prolactin concentration. Endocrine tests should be tailored to the individual patient and not ordered uncritically. The conventional dynamic endocrine tests may precipitate pituitary apoplexy, as most sleep deprived pituitary surgeons can testify.⁵⁷ Inferior petrosal sinus sampling for Cushing's syndrome uses a percutaneous bilateral femoral approach and requires obsessive attention to detail if useful results are to be obtained.⁵⁸ In experienced hands, the procedure is safe but cavernous sinus thrombosis

and brainstem infarction have been seen—heparin and a gentle contrast injection technique are essential.

IMAGING^{59 60}

Magnetic resonance is the first choice for imaging the pituitary and parasellar region as no ionising radiation is involved and bone induced artefact is avoided. Plain skull radiology is seldom indicated except for surgical planning in selected cases. Computed tomography is reserved for emergency use and for the claustrophobic, the MRI incompatible, those too large for the bore of the magnet, and for specialised indications when bone details are useful (CSF leaks and surgical planning). Each neuroradiology department has a standard MRI protocol but this has to be refined for specific clinical indications and close communication between radiologist and clinician is essential if errors are not to occur. Particular care is required with long term, multidisciplinary follow up when miscommunication can so easily occur with missed or mislaid scans making accurate comparisons and timely management decisions difficult.

Clinicians should be aware of the age related changes in pituitary size and characteristics from childhood through puberty and pregnancy to old age. The maximum allowable pituitary height is 6 mm in children, 8 mm in men and postmenopausal women, 10 mm in women of child bearing age, and 12 mm in late pregnancy and the postpartum period.^{61 62}

Microadenomas, defined as less than 10 mm in diameter, are 400 times more common than macroadenomas.⁶³ Magnetic resonance imaging is emerging as a superior technique to CT for the detection of microadenomas. The detection rate varies in the literature from 65% to more than 90%.⁶⁴ This is related to the technique used, the continuing improvement in equipment, the use of contrast, and the size of the microadenoma. Most microadenomas are visible by virtue of their hypointensity on T1 weighted sequences in relation to the normal pituitary tissue (see fig 1B). Focal enlargement of the gland and convexity of the diaphragma sella are less specific adjuvant signs. Infundibular tilt and sella floor thinning or erosion are less useful criteria.⁶⁵ Microadenomas as small as 2–3 mm can now be detected in 75%–90% of cases (with a false negative rate of about 13%), which is very important for surgical planning in patients with pituitary driven Cushing's disease⁶⁶ when combined with bilateral inferior petrosal sinus sampling.^{58 67} Serial MRI studies have shown that about 7% of microprolactinomas progressively expand over 2–8 years.

The immediate T1 weighted scan after gadolinium, with the use of thin slices, is the most useful sequence to increase the sensitivity of detection of small intrasellar lesions: the enhancing normal glandular tissue allows the low intensity microadenoma to become more conspicuous (fig 5).⁶⁸ The ability to obtain a dynamic series of images in seconds rather than minutes has overcome some of the limitations of conventional postcontrast imaging (fig 6).

Figure 6 Microadenoma. Dynamic MRI. 3D F SPGR 3 mm thick slices. Temporal resolution of 20 seconds. Contrast injected after the first image. Note early enhancement of normal gland (first row). Adenoma and gland became almost indistinguishable at later images (bottom row)

Images obtained less than 2 minutes from the start of injection have a detection rate of 90% compared with 60% at 5 minutes.^{69 70} However, some adenomas become less visible, as they also enhance to be isointense with the gland. A few microadenomas show more rapid arrival of contrast material than the normal pituitary tissue suggesting perhaps the development of a direct arterial blood supply.⁷¹ Precontrast T1 weighted images remain important to detect both the few adenomas (5%) which are hyperintense to the normal gland and haemorrhagic lesions.

Computed tomography and MRI are equivalent in detecting the full extent of a macroadenoma (fig 7). The margins tend to be lobulated in at least two thirds of the cases (23% in meningiomas). Sellar enlargement is seen in 94%-100% of pituitary macroadenomas. This is only helpful as a distinguishing feature in a suprasellar mass when it is absent, because its absence favours neoplasms other than a macroadenoma⁷² but does not exclude an aneurysm! The presence of hormone hypersecretion and an adenoma on CT does not exclude the presence of an associated vascular abnormality or intrasellar aneurysm, particularly in patients with acromegaly. Visual symptoms are seen when there is chiasmatic displacement greater than 8 mm above a line from the frontal base and posterior clinoid in the sagittal plane and 13 mm above the upper surface of both internal carotid arteries in the coronal plane.⁷³ Magnetic resonance imaging is very helpful in defining the extent of cavernous sinus involvement, documenting the anatomical effects of medical treatment (bromocrip-

tine, somatostatin), and for surgical planning. The interpretation of early postoperative scans can be difficult and are best left for 3 months unless early radiotherapy is contemplated.⁷⁴

