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Chapter 8

Modern Management of Craniopharyngioma

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Abstract

Craniopharyngiomas (CPs) have had a prominent place in neurosurgery due to both the technical difficulty and controversy regarding the optimal treatment of these benign tumors. Harvey Cushing famously described craniopharyngiomas in 1936 as "the most forbidding of the intracranial tumors." Seventy years later, Rutka still wrote: "There is no other primary brain tumor that evokes more passion, emotion, and as a result, controversy than does the CP." Craniopharyngiomas comprise 1–2% of all brain tumors and occur in a bimodal distribution, with 40% of cases occurring between age 5–15 years and 60% occurring at ages >55 years. The differential diagnosis for craniopharyngioma can include a variety of entities, including pituitary macroadenoma, metastasis, Rathke's cleft cyst, colloid cyst, glioma, meningioma, germinoma, abscess, sarcoid, or aneurysm. Imaging characteristics usually include a solid cystic lesion, speckled with calcifications in 50–80% of craniopharyngiomas (especially pediatric patients), as well a presentation with hypopituitarism and diabetes insipidus, which influence clinical thinking toward establishing this diagnosis.

Keywords: craniopharyngioma, endoscopic, radiation, QOL, molecular

1. Clinical case vignette

A 42-year-old woman presented, as a transfer from an outside hospital, with increased forgetfulness, fatigue, as well as intermittent double vision leading to accidents. In addition, she complained of increased thirst and urination. She was concurrently taking lithium and lorazepam for psychiatric reasons. Imaging with CT revealed a large suprasellar mass extending into the third ventricle (**Figure 1**). The patient had laboratory studies performed (**Table 1**) and underwent a formal ophthalmology examination, which revealed red desaturation and a depressed visual field consistent with compressive optic neuropathy.

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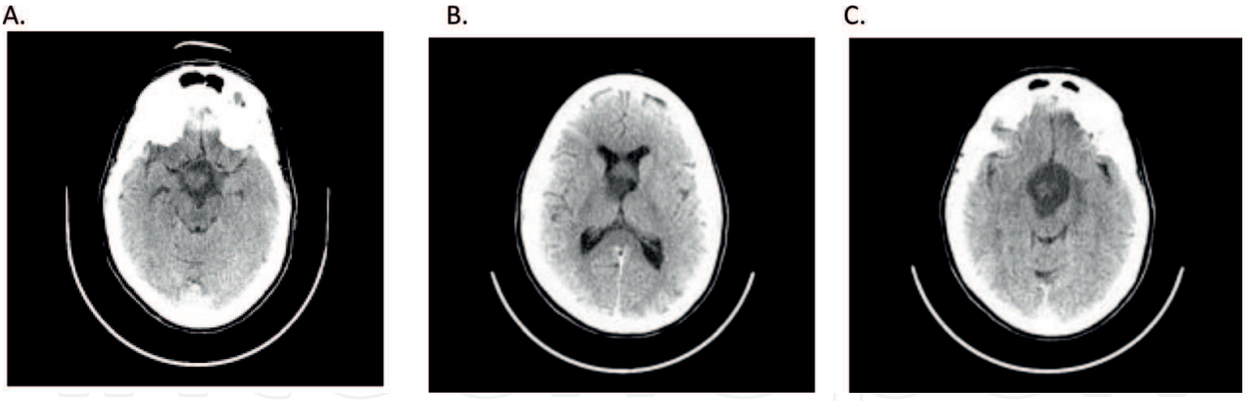


Figure 1. A–C. 4.0 × 3.3 × 4.0 cm, suprasellar mass with cystic and solid components extending into the third ventricle. No calcifications or hydrocephalus is seen.

Laboratory study	Result
Urine specific gravity	1.020
Prolactin	13
Thyroid function tests	TSH 0.17, T_4 4.9, T_3 71, Free T_4 0.8
Luteinizing hormone	< 0.1
Follicle stimulating hormone	< 0.1
IGF-1	201

Table 1. Patient's laboratory findings.

