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Non-adenomatous pituitary tumours

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Apart from pituitary adenomas, a number of tumours may arise from within the sella presenting a diagnostic and therapeutic challenge at a multidisciplinary specialist level. This article focusses on the most commonly diagnosed non-adenomatous pituitary tumours (craniopharyngiomas, Rathke's cleft cysts and meningiomas) and provides data on their pathogenesis, diagnosis and treatment.

Apart from pituitary adenomas, a number of tumours may arise from within the sella presenting a diagnostic and therapeutic challenge at a multidisciplinary specialist level. This article focuses on the most commonly diagnosed non-adenomatous pituitary tumours (craniopharyngiomas, Rathke's cleft cysts and meningiomas). Other non-adenomatous pituitary tumours are shown in Table 1.

Craniopharyngiomas

Epidemiology

Craniopharyngiomas are tumours with an incidence of 0.13 cases per 100 000 person-years.[1] They account for 2–5% of all the primary intracranial neoplasms[2] and 5.6–15% of the intracranial tumours in children.[3–6] They may be detected at any age including the pre- and neonatal periods[7,8], and a bimodal age distribution has been proposed, with peak incidence rates in children 5–14 years old and adults 50–74 years old.[1] In population-based studies from USA and Finland, no gender differences have been found.[1,9]

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Table 1
Non-adenomatous pituitary tumours.

Tumour
Craniopharyngioma
Rathke's cleft cyst
Meningioma
Glioma
Germ cell tumour
Lymphoma/Leukaemia
Metastases
Chordoma
Chondrosarcoma
Haemangiopericytoma
Langerhans cell histiocytosis
Epidermoid/dermoid
Hamartoma
Paraganglioma
Schwannoma/neurinoma
Granular cell tumour
Ganglion cell tumour
Arachnoid cyst

Pathogenesis

Craniopharyngiomas are epithelial tumours arising along the path of the craniopharyngeal duct, the canal connecting the stomodeal ectoderm with the evaginated Rathke's pouch. Their pathogenesis is uncertain; neoplastic transformation of embryonic squamous cell rests of the involuted craniopharyngeal duct or metaplasia of adenohypophyseal cells in the pituitary stalk or gland are the proposed theories.[10] Beta-catenin gene mutations have been identified in the adamantinomatous subtype affecting exon 3, which encodes the degradation targeting box of beta-catenin; this is compatible with an accumulation of nuclear beta-catenin protein (a transcriptional activator of the Wnt signalling pathway). Strong beta-catenin expression has been shown in the adamantinomatous subtype indicating reactivation of the Wnt signalling pathway, which is implicated in the development of several neoplasms.[11,12]

Pathology

Craniopharyngiomas are grade I tumours, according to the World Health Organization (WHO) classification. Rare cases of malignant transformation (possibly triggered by previous irradiation) have been described.[13,14] Two main pathological subtypes have been reported – the adamantinomatous and the papillary – but transitional or mixed forms have also been described.[10,15]

The adamantinomatous type is the most common subtype and may occur at all ages but predominantly affects young subjects during their first two decades of life. It bears similarity with the adamantinoma of the jaw[16] and the calcifying odontogenic cyst[17], raising the possibility that this variant may arise from embryonic rests with enamel organ potential. Macroscopically, they have cystic and/or solid components, necrotic debris, fibrous tissue and calcification. The cysts may be multiloculated and contain liquid ranging from machinery oil to shimmering cholesterol-laden fluid consisting of desquamated squamous epithelial cells, rich in membrane lipids and cytoskeleton keratin. They tend to have sharp and irregular margins, often merging into a peripheral zone of dense reactive gliosis, with abundant Rosenthal fibre formation (consisting of irregular masses of granular deposits within astrocytic processes) in the surrounding brain tissue and the vascular structures. The epithelium of the adamantinomatous type is composed of three layers of cells: a distinct palisaded basal layer of small cells with darkly staining nuclei and little cytoplasm (somewhat resembling the basal cells of the epidermis of the skin), an intermediate layer of variable thickness composed of loose aggregates of stellate cells (termed 'stellate reticulum'), whose processes traverse empty intercellular spaces and

a top layer facing into the cyst lumen with abruptly enlarged, flattened and keratinised to flat plate-like squamous cells (Fig. 1). The flat squames are desquamated singly or in distinctive stacked clusters and form nodules of 'wet' keratin, which are often heavily calcified and appear grossly as white flecks. The keratinous debris may elicit an inflammatory and foreign-body giant cell reaction. The presence of the typical adamantinomatous epithelium or of the 'wet' keratin alone is diagnostic, whereas features only suggestive of the diagnosis in small or non-representative specimens include fibrohistiocytic reaction, necrotic debris, calcification and cholesterol clefts.[10,15]