Rathke cleft cysts and craniopharyngiomas probably have a common origin from Rathke's pouch with occasional cases of ciliated craniopharyngiomas showing features of both. Rathke cleft cysts are mostly small and intrasellar and lined by a single layered cuboidal or columnar ciliated epithelium that may include goblet cells. Squamous metaplasia may transform the lining or the lining may degenerate. Occasionally larger cysts project beneath the optic chiasm. Such cysts are often asymptomatic but are increasingly recognised with the wider use of MRI. Small lesions should not be mistaken for microadenomas and the larger ones with suprasellar extension should be distinguished from craniopharyngiomas as the surgical approach may be different and postoperative radiotherapy is not necessary. Diagnostic features on MRI include a sellar epicentre, smooth contour, the absence of both calcification and enhancement, and, when present, an anteriorly displaced pituitary stalk. The MR signal intensities are typically reduced on T1 and increased on T2 though in more than half of the cases there is hyperintensity on T1 and varying signal on T2.⁷⁵⁻⁷⁷

Craniopharyngiomas are benign squamous epithelial neoplasms that are predominantly suprasellar but sometimes show an intrasellar extension. There are two histological patterns of craniopharyngioma, adamantinomatous and papillary.⁷⁸ The first is composed of lace-like strands of stellate epithelial cells with a basal palisade enclosing many cystic spaces. Degenerative changes are associated with the deposition of cholesterol crystals that confer an oily appearance to the cyst fluid. Masses of eosinophilic, necrotic, keratinised cells that accumulate within the epithelium often become heavily calcified and may dominate the histology of a small biopsy. The less common papillary craniopharyngiomas usually occur in adults and are formed by mature squamous epithelial cells encasing a fibrovascular core.^{79 80} This type does not calcify and only rarely involves the sella. In keeping with the varied histological constituents of craniopharyngiomas, the MR appearances are quite diverse. A prominent cystic component and varying signal intensities of the mixed cystic and solid components are typical features, occurring in nearly 80% of cases. Areas of homogeneous T1 hyperintensities and enhancement of solid as well as the thick wall of the cystic components are highly suggestive of the diagnosis (see fig 7D).⁸¹ Calcification is common especially in childhood tumours and is best demonstrated by CT. The pituitary gland can often be shown separately from the tumour especially by MRI. Suprasellar epidermoids are much rarer tumours but often cannot be radiologically differentiated.

Suprasellar and intrasellar meningiomas arise from the diaphragma, tuberculum, and the dorsum sella as well as the dura of the adjacent cavernous sinuses (see fig 7E). They are

Figure 7 (A) Intrasellar macroadenoma. Extension into right cavernous sinus. (B) Macroadenoma. Coronal T1 weighted image. The suprasellar extension is compromising the left optic nerve (arrow head). Adenoma is extending into the sphenoid sinus. (C) Macroadenoma. Optic chiasm is displaced and stretched resulting in classic bitemporal hemianopia. Note the invasion of clivus and extension to sphenoid sinus. (D) Craniopharyngioma. Sagittal T1 weighted image. Large well defined lobular mass. The cystic component shows high signal and the fluid level is arrowed. Suprasellar calcification was seen on CT. (E) Meningioma. Sagittal T1 weighted image postgadolinium. Enhancing lesion with anterior extension based on planum sphenoidale. The normal size of the pituitary fossa makes macroadenoma very unlikely. (F) Metastasis (bronchial carcinoma) Sagittal T1 weighted image postgadolinium. Sellar and suprasellar enhancing mass extending into the hypothalamic region.

isointense with the grey matter on T1 weighted images but invariably show homogeneous dense enhancement. Obtuse dural margins and dural tail enhancement, in 68% of lesions involving the sella, are helpful in the preoperative diagnosis although they are not specific.^{72 82} Adjacent hyperostosis, best seen on CT, is present in more than one third of cases and is a helpful sign.

Hypothalamic/optic gliomas in the paediatric age group and young adults are slowly growing, benign pilocytic astrocytomas. They are related to neurofibromatosis type I in at least 30% but invariably if there are bilateral

optic nerve gliomas. In adults, hypothalamic gliomas tend to be more aggressive. The full extent of the lesion and invasion of the optic tracts, lateral geniculate bodies, and optic radiation can be readily assessed by MRI (see fig 4).

The table lists the many other lesions that may present in the sellar region which unfortunately do not have pathognomonic imaging characteristics (fig 8) even though their management may be different, reflecting, for example, the radiosensitivity of most germinomas⁸³ and the disseminated nature of a metastasis. Finally, the development of specific radiolog-

Figure 8 (A) Germinoma. Sagittal T1 weighted image postgadolinium. Enhancing sellar and infundibular mass. Second lesion is present in the pineal region. Adolescent female presented with diabetes insipidus and failure to gain height. (B) Tuberculous meningitis. Axial T1 weighted image postgadolinium. Indolent TB meningitis presented with deteriorating vision. Suprasellar tuberculoma with multiple small abscesses spreading mainly through the perivascular spaces. (C) Chondrosarcoma. Coronal T1 weighted image after gadolinium. Skull base tumour extending into the right cavernous sinus displacing the normal pituitary.

ands suitable for positron emission tomography (PET) imaging may contribute to the functional diagnosis and localisation of pituitary lesions and their follow up.

