Surgical Management of Craniopharyngiomas: A Review

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Abstract
Craniopharyngiomas are uncommon benign intracranial tumors that still represent a task in management. Controversy exists concerning the treatment of choice for these tumors. Radical surgery, subtotal resection combined with radiotherapy, or primary irradiation are the frequent treatment modalities. Although an increasing number of reports have appeared stressing the role of primary radiation for these tumors, radical surgery still represents the treatment of choice in most cases, since craniopharyngioma is a benign tumor and many affected patients are at a young age. In this article the authors review different aspects of pathology, clinical presentation, radiology, and management of the craniopharyngiomas. Common surgical approaches are described and both preoperative and postoperative management are outlined.

Key words: craniopharyngioma, hypothalamus, surgery, third ventricle

Introduction
Craniopharyngiomas are considered to be maldevelopmental, histologically benign tumors, which account for approximately 1.2–4% of all intracranial tumors. In children, craniopharyngiomas represent approximately 5–10% of all tumors; or 56% of sellar and suprasellar tumors. Approximately 40% of all craniopharyngiomas are seen in patients 16 years old or younger.

Since craniopharyngioma is a benign tumor, its total surgical removal is the treatment of choice to achieve cure and prevent recurrence. Postoperative complications are sometimes higher, however, when a complete tumor resection is attempted. In recent years, the development and refinement of microsurgical techniques and treatment of endocrine disturbances have tremendously improved the operative results and patient’s postoperative outcome. Nevertheless, many controversies still exist concerning the treatment of choice for these tumors.

In this review article the authors outline important aspects of pathology, clinical presentation, radiology, and surgical management of the craniopharyngiomas.

Origin
Craniopharyngioma is thought to arise from small ectodermal cellular nests that are usually found in the transition area of the pituitary stalk with the pars distalis of adenohypophysis, and sometimes extending to the pars tuberalis at higher levels of the stalk. Two main hypotheses about the origin of craniopharyngioma exist in the literature, both linking the origin of the tumor with these small nests of ectoderm.

The first hypothesis relates the development of craniopharyngioma to embryogenesis of the adenohypophysis. During development, the path between primitive adenohypophysis and stomodeum along the migration of Rathke’s pouch corresponds to the craniopharyngeal duct. Erdheim in 1904 proposed the origin of craniopharyngioma from ectoblastic remnants of primitive craniopharyngeal duct, and adenohypophysis. Recent studies still support this idea. The second hypothesis proposes that the residual squamous epithelium found in the adenohypophysis and anterior infundibulum undergoes metaplasia. Since squamous cell rests were rarely found in children, it was suggested that the craniopharyngioma originates from metaplasia of mature cells of the anterior pituitary rather than from embryonic remnants.

Despite few reports of familial craniopharyngiomas, no definitive genetical relationship has been reported in the pathogenesis of these tumors.
Pathological Features

Craniopharyngiomas are considered to be maldevelopmental, histologically benign, well-encapsulated tumors. Malignant transformation is very rare, but tumor recurrence along the operative track by tumor cell "seeding" has been reported. Grossly, almost all craniopharyngiomas have solid, cystic, and calcified parts. In adults, there are relatively more solid than cystic tumors. Calcification is seen in almost all childhood craniopharyngiomas. Craniopharyngioma has well-defined outlines related to the brain. However, it has a tendency to infiltrate locally the surrounding neural tissue such as the hypothalamus. These areas often undergo intense glial reaction. Small papillary tumor projections into the glial undersurface of the hypothalamus appear on histological slices as detached islands of tumoral epithelium. Cytological studies of these small islands do not support the interpretation of malignancy. Two distinct craniopharyngioma variants have been described. The adamantinous type, or so-called childhood craniopharyngioma, is encountered in virtually all children and in about two-thirds of adults. And the papillary type, so-called adult craniopharyngioma, occurs in about one-third of adults and is very rare in children. Both adamantinous and papillary craniopharyngioma represent benign lesions. However, significant diversity has been emphasized concerning their histopathological features, and clinical aspects. The adamantinous type represents the classic cystic and calcified craniopharyngioma found in children and most adults. The squamous papillary type is characterized by nests of squamous cells embedded in a connective tissue stroma. It is a predominantly solid, non-calcified tumor.

Diversity in clinical behavior and outcome between both tumor types has been recently stressed. The clinical outcome for the squamous papillary type is better and recurrence rate lower than in the adamantinous type.