The papillary variety has been almost exclusively described in adult populations (accounting for 14–50% of the adult cases and up to 2% of the paediatric ones).[18,19] Calcification is rare and the cyst content is usually viscous and yellow. It is generally well circumscribed and infiltration of adjacent brain tissue by neoplastic epithelium is less frequent than in the adamantinomatous type. It consists of mature squamous epithelium forming pseudopapillae and of an anastomosing fibrovascular stroma without the presence of peripheral palisading of cells or stellate reticulin (Fig. 2). The differential diagnosis between a papillary craniopharyngioma and a Rathke's cleft cyst may be difficult, particularly in small biopsy specimens, as the epithelial lining of the Rathke's cysts may undergo squamous differentiation; however, the lack of a solid component and the presence of extensive ciliation and/or mucin production are suggestive of Rathke's.[10,15,18,19]

Location/imaging

Most of the craniopharyngiomas are located in the sellar/parasellar region. The majority (94–95%) has a suprasellar component (purely suprasellar 20–41%/both supra- and intrasellar 53–75%), whereas the purely intrasellar ones represent the least common variety (5–6%).[10,20] Other rare locations include the nasopharynx, the paranasal area, the sphenoid bone, the ethmoid sinus, the intrachiasmatic area, the temporal lobe, the pineal gland, the posterior cranial fossa, the cerebellopontine angle, the midportion of the midbrain or completely within the third ventricle.[10]

Imaging tools for the diagnosis of craniopharyngiomas include plain skull X-rays, computed tomography (CT), magnetic resonance imaging (MRI) and, occasionally, cerebral angiography. Plain skull X-rays, although seldom used nowadays, may show calcification and abnormal sella.[10] CT is helpful for the evaluation of the bony anatomy, the identification of calcifications and the discrimination of the solid and the cystic components; they are usually of mixed attenuation – the cyst fluid has

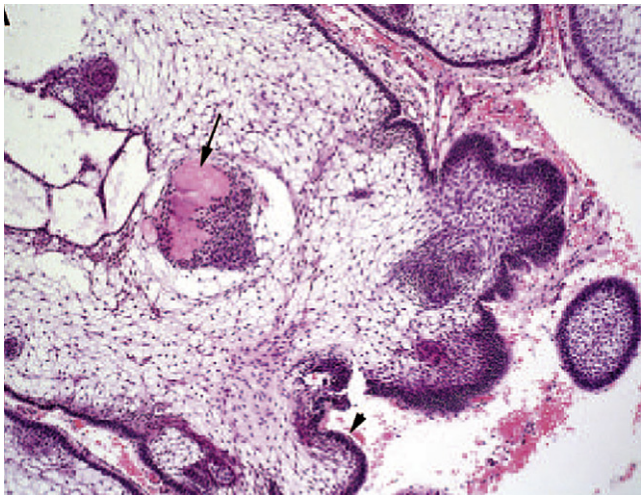

Fig. 1. Adamantinomatous craniopharyngioma. The epithelium consists of palisaded basal layer of cells (*arrowhead*), the intermediate stellate reticulum, and a layer of flattened, keratinized squamous cells. Nodules of "wet" keratin (*arrow*) are a distinctive feature (HE.×10) (from Ref. 10, *Copyright 2006, The Endocrine Society,* with permission).

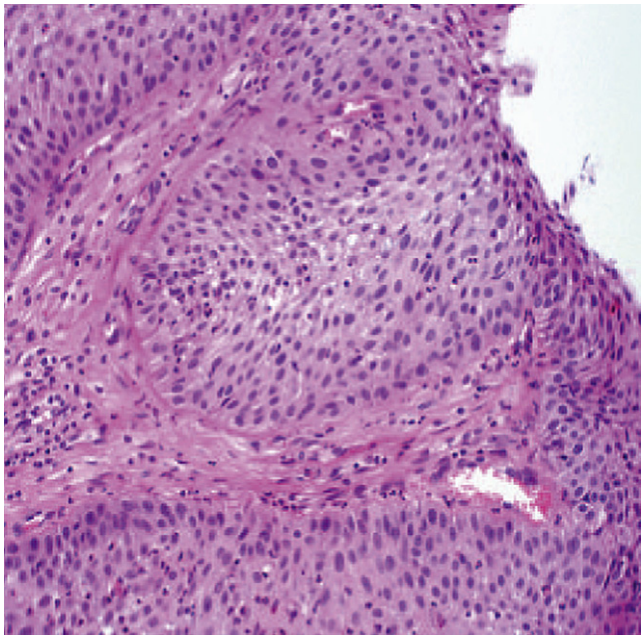

Fig. 2. Papillary craniopharyngioma. The characteristic epithelium in this histological type consists of mature squamous epithelium forming pseudopapillae downward into the underlying tissues. The absence of adamantinomatous epithelium and keratinizing nodules is characteristic (HE.×20) (from Ref. 10, *Copyright 2006, The Endocrine Society,* with permission).

low density and the contrast medium enhances any solid portion, as well as the cyst capsule.[21] (Fig. 3). The MRI is particularly useful for the topographic and structural analysis of the tumour. The appearance of the craniopharyngioma depends on the proportion of the solid and cystic components, the content of the cyst(s) (cholesterol, keratin and haemorrhage) and the amount of calcification present. A solid lesion appears as iso- or hypointense relative to the brain on pre-contrast T_1-weighted images (WIs), shows enhancement following gadolinium administration and is usually of mixed hypo- or