Management

Management ranges from the conservative finding of “incidentalomas” through medical, surgical, and radiotherapeutic strategies depending on the tumour type, size, and invasiveness. The objectives of treatment include restoration of a feeling of wellbeing, relief of pressure symptoms, treatment of hormone excess symptoms, restoration of or substitution for specific system deficits, prevention of tumour regrowth, and reversal of increased long term mortality. Results between series can be compared only if the anatomical, neuropathological, and endocrine characteristics are specified. The definition of a “cure” depends on the specific lesion:

- Non-functioning tumours—no remnant on sequential MR scans; lack of enlargement of a known remnant after surgery and radiotherapy suggests that control has been achieved but longterm follow up is still required.
- Acromegaly—the criteria have become more stringent and now include a glucose suppressed growth hormone less than 2 ng/ml and normalisation of insulin-like growth factor (IGF-1).

- Cushing’s disease—reversal of hypercortisolaemia but care has to be taken with the interpretation of the results.
- Prolactinoma—correction of hyperprolactinaemia; maintained shrinkage of adenoma on sequential MR.

The following sections show some of the difficulties.

Grading systems

Hardy’s original and robust classification was based on skull radiography and CT and for all practical purposes requires only minor modifications to take account of information from MRI despite efforts to create more elaborate systems^{84–86}:

- I Microadenoma less than 10 mm in diameter
- II Macroadenoma without suprasellar extension
- III Macroadenoma with suprasellar extension
- IV Macroadenoma with localised destruction of the floor of the sella
- V Macroadenoma with diffuse invasion
- VI Giant adenomas extending more than 40 mm above the planum sphenoidale or with multidirectional extensions.

Any grading system will be imperfect because no imaging modality can yet distinguish displacement of the cavernous sinus from invasion of the dura. Such invasion can occur even with a small, laterally placed microadenoma.

Neuropathology and biological behaviour

The original classification of adenomas as acidophil (GH $\pm$ prolactin), basophil (adrenocorticotrophin (ACTH)) and chromophobe (prolactin, non-secretory, α -subunits) was based on tinctorial staining properties largely determined by the nature and density of the secretory granules. The combined approaches of electron microscopy, immunocytochemistry, and molecular biology have served to elucidate and characterise the plurihormonal nature of many adenomas with expansion of their classification to include at least 16 different types.⁸⁷ Molecular biological studies have shown that pituitary adenomas are mostly monoclonal, initiated by genomic mutation of a single adenohypophyseal cell and stimulated to proliferate by various hypothalamic, peripheral endocrine, and paracrine factors. Individual tumour cells often contain and may secrete more than one active hormone, in addition to fragments of various precursor molecules. For example, many growth hormone adenomas also contain prolactin and thyrotrophin and many secrete the non-functioning α -subunit that is common to all glycoprotein hormones as confirmed by studies of primary monolayer cultures of human anterior pituitary cells. Such findings are important for advancing our understanding of the role of cell specific transcription factors such as PIT-1 in the development of pituitary adenomas.⁸⁸ Individual adenomas may show either a monomorphous or mixed cell population with variation in fine structure and immunophenotype. Cytoplasmic granularity and positive immunostaining indicate hormone synthesis and storage but not necessarily release and hence there may be poor correlation with serum concentrations of the paramount hormones or their systemic endocrine effects. Whereas macroadenomas tend to be endocrinologically more inert, there is emerging evidence of greater proliferative activity and other differences from smaller but systemically more active adenomas.⁸⁹ Sparsely granulated tumours may be less well differentiated and more aggressive than the densely granulated adenoma as has been documented in acromegaly. To complicate matters, the stem cell chromophobe adenoma synthesises both growth hormone and prolactin but, unlike the common prolactinoma, does not respond to bromocriptine, and shows both oncocyctic change and more aggressive growth.⁹⁰ An unusual growth hormone variant contains both typical adenomatous cells and also clusters of large, sometimes dysmorphic, neurons interpreted as a gangliocytoma. The neurons contain growth hormone releasing hormone and support the hypothesis that hypothalamic releasing hormones promote tumorigenesis in the anterior pituitary.⁹¹ Cushing's disease may be produced by a tiny microadenoma but islands of hyperplasia may be seen—the concept of endocrine cell hyperplasia preceding neoplasia is fully accepted elsewhere, for example, in thyroid C cell hyperplasia. There are at least two other unusual ACTH adenomas that are clinically silent, usually large, and only established by immunostaining to synthe-

size ACTH. One is a basophilic granulated tumour that has a marked tendency to undergo spontaneous haemorrhage and is a cause of pituitary apoplexy. The other is a chromophobe adenoma showing only weak ACTH immunoreactivity but stronger reactivity for β -endorphin, which is also a derivative of the ACTH precursor pro-opiomelanocortin.⁹² Thyrotrophinomas are the rarest of all adenomas and only a few are hyperfunctioning. Immunostaining may reveal sparse thyrotrophs in growth hormone adenomas. Both thyrotrophinomas and prolactinomas may become heavily calcified.⁹³

Some 20%–30% of all adenomas are endocrinologically inactive and include the silent ACTH adenomas, growth hormone tumours, gonadotrophinomas, null cell adenomas, and oncocytomas.⁹⁴ Null cell tumours resemble chromophobe adenomas but show negligible immunoreactivity or ultrastructural evidence of hormone production. Oncocytic cells contain abundant large mitochondria that impart cytoplasmic granularity and eosinophilia which could be mistaken for an acidophilic growth hormone adenoma.⁹⁵ Such tumours may mimic prolactinomas clinically but prolactinaemia is due to raised intrasellar pressure or stalk compression.