Classification of Tumor Location

Craniopharyngioma arises typically in the infundibulo-hypophyseal axis in the sella and suprasellar area occupying frequently the suprasellar cisterns, but may grow in any direction. Since the advent of magnetic resonance (MR) imaging, a better topographic classification of craniopharyngioma could be made recognizing four major types: intrasellar, infundibulum-tuberian, intraventricular, and dumbbell-shaped craniopharyngiomas. Taking the optic chiasm as the reference point, approximately one-third of cases are retrochiasmatic, one-third are subchiasmatic, 20% are prechiasmatic, and 10-15% are intrasellar.

The degree of vertical extension of the tumor can be classified in five grades from Grade I to Grade V. In a horizontal sense, craniopharyngioma may grow anteriorly into the prechiasmatic cistern and subfrontal space, laterally into the subtemporal space, and posteriorly into the interpeduncular and prepontine cisterns, cerebellopontine angle, and foramen magnum.

Clinical Presentation

The clinical presentation of craniopharyngiomas is related to three major clinical syndromes: increased intracranial pressure, endocrine dysfunction, and visual problems. Increased intracranial pressure results from enlarging intracranial mass or obstructive hydrocephalus. Visual deficits may result both from direct compression of the optic pathways by the tumor and secondarily from intracranial hypertension. Endocrine changes are caused by compression of hypothalamic-hypophyseal axis by the tumor.

Children frequently present with symptoms of increased intracranial pressure such as headaches and vomiting due to enlarging intracranial mass. Obstructive hydrocephalus is present in about one-third of the cases. Visual problems are not a frequent complaint. Endocrine dysfunctions are present in one-half of the children, and frequently manifest as short stature and diabetes insipidus. Hypothalamic disturbances include psychomotor retardation, emotional immaturity, apathy, and short-term memory deficits.

Visual deficits and endocrine dysfunction are the most frequent clinical findings in adults. Endocrine dysfunction in adults appears in men as decreased sexual drive and in women as amenorrhea. 80% of the adults complain of visual loss at time of diagnosis. Signs of increased intracranial pressure are less common than in children.

Radiological Investigations

Computed tomography (CT) and MR imaging have become standard evaluation tools in diagnostic work-up for craniopharyngiomas. The development of high-resolution CT provides a better delineation of soft tissue after contrast medium injection, identification of cystic parts of tumor, and visualization of calcification areas. The tumor capsule frequently shows enhancement following injection of contrast.
MR imaging is better than CT in identifying the soft tissue involvement around the tumor, and the displacement of complex anatomical structures of the diencephalon and skull base. The cysts frequently produce a high, uniform signal on T1-weighted images, which is usually seen even when the lesions appear isodense or hypodense on CT scans. Cysts with a low cholesterol content have a low signal on T1-weighted images. Solid tumor parts tend to be homogeneous and have a marked increase of signal intensity on T1-weighted images after injection of gadolinium-diethylenetriaminepenta-acetic acid, that differentiates craniopharyngioma from other suprasellar cysts (Fig. 1). MR imaging has in addition the advantage of providing sagittal and coronal sections of high quality, which are of tremendous importance for planning the surgical approach. In recent years, the development of MR angiography has allowed for the demonstration of major cerebral vessels and their relation to the tumor, reducing the necessity of invasive angiographic studies. However, as CT demonstrates better calcifications, and the bone anatomy of the skull base, both CT and MR imaging should be used as complementary tools in radiological evaluation for craniopharyngioma.

**Surgical Anatomy**

Due to the complexity of the neurovascular structures of the suprasellar area (Fig. 2), surgery of craniopharyngioma represents a real challenge in neurosurgery. Craniopharyngioma is usually adherent to major arteries at the base of the skull, and small perforating arteries coming from the anterior communicating vessels, posterior communicating artery, and branches from the anterior choroidal artery and thalamoperforating vessels. Tumor adhesion to these vessels is one of the most important reasons for incomplete removal. The blood supply for the anterior part of tumor is perforators from the anterior communicating artery and the proximal anterior cerebral artery. The lateral part of the tumor receives branches from the posterior communicating artery, and the intrasellar part of tumor is usually supplied from intracavernous meningo-hypophyseal arteries. Craniopharyngioma does not usually receive blood supply from the posterior cerebral and basilar arteries unless the anterior blood supply for the lower hypothalamus and floor of the third ventricle is absent.