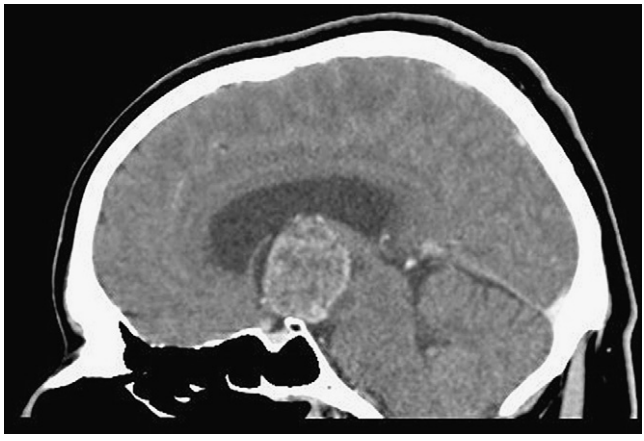

Fig. 3. Craniopharyngioma extending in the suprasellar area associated with mass effect on the third ventricle and hypothalamus. The lesion shows a multicystic appearance with calcifications and a marked inhomogeneous enhancement.

hyperintensity on T_2-weighted sequences (Fig. 4). Large amounts of calcification may be visualised as areas of low signal on both T_1- and T_2-WIs. A cystic element is usually hypointense on T_1- and hyperintense on T_2-weighted sequences. On T_1-WIs, a thin peripheral contrast-enhancing rim of the cyst is demonstrated. Protein, cholesterol and methaemoglobin may cause high signal on T_1-WIs, while very concentrated protein and various blood products may be associated with low T_2-weighted signal.[10,21,22]

The size of craniopharyngiomas has been reported >4 cm in 14–20% of the cases, 2–4 cm in 58–76% and <2 cm in 4–28%.[18,23] Their consistency is purely or predominantly cystic in 46–64%, purely or predominantly solid in 18–39% and mixed in 8–36%.[10] Calcification has been demonstrated in 45–57% and is probably more common in children (78–100%). The calcification patterns vary from solid lumps to popcorn-like foci or less commonly, to an eggshell pattern lining the cyst wall.[21] Hydrocephalus has been reported in 20–38% and is probably more frequent in childhood diagnosed disease (41–54%).[10] There is no agreement on the radiological features discriminating the two histological subtypes.[10] The differential diagnosis includes a number of sellar or parasellar lesions, including Rathke's cleft cyst, dermoid cyst, epidermoid cyst, pituitary adenoma, germinoma, hamartoma, suprasellar aneurysm, arachnoid cyst, suprasellar abscess, glioma, meningioma, sacroidosis, tuberculosis and Langerhans cell histiocytosis. Differention from a Rathke's cleft cyst (typically small, round, purely cystic lesion lacking calcification), or from a pituitary adenoma (in the rare case of a homogenously enhancing solid craniopharyngioma) may be particularly difficult.

Presenting manifestations

The potential proximity to, and the subsequent pressure effects of craniopharyngiomas on vital structures of the brain (visual pathways, brain parenchyma, ventricular system, major blood vessels and hypothalamo-pituitary system) predispose the patients to multiple clinical manifestations, the severity of which depends on the location, the size and the growth potential of the tumour.[18,20,23–26]

The duration of the symptoms until diagnosis ranges between 1 week and 372 months.[20,25–30] The commonest presenting clinical manifestations are neurological, visual and hypothalamo-pituitary; headaches, nausea/vomiting, visual disturbances, growth failure (in children) and hypogonadism

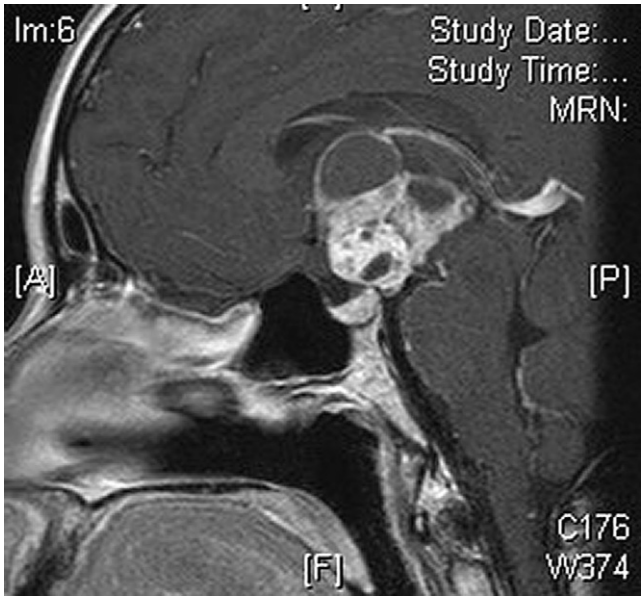

Fig. 4. Suprasellar craniopharyngioma with cyst formation and areas of enhancement following gadolinium administration.