Aggressive adenomas and carcinomas—microscopical extrasellar extension of pituitary adenomas is common but these tumours tend to displace brain, optic nerves/chiasm, and vessels rather than invade them. Adenomas that invade the sphenoid or cavernous sinuses can be regarded as unduly aggressive and pituitary carcinomas are defined by evidence of craniospinal, or systemic metastases, or both. As with other endocrine tumours, nuclear and cellular pleomorphism alone are not reliable markers of invasive potential, but frequent mitoses generally constitute an adverse prognostic sign. Various cell proliferation markers, including proliferating cell nuclear antigen, Ki-67 or MIB 1 staining for Ki67 antigen have been employed in attempts to predict the likelihood of recurrence. High proliferation indices tend to correlate with more aggressive growth but sampling error is a problem and presently, particularly in tiny biopsies, the results are not sufficiently reliable to provide a clear prediction in an individual case.^{89–96} The very rare pituitary carcinomas are most often prolactinomas or ACTH secreting tumours emerging in Nelson's syndrome.⁹⁷ Molecular biological studies disclose multistep mechanisms of tumorigenesis—for example, *ras* oncogene mutation and activation are uncommon in primary pituitary tumours but have been identified in metastases.⁹⁸ Proliferation indices and p53 expression also tend to be higher in the metastases.⁹⁷

Medical management

Dopamine agonists are the first line of management in patients with hyperprolactinaemia—particularly those with a microprolactinoma. Cabergoline, a newer ergot based dopamine agonist, is taken twice weekly as opposed to daily with bromocriptine and is associated with fewer

side effects. Quinagolide is a non-ergot dopamine agonist which has been shown to be effective—particularly in bromocriptine resistant cases—but can be associated with neuropsychiatric side effects when administered in high dosage. Medical therapy is also the mainstay of management for most macroprolactinomas, but with careful coordination between endocrinologists and pituitary surgeons. Clearly, pituitary apoplexy into a macroprolactinoma is an indication for urgent trans-sphenoidal decompression, as bromocriptine can hardly be expected to shrink a haemorrhagic infarct. On the other hand, there is one case report of a third nerve palsy due to apoplexy, treated with bromocriptine to good effect and chiasmal compression secondary to prolactinomas is certainly reversible with medical therapy.⁹⁹ Brain MRI indicates that a significant number of patients have small haemorrhages into the adenoma which are usually asymptomatic but may form the basis for subsequent fibrosis. There is evidence that bromocriptine treatment for 6–10 weeks increases the degree of fibrosis, leading to a greater surgical morbidity thereafter.^{100–101} Therefore, early pituitary surgery should be considered in patients with visual or cranial nerve problems if there is either no improvement or an increase in tumour size despite maximal dopamine agonist therapy, or in the few patients who are intolerant or non-compliant with drug therapy.¹⁰²

Trans-sphenoidal microsurgery (see later) is the primary therapeutic modality of choice in Cushing's disease and specific medical management is very limited. It is useful to treat patients preoperatively with metyrapone, which blocks 11 β -hydroxylase, to reduce the surgical morbidity resulting from the effects of high cortisol concentrations on tissue healing, blood pressure, and immunity.¹⁰³ Metyrapone, ketoconazole (inhibits steroidogenesis), and mitotane (cytotoxic to adrenal cortical cells) cannot be used long term because of their side effects and centrally acting drugs (bromocriptine, cyproheptadine, sodium valproate) are seldom effective. Longterm cure rates of up to 80% are being reported after surgery,^{3 104} reflecting several improvements in management: firstly, inferior petrosal sinus sampling has proved particularly useful in making a firm preoperative diagnosis—particularly in difficult cases; secondly, recent studies indicate that an undetectable morning serum cortisol postoperatively correlates most closely with the likelihood of long term cure. A non-suppressed postoperative cortisol (>150 nmol/l) may therefore be an indication for an early second exploration with more radical pituitary surgery. Ectopic adenomas in the suprasellar part of the pituitary stalk¹⁰⁵ or multiple areas of corticotrophic hyperplasia may contribute to surgical failure. Failed pituitary surgery usually leads to local radiotherapy, particularly as corticotrophic adenomas may be radiosensitive and it is essential to protect against the development of Nelson's syndrome. Radiation treatment takes many years to exert its effect, necessitating the use of bilateral adrenalectomy to achieve biochemical remission of Cushing's disease in the interim. The recent advent of

laparoscopic techniques for adrenalectomy may reduce the morbidity associated with this operation.