The tumor may extend from the sellar region anteriorly in the direction of the subfrontal spaces constituting the so-called prechiasmatic craniopharyngioma. These are frequently cystic tumors and achieve large sizes before diagnosis. When the tumor grows posterior to the chiasm (retrochiasmatic craniopharyngioma) it displaces the pituitary stalk forward, and the chiasm forward and upward, making the optic nerve appear falsely prefixed. Cystic retrochiasmatic craniopharyngioma may reach very large sizes by expanding into the posterior fos-
sa along the retroclival area. The tumor may also displace the chiasm upward (subchiasmatic craniopharyngioma), and the pituitary stalk backward. Both retrochiasmatic and subchiasmatic craniopharyngiomas are frequently solid tumors, and usually grow against the third ventricle, causing compression of the hypothalamus and obstruction of the foramen of Monro. The tumor may become intraventricular by rupturing the floor of the third ventricle.

In rare cases, the craniopharyngioma may arise directly on the floor of the third ventricle. The pathogenesis of intraventricular craniopharyngiomas has been explained by the hypothesis that the pars tuberalis containing squamous epithelial rests of remnants of Rathke’s pouch could rarely grow forward and backward along the pituitary stalk, extending to the infundibulum or tuber cinereum in the floor of the third ventricle.14)

**Treatment**

Several treatment modalities have been proposed for craniopharyngiomas. There is general agreement on the fact that surgery plays a significant role in the treatment of these tumors.27–29) Recurrence rates are much lower after total tumor resection than after subtotal resection even when combined with radiation therapy.35) Management of craniopharyngioma is nevertheless controversial; indications for radiotherapy or a combination of surgery and radiotherapy remain matters of great disagreement among investigators.23) Surgical mortality and morbidity has been reduced since perioperative use of hydrocortisone, and introduction of microsurgical techniques,30) but there have also been an increasing number of reports of equally successful irradiation of these tumors.4,18,19,24,34)

Solid tumors have been treated by radical resection,12,27–29,37,38) partial resection with radiation,24) or primary radiosurgery.4,18) Cystic tumors can be surgically removed,2,12) or stereotactically punctured to reduce the size and instill radionuclide.21,34) The value of chemotherapy and the combination of treatment modalities warrant further evaluation. To achieve long-term tumor control an individualized, flexible treatment approach must be considered.7) Obstructive hydrocephalus and endocrine dysfunction are associated with high peri- and postoperative morbidity, and therefore must be treated before definitive tumor therapy is attempt.39)

**I. Treatment of hydrocephalus**

Presence of hydrocephalus preoperatively was found to have a negative impact on postoperative outcome and mean survival rate.36) Ventricular decompression is recommended if the presenting symptoms are mainly related to hydrocephalus. This allows for brain relaxation, after which a definitive tumor approach is carried out. To treat the hydrocephalus, some authors prefer a shunting procedure, whereas others prefer an external ventricular drainage at the time of surgery.22) Still others prefer a direct tumor approach without ventricular decompression.40) In the case of chronic hydrocephalus without symptoms of increased intracranial pressure, an external ventricular drainage at the time of surgery rather than shunting is preferred to assist in brain relaxation.

**II. Treatment of endocrine disturbances**

Endocrine dysfunction is present in about one-half of children and 80% of adults with craniopharyngioma. High stress doses of corticosteroid before surgery replace corticosteroid requirement rapidly. Hypothyroidism takes several days to correct, and therapy should be started promptly. A normal metabolic state must be restored gradually, especially in the elderly or patients with heart disease. Diabetes insipidus is frequently present in patients with craniopharyngioma. Especially children may present with severe alteration of fluid and electrolytes due to diabetes insipidus. Accurate replacement of deficits along with intravenous or intranasal doses of anti-diuretic hormone (desmopressin) will be necessary. Since diabetes insipidus frequently persists after surgery, therapy with desmopressin usually has to be continued during postoperative care.

**III. Surgical treatment**

Several surgical approaches have been proposed for the removal of craniopharyngiomas.3,15,28,29) For choice of optimal surgical approach four main criteria must be taken into consideration: the shortest route to the tumor, the minimal trauma to surrounding structures, the necessary overview, and the flexibility of approach to reach different directions. Additionally, different patterns of tumor extension, size, consistency, etc., may play a role in choosing the most appropriate approach. Intranasal or intrasellar or suprasellar subdiaphragmatic tumors (Grades I–II) can be operated best via a transsphenoidal approach. In the authors’ experience, the subfrontal approach is the method of choice for primarily suprasellar tumors (Grades III–V). Purely intraventricular craniopharyngioma can be removed by a transcallosal transventricular approach. Small retrochiasmatic tumors may be operated by a subtemporal route, and large retrochiasmatic tumors ex
tending into the posterior fossa down the clivus may be operated by a transpetrosal-transtentorial approach.