(in adults) are the most frequently reported.[10] A summary of the results of various studies, in which however, different diagnostic tests and criteria have been adopted, shows that growth hormone (GH) deficiency is present in 35–95% of the evaluated patients, follicle-stimulating hormone/luteinising hormone (FSH/LH) deficiency in 38–82%, adrenocorticotrophic hormone (ACTH) deficiency in 21–62%, thyroid-stimulating hormone (TSH) deficiency in 21–42% and diabetes insipidus (DI) in 6–38%.[10]

Treatment

Surgical removal combined or not with external beam irradiation

Craniopharyngiomas are a significant neurosurgical challenge, as their often large size, sharp and irregular margins and adherence to vital neurovascular structures do not allow a clear line of cleavage, and thus, make complete resection difficult and potentially hazardous to critical brain areas. The attempted extent of excision has been a subject of significant debate and depends on the size[18,23,31,32] and location of the tumour[23,26,32], the presence of hydrocephalus[23,31], of >10% calcification[23] and of brain invasion[26] as well as on the experience, the individual judgement during the operation and the general treatment policy (aggressive or not) adopted by each neurosurgeon. The perioperative morbidity ranges between 1.7% and 5.4% for primary operations.[10,20,23,25] Recurrent tumours may arise even from small islets of craniopharyngioma cells in the gliotic brain adjacent to the tumour, which can remain even after gross total resection. The mean interval for their diagnosis after various primary treatment approaches ranges between 1 and 4.3 years and relapses as late as 36 years after initial therapy has been reported.[10] Series with radiological confirmation of the extent of resection show recurrence rates following gross total removal between 0% and 62% at 10 years follow-up. These are significantly lower than those reported after partial or subtotal resection (25–100% at 10 years follow-up). In cases of limited surgery, adjuvant radiotherapy (RT) improves significantly the local control (recurrence rates 10–63% at 10 years follow-up). Series with statistical comparisons of the recurrences achieved by gross total removal or combination of surgery and radiotherapy have not provided consistent results. Finally, radiotherapy alone, which however, can be offered to selected tumours, provides 10 years recurrence rates ranging between 0% and 23%.[20,23,25,26,31,33–38] In cases of predominantly cystic tumours, fluid aspiration provides relief of the obstructive manifestations and facilitates the removal of the solid tumour portion; the latter should not be delayed, as there is significant risk of cyst refilling (reported in up to 81% of the cases at a median period of 10 months).[20,23]

It has been suggested that the tumour control correlates with the irradiation dose and doses ≤5400 cGy are associated with poorer outcome.[39] The growth rate of craniopharyngiomas varies considerably and reliable clinical, radiological and pathological criteria predicting their behaviour are lacking. Thus, apart from significant impact of the treatment modality, attempts to identify other prognostic factors (age group at diagnosis, sex, imaging features, pathological subtypes and immunoreactivity of the tumour proliferation marker MIB-1) have not provided consistent results.[10]

The management of recurrent tumours remains difficult, as scarring/adhesions from previous surgeries or irradiation decrease the chance of successful excision. In such cases, total removal is achieved in a significantly lower rate compared with primary surgery (0–25%) and is associated with increased perioperative morbidity and mortality (10.5–24%).[20,23,26,40] The beneficial effect of radiotherapy (preceded or not by second surgery) in recurrent lesions has been clearly shown.[10,20,38,41]

Other treatment options

Intracavitary irradiation (brachytherapy) is a minimally invasive approach involving stereotactically guided instillation of beta-emitting isotopes into cystic craniopharyngiomas. It delivers higher radiation dose to the cyst lining than the one offered by external beam radiotherapy and it causes destruction of the secretory epithelial lining, elimination of the fluid production and cyst shrinkage.[42] A number of beta- and gamma-emitting isotopes (mainly ^{32}phosphate, ^{90}yttrium, ^{186}rhenium and ^{198}gold) have been used; as none of them has the ideal physical and biological profile (i.e. pure beta emitter with short half-life and with tissue penetrance limited to cover only the cyst wall), there is no consensus on which is the most suitable therapeutic agent. Based on studies with the largest series of patients and with relatively long follow-up periods, intracavitary irradiation seems to offer a good prospect for the reduction/stabilisation of cystic craniopharyngiomas. This, combined with its reported

low surgical morbidity and mortality, renders intracavitary irradiation an attractive option for predominantly cystic tumours, particularly the monocystic ones. Its impact on the quality of survival and long-term morbidity (particularly vision, neuroendocrine and cognitive function) remains to be assessed.[10,43–45] The intracystic installation of the anti-neoplasmatic agent bleomycin has been proposed for the management of cystic tumours. The small number of published series (based mostly on limited number of patients and with variable total doses and time intervals between repeated instillations) show tumour control rates between 0% and 100%.[46–48] Direct leakage of the drug to surrounding tissues during the installation procedure, diffusion though the cyst wall or high drug dose have been associated with various toxic (hypothalamic damage, blindness, hearing loss, ischaemic attacks and peritumoural oedema) or even fatal effects.[10] The value of this treatment option in the tumour control or even in the delaying of potentially harmful surgery and/or radiotherapy, as well as the optimal protocol and the clear-cut criteria predicting the long-term outcome remain to be established in large series with appropriate follow-up.

