Orbital meningiomas: surgery, radiotherapy, or hormones?

Orbital meningiomas generally arise from the sphenoid and cause ophthalmic problems by virtue of an expanding mass near the orbital apex. These benign tumours often have a soft tissue component within the orbit, cranium, or temporalis fossa (Fig 1) and may induce hyperostosis of the postero-lateral wall of the orbit. Symptoms are generally caused by displacement of the globe – with diplopia or progressive proptosis – or compression of nerves and vessels at the orbital apex. Embrassment of flow through orbital veins can lead to enlargement of the episcleral vessels and chemosis, while compression of the third to the sixth cranial nerves at the superior orbital fissure may cause neurological deficit. Narrowing of the optic canal by tumour or hyperostosis causes the serious complication of visual loss; such loss is frequently slow and steadily progressive, but may show periods of faster progression ('stuttering' visual loss).

Treatment of sphenoidal meningiomas may not be required in the elderly or where the symptoms are minor and only slowly progressive. However, the currently available treatments are often unsatisfactory for younger patients with significant visual impairment and for patients with grossly disfiguring proptosis.

Surgery
Surgical resection of intracranial meningiomas is generally recognised to be the treatment of choice, although such surgery may be impossible or may carry high morbidity. Sphenoidal meningiomas are intimately related to the anterior visual pathways, superior orbital fissure, and to the frontal and temporal lobes; resection of these extensive, deep seated lesions is generally incomplete and the morbidity is greater than that for many other intracranial meningiomas.

Where sphenoidal wing meningiomas are slow growing, especially in the elderly, surgical efforts may usefully be directed towards the 'camouflage' of proptosis and prevention of corneal exposure: adequate recession of the retractors in the upper and lower eyelids, together with closure of the lateral (and occasionally medial) canthus, are oculoplastic procedures of particular value in such cases.

Radiotherapy
As with many slowly dividing tumours, high doses of radiotherapy (between 50 and 100 Gy) appear necessary to affect the growth of meningiomas. Such doses carry two small, but significant, risks – namely, the induction of malignant transformation within the parent meningioma and the formation of new tumours, either meningiomas or sarcomas.

Adequate radiotherapy for sphenoidal meningiomas is further complicated by the intimate relationship between the tumour and the optic nerve. Visual failure from neoplastic compressive optic neuropathy becomes evident only after marked loss of optic nerve microvasculature and neurons; yet further damage to the optic nerve blood supply from tumour irradiation is, therefore, likely to exacerbate visual loss.

Hormones and tumour growth
Epidemiological evidence gained over several decades has suggested that growth of intracranial meningiomas is influenced by female hormones. The tumours are more than twice as common in women as in men and the growth of (or symptoms caused by) some of these tumours increases during pregnancy and may lessen after the delivery or termination of pregnancy. Hormonal sensitivity for meningiomas is further suggested by reports of an association between the occurrence of meningiomas and breast cancer, a large proportion of breast tumours having hormonal receptors and demonstrating sensitivity to oestrogens. Furthermore, women with meningiomas, as with other hormonally sensitive tumours (such as breast or endometrium), have an increased incidence of obesity. A mechanism for the link between meningiomas and sensitivity to female hormones was first suggested by the demonstration of oestrogen receptors in some meningiomas. However, later investigations have shown such tumours to predominantly contain progesterone, rather than oestrogen, receptors (generally >70% and <20% of studied tumours, respectively); this is in contrast to breast cancer, where oestrogen receptors predominate. Other receptors, such as those for androgens, somatostatin or epidermal growth factors, have been demonstrated within meningiomas.

Tissue from meningiomas can be established in culture and has allowed the assessment of hormonal and autocoial effects upon tumour growth. Substances thus investigated include several progesterogens (progesterone, medroxyprogesterone, norethisterone), oestradiol, dihydrotestosterone (an androgen), hydrocortisone, insulin, bromocriptine (a dopamine agonist), and various growth factors (epidermal, fibroblast, platelet derived). Many also report the effect of antagonists to these substances – to progesterogens (RU486), oestrogens (tamoxifen), and to androgens (cyproterone and 11α-hydroxyprogesterone). Unfortunately the results from in vitro studies are frequently contradictory, showing marked variation in the proportion of responsive tumours, marked variation between tumours in the sensitivity to drugs, and often opposite responses from different tumour lines.

Figure 1  Right sphenoidal wing meningioma within the orbit, middle cranial fossa, and temporalis fossa.
Hormones and clinical therapy

The observation that patients with meningiomas often worsen during pregnancy led to the premise that growth of these tumours may be sensitive to the high levels of circulating progestogens. This view was strengthened by a study in which cells from a human meningioma were implanted into athymic, immunologically 'nude' mice: control mice showed tumour growth, whereas those treated with an antiprogestogen drug, mifepristone (RU486 or RU486), demonstrated a significant reduction in tumour size.4

Clinical investigations have demonstrated that pretreatment of patients with the progestogen agonist medroxyprogesterone acetate (MPA) reduces progesterone receptor activity within meningiomas,5 but the agonist mestrol would appear to be without effect on tumour growth when administered for periods of between 1 week and 1 month.6 In the latter study there were several side effects and the drug had to be discontinued in some patients. Likewise, treatment of patients with tamoxifen, an oestrogen antagonist, was without significant effect upon tumour growth.7

More recently, however, it has been shown that some patients get a useful response, either subjective (with improved symptoms) or objective (with reduced tumour size on computed tomography (CT)), in response to systemic mifepristone.8 Although a mild therapeutic response was observed in five of 13 patients, most experienced significant side effects such as nausea, fatigue, hot flushes, alopecia, or gynaecomastia.9 Many of the side effects are due to direct antagonism of progesterone or to overexpression of the hypothalamo-pituitary (HPA) axis. Overactivity of the HPA axis is due to partial antagonism of cortisone receptors by mifepristone and results in raised levels of the hormones adrenocorticotropin and oestradiol.10 Anaplastic ('malignant') meningiomas may have a lower incidence of bearing progesterone receptors11 and it is of particular interest that, of the three patients in whom tumour growth continued, two had 'malignant' meningiomas.12 Likewise, it has been suggested that the presence of oedema (CT scan) around intracranial meningiomas is an indication of the presence of progesterone receptors in the tumour13 and, hence, their possible sensitivity to hormonal manipulation.

The future

Further objective investigations of antiprogestogen therapy (and other) meningiomas that are not amenable to resection. Together with the development of antiprogestogen drugs without cortisone receptor antagonism, such studies may provide hope for patients in whom, at present, large sphenoidal wing meningiomas cause relentless visual loss and gross cosmetic embarrassment.

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