Total surgical resection of craniopharyngioma is closely related to tumor size, surgical approach, surgeon's experience, and obviously, the attempt to perform a radical resection. Recent series show total removal rates as high as 90% or higher for craniopharyngioma of all sizes using mainly the subfrontal and pterional approaches.26,38

**Subfrontal approach:** This is the senior author's approach of choice for removal of craniopharyngiomas. For many years, we have used the bifrontal approach with preservation of the olfactory nerves to resect these tumors.26-28 In recent years, an unilateral "frontolateral" approach has been preferred to the bifrontal exposure.

Craniopharyngioma frequently displaces the hypothalamus and optic chiasm upward, creating a large space for dissecting important neurovascular structures. After tumor enucleation, a good view of all important structures is achieved. Large retrochiasmatic tumors with extension forward may convert the lamina terminalis in a paper-thin membrane that can be opened to achieve a view into the third ventricle.

The frontolateral approach starts with a frontotemporal incision. One lateral burr hole is placed at the root of the zygomatic process of the frontal bone. A small slit can be made in the aponeurosis of the temporal muscle to expose the bony ledge at the temporal fossa. The burr hole is placed directly on that ridge, closely to the floor of anterior cranial fossa. A small craniotomy flap is done, usually without opening the frontal sinus. The dura is opened with a frontobasal incision. The arachnoid cisterns are opened progressively as the frontal lobe is gently retracted. It has proved useful to expose the anterior skull base more from the lateral side, using the lesser sphenoid wing as a landmark. In the case of a bifrontal exposure, the olfactory nerves are preserved by carefully dissecting them away from the cortical surface.

Both optic nerves are exposed. The basal cisterns are then opened to expose the chiasm and to drain cerebrospinal fluid allowing further exposure. In cases of a prefixed chiasm, the tumor removal is then performed between the optic nerves. After tumor debulking the optic pathway is decompressed, and the pituitary stalk comes into view. The pituitary stalk can be identified by its striate appearance. If there is no tumor infiltration the pituitary stalk should be preserved. In cases of large retrochiasmatic tumor giving the chiasm an appearance of prefixity or in true prefixed chiasm, the approach is through the lamina terminalis (Fig. 3). This approach provides access to the inferior part of the third ventricle. Some authors approach the lamina terminalis through the interhemispheric space sometimes with division of the anterior communicating artery.29 By debulking the tumor through the lamina terminalis more space is obtained between the chiasm and the carotid arteries to allow a frontolateral approach for removal of the remaining tumor. Tumor with lateral extension beyond the carotid is usually soft and can be removed from a frontolateral approach.

During tumor dissection care must be taken to stay within the arachnoid planes. Dissection of the tumor from the arterial wall may weaken the adventitia and cause dilatation of major vessels. Tumor dissection on the floor of hypothalamus should be carried out carefully, not to injure functioning nerve tissue. No attempt is made to remove calcified parts of tumor that are attached to the optic nerves or chiasm until the tumor mass has been enucleated. Once the tumor is debulked, calcified portions fall away from the optic nerves enough to allow complete removal. When the pituitary stalk is involved its section is preferable to pulling it with attached tumor because of the risk of hypothalamus injury. Sectioning the pituitary stalk must be done as distal as possible because a remnant of the stalk may recover the production of antidiuretic hormone.

When the tumor extends downward in the sella and even in the sphenoid sinus, direct access can be gained by drilling the tuberculum sellae. This provides a good view into the sella, which allows for further tumor excision. If the pituitary stalk is already cut, the sella can be completely curetted. To avoid cerebrospinal fluid leakage the sphenoid sinus is
packed with muscle pieces and covered with the same galea-periosteum flap that is used for closing the frontal sinuses.

**Transsphenoidal approach**: This is the optimal procedure for intrasellar and suprasellar infradiasmatic craniopharyngiomas (Grades I-II). This approach involves the nasoseptal or sublabial parasagittal route and opening the sphenoid sinus. By opening the dura care must be taken not to enter the cavernous sinuses. Anterior compression of the anterior pituitary is a frequent finding and splitting the pituitary is usually necessary to provide access to the tumor. The tumor capsule can usually be dissected free from the dura. Removal of the superior portion of the tumor often involves resection of the diaphragma that is usually attached to the tumor. The pituitary stalk can be preserved in most of the cases.

Using endoscopic technique, the area beyond the sella can also be visualized. If suprasellar tumor calcifications are found complete tumor removal is unlikely, and a subfrontal approach will be necessary to accomplish complete excision. Great caution must be used to avoid trauma to the optic nerves and chiasm. Craniopharyngioma with suprasellar extension and attachments to optic chiasm, hypothalamus, or vascular structures should not be removed by the transsphenoidal approach. For infradiasmatic tumors however, it is the approach of choice. Low surgical morbidity, and improvement of hyperprolactinemia and preoperative visual deficits have been reported.