Stereotactic radiosurgery delivers a single fraction of high-dose ionising radiation on precisely mapped targets keeping the exposure of adjacent structures to a minimum. Tumour volume and close attachment to critical structures are limiting factors for its application with 10 Gy and 15 Gy being the maximum tolerated doses to the optic apparatus and the other cranial nerves, respectively. Published studies suggest that it achieves control of primary or recurrent tumour in a substantial number of patients with small volume lesions (complete/partial resolution: 67–90%).[49–51] Stereotactic radiosurgery may be particularly useful for well-defined residual disease following surgery or for the treatment of small, solid, recurrent tumours, particularly after failure of the conventional radiotherapy. In cases of large cystic portions, multimodality approaches with instillation of radioisotopes or bleomycin may offer further benefits.[10,52] Studies with long-term follow-up evaluating the optimal marginal dose, its role in the prevention of tumour growth and its effects on the neurocognitive and neuroendocrine functions are required.

Long-term outcome after surgery and conventional external beam irradiation

Morbidity

The long-term morbidity of patients with craniopharyngiomas mainly involves endocrine, visual, hypothalamic, neurobehavioural and cognitive sequelae, which compromise psychosocial integration and quality of living. These complications are attributed to the damage of critical neuronal structures by the primary or recurrent tumour and/or to the adverse effects of the therapeutic interventions. Notably, the severity of the radiation-induced late toxicity is associated with the total and per fraction doses, the volume of the exposed normal tissue and the young age in childhood populations.[53–55]

In series including subjects with various treatment modalities and follow-up periods, the frequency of pituitary hormone deficits ranges between 88% and 100% for GH, 80% and 95% for FSH/LH, 55% and 88% for ACTH, 39% and 95% for TSH and 25% and 86% for antidiuretic hormone (ADH).[10] Compromised vision has been reported in up to 62.5% of the patients treated by surgery, combined or not with radiotherapy during an observation period of 10 years. The visual outcome is adversely affected by the presence of visual symptoms at diagnosis and by daily irradiation doses above 2 Gy.[56,57]

Hypothalamic damage may result in hyperphagia and uncontrollable obesity, disorders of thirst and water/electrolyte balance, behavioural and cognitive impairment, loss of temperature control and disorders in the sleep pattern.[10] Obesity is the most frequent manifestation affecting 26–61% of the patients treated by surgery combined or not with radiotherapy and it is a consequence of the disruption of the mechanisms controlling satiety, hunger and energy balance.[20,25,38,58] Factors associated with significant hypothalamic morbidity have been proposed to be young age at presentation in children, manifestations of hypothalamic disturbance at diagnosis, hypothalamic invasion, tumour height greater than 3.5 cm from the midline, attempts to remove adherent tumour from the region of hypothalamus, multiple operations for recurrence and hypothalamic radiation doses $>$51 Gy.[10]

The compromised neuropsychological and cognitive function in patients with craniopharyngioma contributes significantly to poor academic and work performance, disrupted family and social relationships and impaired quality of life. In a series of 121 patients treated by surgery with or without adjuvant radiotherapy and followed-up for a mean period of 10 years, 40% had poor outcome

(the assessment was based on motor and visual deficits, dependence for activities of daily living, Karnofsky Performance Scale, school and work status and debilitating psychological or emotional problems).[25] Karavitaki et al.[20] in a series of 121 patients treated by surgery with or without RT, found cumulative probabilities for permanent motor deficits, epilepsy, psychological disorders necessitating treatment and complete dependency for basal daily activities at 10 years follow-up of 11%, 12%, 15% and 9%, respectively. At the same time period, almost one-fourth of the adults or children were unable to work in their previous occupation or were behind their expected school status. It has also been shown that the mean morbidity scores (based on endocrine deficiencies, vision, motor disorders and epilepsy, learning difficulties, behavioural problems, intelligence quotient (IQ) and hypothalamic dysfunction) of children with additional surgery for recurrence were higher than the ones after their initial surgery and higher than those of children without recurrence.[31] There is no consensus on the therapeutic option with the least adverse impact on the neurobehavioural outcome necessitating prospective studies with formal neuropsychological testing and specific behavioural assessment prior and after any intervention.

Mortality

The overall mortality rates of patients with craniopharyngioma have been reported to be 3–6 times higher than that of the general population with survival rates ranging between 83% and 92.7% at 10 years.[10] Apart from the deaths directly attributed to the tumour (pressure effects to critical structures) and to the surgical interventions, the risk of cardio-/cerebrovascular and respiratory mortality is increased.[20,23,59,60] Furthermore, in childhood populations, the hypoadrenalism and the associated hypoglycaemia as well as the metabolic consequences of ADH deficiency and absent thirst may contribute to the excessive mortality.[38,61] The impact of tumour recurrence on long-term mortality is widely accepted and the 10-year survival rates in such cases range between 29% and 70% (depending on the subsequent treatment modalities).[20,62]

Treatment algorithm

A clear consensus on the best therapeutic approach of primary or recurrent craniopharyngiomas has not been established as yet. Based on the published data, the proposed treatment algorithm is shown in Fig. 5.