2. Overview

Craniopharyngiomas (CPs) have had a prominent place in neurosurgery due to both the technical difficulty and controversy regarding the optimal treatment of these benign tumors. Harvey Cushing famously described craniopharyngiomas in 1936 as "the most forbidding of the intracranial tumors." Seventy years later, Rutka still wrote: "There is no other primary brain tumor that evokes more passion, emotion, and as a result, controversy than does the CP" [1]. Craniopharyngiomas comprise 1–2% of all brain tumors and occur in a bimodal distribution, with 40% of cases occurring between age 5–15 years and 60% occurring at ages >55 years.

The differential diagnosis for craniopharyngioma can include a variety of entities, including pituitary macroadenoma, metastasis, Rathke's cleft cyst, colloid cyst, glioma, meningioma, germinoma, abscess, sarcoid, or aneurysm. Imaging characteristics usually include a solid cystic lesion, speckled with calcifications in 50–80% of craniopharyngiomas (especially pediatric patients), as well a presentation with hypopituitarism and diabetes insipidus, which influence clinical thinking toward establishing this diagnosis.

3. Subtypes of craniopharyngioma

Craniopharyngiomas are benign lesions which arise from the neuroepithelium in the sellar region. They are classically subdivided into two distinct entities based on both genetic and morphologic differences. Adamantinomatous CP (aCP), primarily seen in childhood, occurs more commonly than papillary CP (pCP), which is more often seen in adults [2]. In histologic sections, adamantinomatous CP is poorly circumscribed, often multi-cystic and calcified, and is associated with β-catenin and epidermal growth factor receptor (EGFR) overexpression. Papillary CP, on the other hand, is well-circumscribed, less calcified, characterized by solid components, and displays less adherence to surrounding structures [2]. Furthermore, pCP is made up of fibrovascular stroma lined by well-differentiated squamous epithelium [2, 3].

In terms of histologic appearance, aCP usually shows nests and trabeculae of epithelium in fibrocollagenous stroma, with peripheral cells showing nuclear palisading, loose central cells termed "stellate reticulum," and abundant keratin, cholesterol crystals, necrosis, and inflammation. Papillary CP is well circumscribed, composed of the cores of fibrovascular stroma lined by well-differentiated squamous epithelium that may separate to form pseudopapillae which resembles squamous papilloma and without xanthogranulomatous inflammation. In molecular staining of these tumors, the lack of expression of CK8 and CK20 keratin suggests a craniopharyngioma, which differentiates them from Rathke's cleft cyst or pituitary pars intermedia. More recently, VE1 staining has also been utilized to identify BRAF mutations which can help to differentiate between Rathke's cleft cyst and craniopharyngioma [4].

4. Origin of craniopharyngioma

Craniopharyngiomas were long thought to arise as an embryonic malformation from the anterior superior margin of the pituitary from residual Rathke's pouch. Due to their embryonic origin, they may even co-opt the blood supply of the wall and floor of the ventricle. More modern studies have demonstrated that aCP can arise due to paracrine actives of β-Catenin mutated cells, whereas pCP can arise via metaplastic transformation [2].

5. Clinical presentation

A triad of symptoms, involving visual impairment, neurological decline, and cognitive compromise, is generally seen in patients presenting with CP. The extent of morbidity associated with CP is closely related to both the specific tumor location and its size. Hypothalamic disease in patients can present as obesity (>50%), diabetes insipidus, thermoregulation disorder, somnolence, sleep apnea, and arrhythmia. Hypothalamic lesions, in particular, are associated with increased rates of neurocognitive decline, and the importance of these neuropsychological issues is evident in that fact that many of these patients continue to report cognitive issues at follow-up, preventing return to previous performance at work or school. Clinically significant hypopituitarism, usually involving several anterior pituitary hormones, occurs in the majority

of patients presenting with CP. In nearly 90% of patients who are present with hypopituitarism in the long term, there is a significantly higher mortality risk related to both cardiovascular and cerebrovascular mortality, with an especially higher risk in females compared to males. The evidence from multiple cohorts of patients suggests that the increased exposure to sex hormones also manifests as cardiovascular risk greater in females compared to males [5].