Trans-sphenoidal hypophysectomy is also the treatment of choice in acromegaly.¹⁰⁶ The likelihood of a surgical response seems proportional to tumour mass and extrasellar spread, with a 70% cure rate for adenomas associated with circulating growth hormone concentrations of 100 mU/l but only a 40% cure rate with concentrations greater than 100 mU/l.^{3 107} Once again, radiotherapy is used postoperatively when surgery has failed, but can take 10–20 years to achieve biochemical control. Moreover, it is now recognised that the increased growth hormone concentrations associated with active acromegaly are associated with considerable excess cardiorespiratory mortality and morbidity and possibly a risk of colonic neoplasia.¹⁰⁸ Accordingly, medical therapy is used to reduce mean growth hormone to safe concentrations of less than 5 mU/l. A minority (10%) of acromegalic tumours, especially those that also secrete prolactin, respond to bromocriptine.¹⁰⁹ For the remainder, octreotide (a somatostatin analogue),¹¹⁰ is administered by thrice daily injection, but newer highly effective fortnightly or monthly depot preparations are now available. Octreotide treatment can also be used preoperatively to shrink extrasellar tumour extension, but it is not known whether this improves the surgical outcome. Octreotide may also have a role as the primary longterm treatment modality, despite the risk of gall stones and the expense, in an older patient with mild acromegaly, a circumscribed tumour without local compression, perhaps with added factors (for example, cardiac failure) which constitute a poor operative risk. Finally, octreotide is also highly effective in controlling hyperthyroidism due to rare pituitary thyrotrophin secreting adenomas which have not been controlled surgically.

Although many of the non-functioning adenomas are derived from the gonadotroph lineage, they are generally unresponsive to medical therapies including dopamine agonists, growth hormone, and somatostatin analogues. In this context, radiotherapy plays an important part in arresting growth of the postoperative tumour remnant but this needs careful follow up with serial MRI as there are no circulating hormonal markers which can be measured to monitor residual tumour activity.

Surgical management

Surgical approaches for “sellar” lesions have evolved since Sir Victor Horsley's first craniotomy in 1889 and range from the straightforward transphenoidal operation to the complex multidisciplinary anterior skull base and transventricular/transcallosal approaches (fig 9). Subspecialisation is required if the patient is to be offered safe, appropriate treatment. Modern transphenoidal surgery, of which there are many excellent accounts,^{2 3 111} is very safe, with a mortality in well trained hands of 0.2%–1% depending on the case mix, and is suitable for the great majority of pituitary tumours. It is also inexpensive when compared

with drug therapy. Transnasal, sublabial transseptal, and transthemoidal approaches each have their advocates—it is useful to be able to use each route in selected cases particularly for reoperations. Transnasal endoscopy¹¹² has not yet been widely adopted except for repair of some CSF leaks. Refinements such as intraoperative hormone assays are not generally available.

Contraindications to the transphenoidal approach include dumb-bell tumours (tight diaphragma prevents access to the suprasellar extension from below), inaccessible extrasellar extensions (subfrontal, subtemporal, and retrosellar—where a combined or staged approach is preferable—see later), and intrasellar vascular lesions including aneurysms and “kissing” carotids. With the use of an image intensifier and the awareness that this ensures safety only in the anteroposterior plane, it is possible and reasonably safe to drill through an incompletely pneumatized sphenoid air sinus. Chronic sinusitis and polyps should be rigorously dealt with by an ear, nose, and throat colleague before transphenoidal surgery. Particular care needs to be taken with reoperations especially if the first operation has been undertaken elsewhere and the midline anatomical landmarks have been removed, circumstances in which the information from preoperative CT with bone windows is useful.

Patients should be counselled that there is a small risk of infection of 1%–2% (meningitis; sinusitis; septal or pituitary abscess) and that there is no evidence that prophylactic antibiotics are of any value except perhaps in patients with Cushing’s disease or recent sinusitis. Septal perforation, numb teeth, and a saddle nose are potential late complications but much less important than those of subfrontal retraction via a craniotomy. Significant haemorrhage is unusual (<1%). Damage to the internal carotid artery or rupture of an unsuspected intrasellar aneurysm can be readily controlled with a muscle pack. When intraoperative arterial injury is suspected, postoperative angiography is essential to forestall any delayed, life-threatening epistaxis.¹¹³ The usual cerebrovascular techniques may be required including balloon occlusion, clipping or coiling of an aneurysm, and embolisation of a torn sphenopalatine artery. Arterial injuries should become even rarer with routine preoperative MRI. Some tumours continue to ooze and the patient may awake with a fine drain issuing from one nostril, the other end of which is within the tumour bed, in addition to the usual self-expanding nasal packs. Suprasellar extensions may be encouraged to descend with the injection of Ringer’s lactate (10 ml–30 ml) or air into a lumbar CSF catheter. If a suprasellar extension does not descend, there is a risk of haemorrhagic infarction in the remnant necessitating urgent return to the operating theatre. If there is any doubt about the state of the remnant or about haemostasis, early CT is helpful. Postoperative CSF leaks are uncommon (1%–6%) when there is an aggressive policy for sealing the pituitary fossa and sphenoid sinus if there is the slightest hint of CSF intraopera-

tively. A sandwich technique of muscle or fat with tissue (triple fibrinogen) glue, combined with lumbar CSF drainage for a few days, works well. Patients should be warned that they may wake up with a lumbar catheter and may have a low pressure headache for a few days. Visual deterioration is rare after transphenoidal surgery (<0.5%) and immediate CT should be performed to exclude a remediable cause. Curettage of lateral extensions may provoke a third or sixth nerve palsy but such palsies are usually temporary.