Rathke's cleft cysts

Rathke's cleft cysts are benign sellar and/or suprasellar lesions found in 13–33% of routine autopsies.[63,64] The dominant hypothesis on their pathogenesis suggests that they arise from remnants of the Rathke's pouch (a structure apparent during the third week of gestation, formed by the infolding of simple ciliated columnar epithelium lining the roof of the stomodeum and giving rise to the anterior and intermediate lobes of the pituitary gland).[65,66]

Rathke's cleft cysts are smoothly marginated cysts usually ranging between a few millimetres and 1–2 cm; cases with size up to 45–50 mm have also been reported. Their contents vary from clear CSF-like fluid to thick mucoid (consisting of cholesterol and protein) material.[63,67–69] They are lined by single or pseudo-stratified cuboidal or columnar epithelium with or without cilia and with goblet cells. Squamous metaplasia (posing difficulty in the differential diagnosis from craniopharyngiomas) with cholesterol clefts and eosinophilic amorphous material, macrophages and lymphocytes has also been described.[70–72] Intracystic nodules of mucinous material may also be present.[63]

The symptomatic cases are rare[67] and are associated with pressure effects to adjacent structures. The most frequent presenting manifestations include headaches (49–81%), hypopituitarism of varying degrees (24–88%), hyperprolactinaemia (19–77%), visual disturbance (38–47%), and diabetes insipidus (11%).[64,71–73] Rarely, aseptic meningitis or haemorrhage into the cyst may occur.[74] Cases with co-existent pituitary adenoma have been reported.[75]

Their imaging features vary and the neuroimaging diagnosis may be difficult. Forty per cent are completely intrasellar. Although 60% have some suprasellar extension, the entirely suprasellar cases are rare.[63,71] On CT, the cyst density ranges from hypodense, to isodense or to mixed.[67,71] On MR

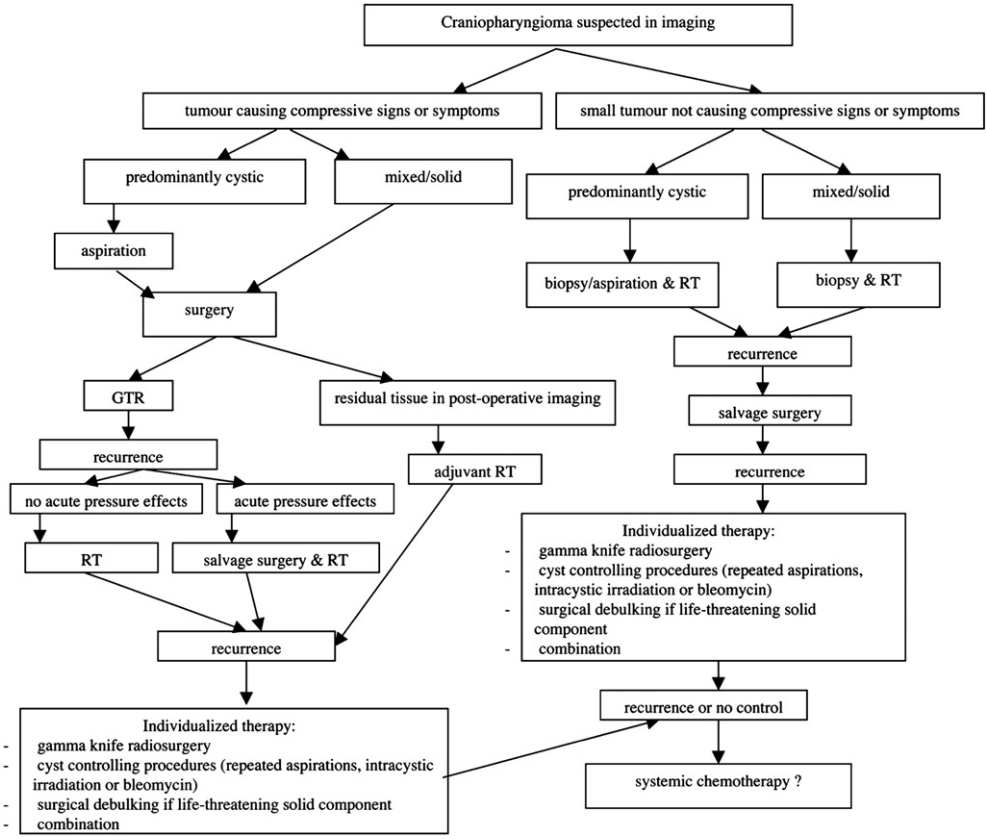

Fig. 5. Treatment algorithm for craniopharyngiomas (from Ref. 10, *Copyright 2006, The Endocrine Society,* with permission).