6. Surgical treatment

Surgical resection of craniopharyngiomas is challenging due a number of different considerations, primary of which is the importance of the surrounding neurovascular structures. Risks of surgery include iatrogenic infarction, damage to the optic chiasm, cerebrospinal fluid (CSF) leak, anosmia, CN III–VI palsies, seizures, and a relatively high rate of incomplete resections and recurrences. Anatomic considerations play an especially important role when assessing the appropriate surgical approach. The location of CP can be described in relation to the optic chiasm, as either prechiasmatic (which displaces the chiasm posteriorly) or retrochiasmatic (which displaces the chiasm anteriorly) [6]. While prior classification schemes designed for transcranial surgery described CP in relation to the optic chiasm and the third ventricle, Kassam et al. developed a novel classification based on the infundibulum which was used for the expanded endoscopic approach. Craniopharyngiomas are grouped as pre-infundibular (Type I), trans-infundibular (Type II), or post-infundibular (Type III) locations and occasionally are located in the intraventricular region only (Type IV) [7]. Major variables that can also affect the outcome in these patients include the tumor configuration, patient's age, and medical comorbidities, as well as the surgeon and center experience and availability of essential facilities such as intra-operative imaging, ICU care, and multidisciplinary medical management under endocrinology and radiation oncology.

The risk of recurrence is significant in patients with CP, especially if gross total resection (GTR) is not achieved. Regardless of improved surgical techniques, post-mortem studies performed by Bartlett et al. demonstrated tumor remnants that can remain attached to vital structures such as the optic chiasm, hypothalamus, and/or critical vascular. These remnants can act as a nidus for tumor growth post-surgery, leading to the relatively high rates of recurrence (about 33% within 36 months of surgery) observed in CP patients [8] (**Figures 2** and **3**).

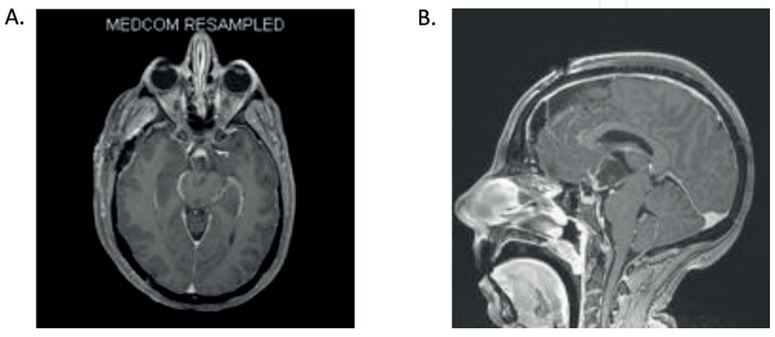


Figure 2. (A) Type IV supra-infundibular craniopharyngioma with intraventricular extension and (B) post-operative MRI demonstrates near-total resection of tumor with the opening of the lamina terminalis.

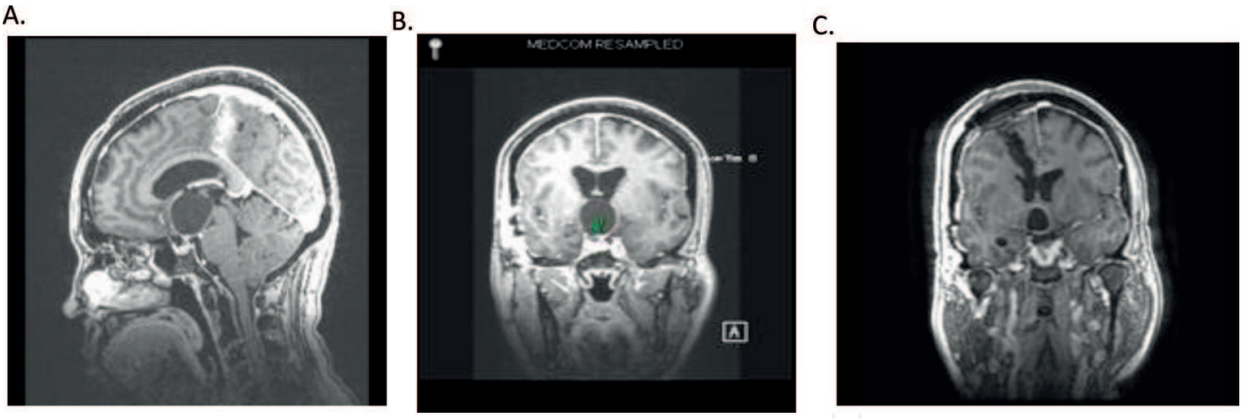


Figure 3. Recurrent cyst at 6 months follow-up. (A) Sagittal and coronal T1; (B) and (C) coronal T1 after transcortical approach involving septostomy with fenestration of the lateral ventricles and third ventriculostomy.