Postoperative diabetes insipidus is overdiagnosed and overtreated! It is not unknown for elderly patients to be discharged on deamino-D-arginine vasopressin only to return in hyponatraemic coma. Except in the case of children after craniotomy for extensive craniopharyngiomas, when the thirst mechanism and hypothalamus may be defective, it is safer to follow the fluid balance chart and reassure the patient—nasal packs make mouth breathing inevitable and patients want to keep their mouths moist. The diagnosis of diabetes insipidus should be based not just on urinary output (>2500 ml/day) but also on an increased plasma osmolality (>300 mosmol/kg) and dilute urine (<300 mosmol/kg). Sleep deprivation should be avoided by introducing deamino-D-arginine vasopressin first at night.

Delayed hyponatraemia may occur spontaneously up to 2 weeks postoperatively in about 2% of patients.^{114–115} The original concept was that this reflected release of antidiuretic hormone from degenerating posterior pituitary neurosecretory terminals (SIADH) or was the result of overenthusiastic cortisol withdrawal particularly in patients with Cushing’s disease whose receptors had become adjusted to a very high cortisol concentration. However, antidiuretic hormone concentrations may not be raised. Treatment is by mild fluid restriction and salt replacement.

Patients should be warned that they may need second operations, long term follow up and long term hormone replacement as well as adjuvant therapy (for example, bromocriptine, somatostatin, radiotherapy). It is difficult to give a precise risk of postoperative hypopituitarism as it depends on the preoperative status and tumour type and morphology¹⁰¹ but an overall figure of up to 10% is sensible. There is the potential for improvement in pituitary function in a minority of patients after transphenoidal decompression of non-functioning pituitary adenomas (16%–57% depending on the series and pituitary sector investigated).^{116–117} It would be unusual for there to be any deterioration in pituitary function after transphenoidal marsupialisation of an intrasellar cyst in a young person. By contrast, it would be intended that reoperation for refractory Cushing’s or Nelson’s disease would result in hypopituitarism.

In addition to transphenoidal surgery, more complex tumours including craniopharyngiomas require various approaches (fig 9) that may carry very significant risks. The judgement and experience of a multidisciplinary team is invaluable.^{2 118–121} There is a temptation with multilobular suprasellar extensions

Figure 9 (A and B) Preoperative and postoperative transcallosal excision of a third ventricular craniopharyngioma (coronal T1 weighted images). Note the small residual tumour in the floor of the third ventricle which was subsequently treated with radiotherapy.

of pituitary adenomas, for example, to chase every lobule via pterional, subfrontal, translamina terminalis and subtemporal routes but the morbidity and mortality may be unacceptable to the patient. Great care has to be taken when dissecting around the chiasm. A more conservative transphenoidal decompression plus a restrained craniotomy followed by radiotherapy may achieve a much better quality of life for the patient even if the postoperative scans are less impressive. Lateral extensions invading the cavernous sinus and engulfing the carotid artery are seldom amenable to any surgical route and are the province of the radiotherapist.

Current issues in radiotherapy treatment of pituitary tumours

There is a consensus that radiotherapy should not be given routinely postoperatively and each patient must be considered individually. With the hypersecreting adenomas, there is a tumour marker to guide adjuvant therapy. With the "non-secretors" in which there has been complete tumour removal at operation as judged on postoperative imaging, detectable recurrence occurs in 16% but further therapy was only required in 6%.¹¹⁷ If a small residual tumour is seen on postoperative imaging, radiation may be withheld until a change indicating evident growth is seen or repeat surgery offered without radiotherapy.^{122 125} Postoperative imaging can be deceptive and not all residual tissue is a tumour remnant. Radiotherapy is useful for the very occasional patient who is too frail for surgery.

Radiotherapy has a very high therapeutic ratio, defined by the balance of tumour control rates which are very high, and normal tissue complication rates which are extremely low. For non-functioning adenomas, tumour control is defined as lack of progression of macroscopic disease. For hormone secreting adenomas, reduction of hormone production is also required. After radiotherapy, rates of freedom from progression are extremely high, and

should be around 95% at 10 years,¹²⁴⁻¹²⁸ and 88% at 20 years.¹²⁴ Secreting tumours fare marginally worse in some series, 89% versus 97% at 10 years and 69% versus 96% at 20 years,¹²⁴ though others record equal control rates of over 90%.^{125 126} Survival rates are excellent, although there is a slightly increased relative risk of death in patients with pituitary tumours requiring radiotherapy.¹²⁴