imaging, they have a variable T_1 signal (hyper-, hypo- or isointense) depending on their content; thus, on T_1 images, approximately half are hyperintense and half hypointense, whereas on T_2 images, 70% are hyperintense and 30% iso- or hypointense (Fig. 6). Cysts with high protein concentration show high T_1 signal intensity and usually have a low intracystic water content leading to T_2 signal decrease.[63,71] Rim enhancement may be seen in a small number of cases and has been attributed to changes due to squamous metaplasia, inflammation or deposition of haemosiderin or cholesterol crystals in the cyst wall.[64,72] Rim enhancement may be also present when a circumscribed area of pituitary tissue is present peripheral to the cyst.[72] Small intracystic nodules corresponding to proteinaceous concentrations may be demonstrated presenting with lower T_2 and higher T_1 signal intensity than the rest of the cyst. The nodules do not enhance and are virtually pathognomonic for the Rathke's cleft cysts.[63] The differential diagnosis includes craniopharyngiomas (typically showing calcification, may be multilobulated or with an irregular shape or rim enhancement, demonstrating heterogeneous or strong homogeneous enhancement as well as solid enhancing nodules in the cyst), cystic pituitary adenoma or other non-neoplastic cysts.[63]

The symptomatic cases are managed by surgery (mostly through the transsphenoidal route).[64] The endocrine outcome following surgery remains poor, as the reversal of pituitary deficits is not common.[64,71] The risk of recurrence following evacuation and biopsy ranges between 8% and 33%.[64,67,72,73] Although not widely accepted, the extent of removal (gross total vs. partial) may predict relapse.[64] Radiotherapy is not routinely used in their primary treatment and apart from a few reported cases of external beam irradiation offered in recurrent cysts[67], its role in preventing further recurrence is unclear.

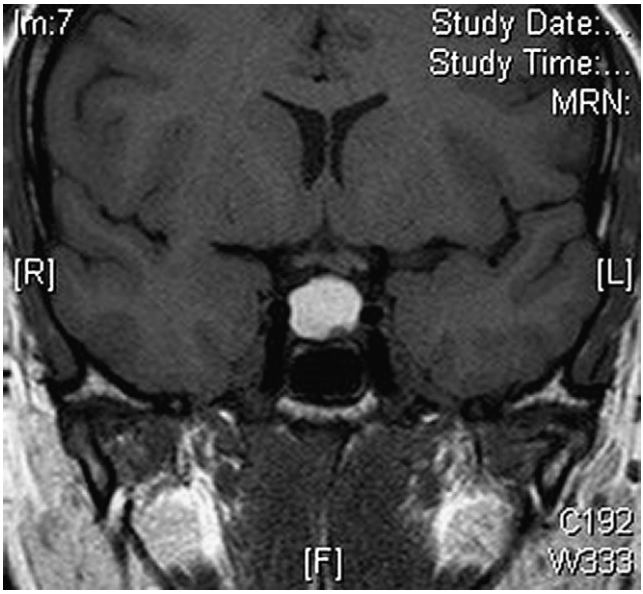

Fig. 6. Rathke's cleft cyst with high signal intensity and suprasellar extension.

Meningiomas

Meningiomas are WHO grade I tumours arising from arachnoid cells. They have an annual incidence of six cases per 100 000 population.[76] and are the most common benign intracranial tumour accounting for 13–26% of all primary intracranial tumours.[77] They can arise from the dura at any site, most commonly the skull vault, from the skull base and at sites of dural reflections.[78]

Macroscopically, they are usually well-circumscribed masses with a lobular architecture. Occasionally, they may grow in a more diffuse pattern over the dura. Their histological grading is based on the current WHO classification; around 90% are WHO grade I, 5–7% are atypical meningiomas (WHO grade II) and 1–3% are anaplastic variants (WHO grade III).[78] The mechanisms involved in their molecular pathogenesis and in their malignant progression are not clear. Notably, gene expression profiling with microarrays has enabled differentiation of WHO grade I from grade II and III tumours and has confirmed altered expression of growth-hormone receptor, insulin-like growth factor II, insulin-like growth-factor binding protein 7 and endothelin receptor A.[79]

Their presenting manifestations are attributed to compression of adjacent structures and are usually visual disturbances and pituitary dysfunction. Notably, they may increase in size during pregnancy.

MRI is the most helpful imaging modality for the detection of meningiomas. They are isointense on T_1. Forty per cent are hyperintense on T_2WI. They show homogeneous, intense enhancement after contrast (Fig. 7) and a linear, enhancing dural tail extending away from the lesion.[80] CT is complementary in diagnosis by demonstrating intratumoural calcification, hyperostosis and expansion of the sphenoid sinus (pneumosinus dilatans) that may sometimes be associated with meningiomas.[80]

Their management depends on the presenting manifestations, the age of the patient and their site and size.[78] Asymptomatic meningiomas can be managed conservatively with regular imaging.[81] Surgery is the treatment of choice for symptomatic or growing lesions. The main factors predicting recurrence and survival are extent of resection and tumour grade.[82–84] The reported 10-year recurrence rates are 25% following gross total resection and 61% following less than total resection.[82] Furthermore, patients with not-completely-resected tumours have a 4.2-fold relative excess risk of death compared with those who had complete removal; and patients with malignant tumours have a 4.6-fold excess