7. Modern case series

Surgical resection can involve an open craniotomy or—alternatively—an endoscopic transnasal approach. A series of open surgical resection employing the frontolateral approach for extensive craniopharyngiomas greater than 4 cm in size reported by Gerganov et al. demonstrated a gross total resection rate (GTR) of 87.5% by microscopic inspection and 62.5% when based on post-operative MRI. Visual improvement was achieved in a significant number of patients (37.5%) in this study. Side effects included new hormonal dysregulation (56.2%) and new diabetes insipidus (75%) [9]. The rate of GTR resection in adults employing this approach is comparable to rates achieved in pediatric patients and compares well with studies employing various other open techniques [10–13]. A complex transpetrosal approach was described by Al-Mefty et al. for CP located in the post-infundibular space [14].

A modern endoscopic series reported by Koutoursiou et al. of 47 adults and 17 children demonstrated comparable GTR, near-total, subtotal, and partial resection rates of 37.5, 34.4, 21.9, and 6.5%, respectively. Major complications reported in this series included CSF leak (23.4% initially and about 10% after the introduction of the modern endonasal flap) and again recurrence rates of 34.4% [15]. An analysis of the reported endoscopic series by Laws et al. found that endoscopic approaches for craniopharyngiomas are suitable especially if tumors are found to have a median intrasellar and subchiasmatic location, with no parasellar solid component and no growth along the pituitary stalk [16]. However, tumors that extend to the optic chiasm and the third ventricle may also be undertaken using the endoscopic approach if performed by experienced teams [17]. For patients requiring re-operation due to recurrence, the endoscopic approach was also shown to be effective, with no significant increase in the rates of complications according to some authors [18]. The endoscopic transsphenoidal approach offers a number of advantages including a surgical view in the axis of the tumor and the optic chiasm. Laws also suggest that while resection of craniopharyngioma is commonly associated with hypopituitarism, the transsphenoidal approach may offer the advantage of the reduced risk of permanent diabetes insipidus [19].

However, the endoscopic approach has certain disadvantages in that it is not well suited for masses that are postchiasmatic or for lesions with prominent lateral extensions [16]. In situations of a recurrent craniopharyngioma after craniotomy, the trans-nasal approach may offer the distinct advantage of a previously untouched approach to the lesion, and an endoscopy enables the surgeon to assess the anatomy of the subchiasmatic and retrochiasmatic regions more closely. If preservation or restoration of vision is the primary goal, this should be strongly considered. Endoscopic approaches also offer the advantage of reducing morbidity associated with brain retraction typically employed during transcranial approaches [16].

A comprehensive literature review performed by Komotar et al. claimed higher rates of GTR with endoscopic surgery compared to open resection (66 vs. 48%), higher likelihood of visual improvement (56 vs. 33%), although with a higher risk of CSF leak (18.4 vs. 2.6%). However, it is important to note that the paper suffers from systematic methodological flaws and selection bias since the mean follow-up time for the patients who underwent open resection in this study was 65 months, as opposed to 25.1 months for the endoscopically treated group [20]. More recent series comparing the two approaches were not able to establish similar significant differences in treatment outcomes.

In conclusion, the endoscopic approach may be most appropriate in certain patients who present with intrasellar and Type I lesions, whereas an open resection, employing a frontotemporal craniotomy, may be more suitable for intra-infundibular or post-infundibular lesions. In patients presenting with cystic CP, stereotactic management is appropriate to aspirate the cystic component of the mass before pursuing other avenues of treatment (e.g., radiation therapy).