Despite the excellent rates of tumour control, control of hormone secretion is poorer, with up to 20%-40% of patients failing to gain control of hypersecretion,^{126 128 129} even with protracted follow up. These rates of hormone control can be improved by a further 20% by the addition of medical treatment.¹²⁶ The effects of radiotherapy on tumour hormone production may take several years to become maximal, so the timing of assessment of this end point must be chosen carefully. As hormone concentrations are reduced by about a first order reaction, the initial hormone concentration will in part determine the time required for normalisation, if control is achieved.^{129 130}

Radiotherapy dose

Doses of 45-50 Gy in 25-30 fractions are typical, well tolerated, and highly effective. The few studies which report results of a wider range of radiotherapy doses show a dose response, with lower rates of control associated with lower doses.^{128 131} The use of lower doses for patients with acromegaly has been investigated as a way to reduce the risk of pituitary insufficiency.¹³² A dose of 20 Gy in eight fractions seems to achieve relatively good control rates,¹³² though this has not been formally compared with conventional larger doses, and the long term outcome is not certain.

It is known that individual differences exist in normal tissue radiosensitivity in some tissues and it is very likely that this applies to the CNS also, but it is not yet possible to predict prospectively.¹³³ Avoidance of damage to any patient thus requires the choice of dose which

Figure 10 Probability of hypothalamic-pituitary axis dysfunction after treatment for pituitary adenoma. A (redrawn from Littley et al¹³⁷) shows data from 165 adults treated with radiotherapy doses of 37.5–42.5 Gy in 15–16 fractions with a median follow up of 4 years, which is relatively short. B (redrawn from Tsang et al¹²⁵) shows data for 160 patients with a median follow up of 8.5 years. Radiotherapy doses were typically 45 Gy in 22–23 fractions for minimal residual disease (in 95), 50 Gy in 25 fractions for gross residual disease (in 41), and 40–42 Gy in 25 fractions for unspecified reasons. There are obvious differences between the two series which may reflect the different dose fractionation schedules used.

is safe for even the most sensitive patient. This variation in individual sensitivity is probably the major reason that higher doses have been given to some patients without inflicting damage.

Complications of radiotherapy

Complications of radiotherapy can be divided into “acute”, occurring during or just after the course of radiotherapy, or “late”, occurring 6 months up to many years after treatment. Acute side effects are rarely serious and include a mild skin reaction, loss of temporal hair, and secretory otitis media, due to inflammation of the anterior part of the eustachian tube. This normally settles spontaneously but requires a myringotomy in 2%–3%.^{125 126} However, it is the late complications which determine safe doses and define the therapeutic ratio.

LATE COMPLICATIONS

Visual impairment

In a series of 411 patients treated at the Royal Marsden Hospital with 45–50 Gy in 25–30 fractions, 305 patients had a detectable visual defect before treatment, and 55% improved after radiotherapy. Only two (0.5%) developed late deterioration of vision presumed to be due to radiotherapy, and both actually retained vision.¹²⁴ In a large series from Princess Margaret Hospital in Toronto, out of 160 patients with non-functioning adenomas treated with a median dose of 45 Gy, there were no cases of visual damage, and of the 145 cases with secreting tumours treated with a median dose of 50 Gy one patient (who received 42.5 Gy in 22 fractions) developed deterioration in the vision of the left eye only.^{125 126} Surgical exploration of this patient showed dense fibrotic tissue adherent to the left optic nerve and a postfixed chiasm, with herniation of the left optic nerve into the empty sella. This was considered to be due to the combined effects of surgery and radiotherapy,¹²⁶ and gives an incidence of visual impairment of 0.3%.

Brain necrosis

Radiation necrosis has been described in patients having pituitary irradiation, but most cases occurred many decades ago, with what would now be considered poor techniques, often with low voltage machines (for example, 250–300 kV, rather than 6 MV typically used now), and with higher doses than currently prescribed.¹³⁴ Provided the dose is 50 Gy or less, and the fraction size is 2 Gy or less, the risk of necrosis should be extremely small or absent.^{134 135}

Hypothalamic-pituitary axis dysfunction is dependent on radiotherapy dose: and also on dose per fraction

With clinical doses, failure occurs in many patients after pituitary radiotherapy, and is certainly dose dependent.¹³⁶ As noted above, smaller doses (20 Gy in eight fractions) have been used to treat acromegaly,¹³² on the basis that the risk of dysfunction of the hypothalamic-pituitary axis will be reduced and its onset delayed relative to “conventional” doses. This warrants further investigation in a clinical trial setting. It may be that a similar dose but given with a lower dose per fraction will further reduce the risk of hypothalamic-pituitary axis insufficiency. As well as total dose, the dose per fraction has an additional effect,¹³⁶ such that larger doses per fraction, especially doses over 2 Gy per fraction, produce a disproportionate effect on the axis. Even with dose fractionation schedules which relatively spare the axis, there is a high incidence of failure, which rises with time and probably has no plateau (fig 10), even beyond 15 years. Some 50%–70% of patients require replacement of gonadotrophins, glucocorticoids, and thyroxine.^{124 125 137} This high incidence is the product of initial tumour damage and surgery, as well as the effects of radiotherapy which probably accounts for 10%–20% of patients who develop it.^{125 126} Associated with dysfunction of the hypothalamic-pituitary axis

is hyperprolactinaemia, although this is usually not permanent or extreme.¹³⁷ Also striking is the complete loss of growth hormone production by 5 years. It is virtually unknown for patients to develop diabetes insipidus as a result of radiotherapy for pituitary tumour.¹³⁸ Hypopituitarism in adults does carry a slight survival disadvantage, which is not fully eliminated by replacement with cortisol, thyroxine, and sex hormones, and it is possible that growth hormone deficiency is a factor.¹³⁹