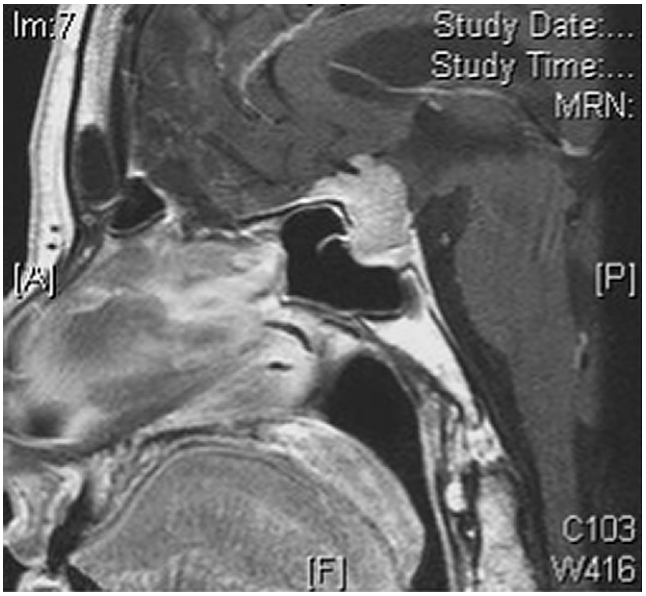

Fig. 7. Intra- and suprasellar meningioma displacing the optic chiasm showing intense enhancement after contrast administration.

mortality compared with those with benign lesions.[83] The beneficial effect of radiotherapy has been reported after incomplete resection, following recurrence, and when tumour histology has shown atypia or anaplasia.[78] Retrospective studies of patients with cavernous sinus or benign skull base meningiomas have shown that external beam radiotherapy alone or following subtotal resection is associated with 10-year progression-free survival rates between 83% and 93%.[85–87] Stereotactic radiotherapy has proved safe and efficacious for skull-base meningiomas with progression-free survival rates of 97% and 93% at 3 and 4 years follow-up, respectively.[88,89] In the late 1980s, stereotactic radiosurgery emerged as an alternative option to surgery for patients with cavernous sinus meningiomas with a number of reports showing high tumour control rates (73–93% at 10 years follow-up).[90,91] Finally, it has been proposed that mifepristone, a progesterone and glucocorticoid receptor antagonist, has provided benefit (improvement in visual fields or on imaging features) in 29% of patients with unresectable meningioma[92]; further studies are required to assess the place of this agent in the management of meningiomas.

To summarise, this article focussed on the most commonly diagnosed non-adenomatous pituitary tumours (craniopharyngiomas, Rathke's cleft cysts and meningiomas).

Craniopharyngiomas are rare tumours diagnosed during childhood or adult life and associated with significant morbidity and mortality. Despite their benign histological appearance, they may have an unpredictable growth pattern, which, combined with the lack of randomised trials, makes the establishment of an optimal therapeutic protocol difficult. Currently, surgical removal followed by external beam irradiation, in cases of residual tumour, is the main treatment option. Apart from the type of primary treatment, the identification of clinical, imaging, pathological and molecular parameters predicting patients with a better prognosis is problematic. The central registration of patients with these challenging tumours may provide correlates between therapies and outcomes that may further guide us in the future.

Rathke's cleft cysts are benign lesions found in 13–33% of routine autopsies. The symptomatic cases are rare and are managed by surgery.

The management of meningiomas depends on the presenting manifestations, the age of the patient and their site and size. The main factors predicting recurrence and survival are extent of resection and tumour grade. The beneficial effect of radiotherapy has been reported after incomplete resection,

following recurrence, and when tumour histology has shown atypia or anaplasia. The mechanisms involved in their molecular pathogenesis and in their malignant progression need to be clarified.

Practice points

- Craniopharyngiomas are epithelial tumours associated with significant morbidity and mortality; apart from the impact of the type of primary treatment, reliable clinical, radiological and pathological criteria predicting their behaviour are lacking.
- Adjuvant radiotherapy following partial removal of a craniopharyngioma reduces the recurrence rates significantly.
- The symptomatic cases of Rathke's cleft cysts are rare and the risk of recurrence following evacuation and biopsy ranges between 8% and 33%.
- In meningiomas, the main factors predicting recurrence and survival are the extent of resection and tumour grade with radiotherapy following incomplete resection improving the outcome.

Research agenda

- In craniopharyngiomas, the identification of parameters designating patients with a better prognosis and the establishment of prognostic factors at the pathological or molecular level are needed.
- Trials fully assessing the impact of novel or improved therapeutic modalities in subjects with craniopharyngioma are required.
- Further research on the pathophysiology and management of hypothalamic obesity is mandatory, in order to improve the long-term prognosis of patients with craniopharyngioma.
- The mechanisms involved in the molecular pathogenesis and in the malignant progression of meningiomas need to be clarified.

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