8. Radiation therapy for craniopharyngioma

For much of the intervening decades since neurosurgery for CP was described, the debate largely revolved about the optimal treatment strategy, whether aggressive surgical resection or conservative surgery offered patients the best option. Among the two fundamental schools of thought regarding the optimal approach to treat craniopharyngioma, one advocated for GTR for all patients with radiation reserved for salvage therapy due to anticipated adverse effects of radiation [21]. The alternative management suggested was that of a subtotal resection or biopsy and cyst decompression in combination with adjuvant radiation therapy. Advantages of this approach include lower morbidity and improved quality of life [22]. Although the surgical goal remains maximal tumor resection with minimal morbidity, it is estimated that 33% of patients will present with some form of recurrence within the first few years. It is especially clear that radiation therapy is a key element of treatment for these patients with recurrent craniopharyngioma.

In a comprehensive review of a published series of CP patients, Yang et al. were able to demonstrate that subtotal surgery in conjunction with post-operative radiation results in improved survival in patients with CP [23]. This approach employing rather conservative surgery has the advantage of reducing the risks of hypopituitarism and hypothalamic injury. The results from various meta-analyses were corroborated and further expanded with evidence obtained from a

large single-center series [24]. Conservative resection with adjuvant radiation was found to be a superior strategy in treating patients. Schoenfeld et al. reported a cohort of patients in which there was no significant difference between GTR and subtotal resection (STR) with radiation therapy (XRT) in terms of overall survival or progression-free survival at 2 years [25], with less endocrinological side effects observed in the STR group.

The key to progression-free survival appears to be conservative surgery with subsequent radiation therapy. Radiation therapy can include various regimens employing conventional external beam radiation therapy, stereotactic radiosurgery, or proton beam therapy. Although radiation offers patients the possibility of treatment with reduced morbidity and mortality, side effects of radiation include enlargement of a cystic tumor, fatigue, skin effects, increased intracranial pressure, and transient or permanent optic neuropathy. Moreover, radiation may have long-term effects such as hypopituitarism in 30–50% of patients, cranial nerve palsies, cerebrovascular diseases, and secondary malignancies. Fortunately, radiation therapy offers excellent outcomes with progressive-free survival between 5 and 10 years of 90% and 100%, respectively [26].

9. Future directions

As with many other cancers, targeted molecular therapies offer the promise of effective treatment without the need for extensive surgery or radiation. Genetic studies of aCP and pCP identified genetic characteristics of each subtype, that may eventually be targeted by specific molecular therapies for CP. Genomic analysis of aCP revealed mutations in CTNNB1 (β-catenin) in nearly all cases and BRAF mutations in most pCPs. These signaling pathways are currently being interrogated for targeted molecular therapies. Inhibitors of the BRAF proto-oncogene employing modern drugs such as Dabrafenib or Vemurafenib, or by prescribing MEK inhibitors, such as Trametinib, are already being studied as therapies for pCP. Inhibition of similar molecular pathways in melanoma, amelanoblastoma, hairy cell leukemia, and pleomorphic xanthoastrocytoma has already demonstrated the clinical promise of these therapies [27, 28]. Multicenter phase-2 clinical trials at the National Cancer Institute are currently underway evaluating BRAF/MEK inhibition in the treatment of craniopharyngioma [27].

Regardless of the therapeutic strategies that are utilized, it is evident that craniopharyngiomas continue to present a distinct oncologic challenge that still needs to be overcome. Quality of life is a key consideration in this disease, and long-term follow up, involving a multidisciplinary team, is a necessary element of care of these patients. The combination of minimally invasive surgery and radiosurgery will, in the near future, result in a minimally morbid approach to this disease to allow patients improved quality of life.

10. Conclusions

Since Cushing's early writings, describing surgery for craniopharyngioma, our strategies to treat this challenging disease have evolved with modern technology to include endoscopic and

radiation therapy. The widespread availability and adoption of these techniques have led to endoscopic treatment and radiation therapy becoming indispensable facets of treatment of craniopharyngioma. As our molecular understanding of craniopharyngioma continues to grow, there is considerable hope for the development of effective targeted therapies.

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