Vascular damage

Damage to the large vessels around the pituitary gland has not been noted with radiotherapy, but such damage at other sites is described, although typically with higher doses than standard pituitary treatment.¹⁴⁰ Occlusion of one or both carotid arteries might have catastrophic consequences, and is one reason against the use of stereotactic radiosurgery for the initial treatment of large target volumes or for retreatment for tumours close to these large vessels.

Cognitive dysfunction

Impairment of memory and executive function has been found in patients with pituitary tumours. One recent study suggested that neither surgery nor radiotherapy alone affected cognitive function, but that combined treatment caused some dysfunction.¹²⁷ However, other detailed psychometric studies suggest that pituitary radiotherapy does *not* lead to impairment of cognitive function.^{141 142}

Risk of second tumour

Exposure to radiation, including therapeutic radiation, carries a small but significant risk of developing a second tumour, extending for at least two decades after exposure. In one series of 334 patients treated with conservative surgery and radiotherapy and followed up for a median of 11 years, a total of five second tumours occurred, although only three of these were malignant. This gives a cumulative risk of second tumour of 1.3% in the first 10 years after radiotherapy and 1.9% over 20 years.¹⁴³ Summing the cases in the relevant literature, a total of 1510 patients followed up for an average of 10 years developed 13 new second tumours, giving an approximate incidence of 0.86%.¹⁴³⁻¹⁴⁷ The absolute risk may in fact be slightly lower than this, as developments in radiotherapy techniques and equipment have almost certainly reduced the risk below these concentrations.¹⁴⁸

Newer developments in radiotherapy

STEREOTACTIC RADIOSURGERY

It is difficult to see how this technique could improve the outcome for pituitary tumours in most circumstances, especially as standard external beam radiotherapy gives such good results.¹⁵² Stereotactic radiosurgery is characterised by the use of a large dose of radiotherapy given as a single fraction and delivered with high accuracy. The use of a large single fraction may be effective against tumours. Indeed, the technique was originally

developed as a method of giving a dose designed to cause necrosis of the target, and its therapeutic ratio is provided by the rapid drop from high to low dose (called the penumbra) which occurs over a distance of just a few millimetres, and which allows avoidance of critical structures. However, large single fractions are the antithesis of fractionated treatment and can be extremely damaging to normal tissues if they are inadvertently treated. Thus the technique, even with its high precision, is far from ideal for treatment in which the target has to include tumour extension onto or around the critical normal tissues. Relatively few patients with pituitary disease have tumours which are truly confined to the pituitary fossa without some encroachment laterally or superiorly. The optic nerves and chiasm, the nerves associated with the cavernous sinus, and possibly the carotid arteries, are highly susceptible to radiation damage, particularly when the dose per fraction is large, as in stereotactic radiosurgery. If a tumour abuts the optic chiasm, for example, it is possible to limit the dose at the edge of the tumour to safe levels, but this is at the expense of lowering the dose to part of the tumour. Thus, stereotactic radiosurgery is unlikely to improve tumour control over conventional radiotherapy.

Many patients with pituitary adenomas have apparently been successfully treated using stereotactic radiosurgery.^{149 150} However, as yet there is no evidence that it produces superior results. Proton and heavy ion beams which can deliver relatively focused radiotherapy have also been employed, though likewise do not necessarily confer any particular advantage.¹³⁰ Despite some enthusiastic reports, catastrophic damage has been described after stereotactic radiosurgery. Rocher *et al*¹⁵¹ treated 135 patients with stereotactic radiosurgery, including 36 with pituitary adenomas. Over a short period of follow up, the rate of pituitary tumour control was comparable with conventional external beam radiotherapy. The complication rate, however, was excessive. Twelve patients (33%) had serious visual complications, including two who developed bilateral blindness. These complications were directly attributable to the proximity of the tumour, and hence the high dose volume to the chiasm. This group has now abandoned the use of stereotactic radiosurgery for pituitary tumours.

CONFORMAL RADIO THERAPY

Conformal radiotherapy uses advanced radiotherapy treatment planning in three dimensions to achieve better conformation of treatment volume to target volume. This allows reduction in the volume of normal tissue irradiated around the target. Conventional dose fractionation is normally used with conformal radiotherapy. As conventional external beam radiotherapy is so safe and effective, conformal radiotherapy would not be considered necessary in most cases. However, it is likely that the indications will expand with time. It is possible that the technique might lower doses to the hypothalamus, although this requires formal evaluation. Conformal

radiotherapy is likely to have an advantage for treating children, by reducing cognitive dysfunction. Currently, its place may be in treating particularly extensive tumours, for retreatments, or for treating children.

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