**Pterional approach**: This approach has been the approach of choice by some authors. It may be used alone or in combination with a transsphenoidal or transcallosal approach to access large craniopharyngiomas. It allows for a more lateral view than the subfrontal approach although it does not offer a primarily anterior view. Tumor dissection is done in the parachiasmal spaces such as prechiasmatic, optico-carotid, or carotidio-tentorial spaces, in the triangle superior to the carotid bifurcation, and through the opening of the lamina terminalis. The technique of tumor removal is the same as the one performed through the subfrontal approach.

**Transcallosal approach**: This is used for primarily intraventricular craniopharyngiomas. The transcallosal approach is carried out through a small paramedian frontal craniotomy with the posterior margin just behind the coronal suture line. The dura flap is turned over the superior sagittal sinus and the exposure is made along the falx with minimal retraction of the frontal lobe away from the falx. The corpus callosum is exposed, and an about 2 cm long transcallosal incision is made between or just right lateral to the pericallosal arteries. The incision is done over the location of the foramen of Monro that is usually 1 cm anterior to the interauricular line. This approach provides access into the lateral ventricles just at the dilated foramen of Monro. Tumor capsule is easily visualized. Internal decompression by aspiration of cystic parts and piecemeal removal of solid calcified parts is carried out. An attempt must be made not to damage the fornice, the anterior commissure, the choroid plexus, the choroidal arteries, and the veins of the wall and floor of third ventricle.

**Transcortical approach**: The transcortical-transventricular approach has been reserved for those cases with large ventricles and tumor extending to the dorsal surface of the frontal lobe.

**Subtemporal approach**: This approach has been used for primarily retrochiasmatic and predominantly unilateral tumors. A temporal flap is elevated and extended to the base of skull. The temporal lobe is retracted and the cisterns are emptied. The tentorium may be divided to access posterior portions of tumor. Care must be taken not to damage the fourth nerve running at the tentorium surface. If the tumor extends to the posterior fossa along the clivus the subtemporal approach may be combined with a transpetrosal approach. In the senior author's experience this is rarely necessary, however.

**Combined approaches**: Standard approaches can sometimes be combined with each other to improve tumor removal. The subtemporal-transpetrosal approach is mentioned above. The pterional approach can be combined with the transcallosal approach for removal of adherent and calcified tumor parts within the third ventricle. The subfrontal approach combined with the pterional approach provides good access to lateral parts of tumor within or beyond the sylvian fissure.

**Aspiration and drainage of cystic craniopharyngioma**: Stereotactic aspiration of cystic craniopharyngiomas has been used recently either before radiotherapy, or for isotope instillation into the cyst cavity. Cyst drainage is usually done by inserting a catheter connected to a subcutaneous Ommaya reservoir into the cyst to facilitate repeated aspirations. In children, cyst puncture has sometimes been used to gain time until the child’s development is completed and radiotherapy can be performed.

**Surgical complications and management**: Surgical morbidity is still high in most series of craniopharyngiomas, mainly due to endocrine, ophthalmological, and neuropsychological disturbances. During tumor resection, the pituitary stalk is frequently damaged and endocrinopathy is almost al-
ways present after surgery. Diabetes insipidus is the most frequent endocrine disorder. Care must be taken not to give too much fluid during the 1st postoperative days, otherwise water intoxication is likely to occur due to increased release of antidiuretic hormone from the damaged pituitary stalk. Short-acting vasopressin preparations like desmopressin is preferred to long-acting preparations due to the rebound effect. Desmopressin is given first intravenously, and later by nasal spray. Sometimes partial or complete recovery of hypothalamic endocrine function may be observed long after surgery.

All patients undergoing craniopharyngioma surgery must be regarded as having hypoadrenalism postoperatively. High doses of hydrocortisone are give for the 1st days and then gradually reduced to physiological daily requirement. Most of the patients have hypothyroidism after surgery, and doses of levothyroxin are started in the 2nd week. Further endocrine dysfunctions are evaluated 1 to 2 weeks after surgery, and hormone replacement given according to physiological requirements.

With development of refined microsurgical technique severe hypothalamic trauma during surgery has become unlikely. More often however, minor surgical trauma to the hypothalamus may result in hypothalamic dysfunctions such as sleep disorders, memory deficits, apathy, and appetite changes, all having a significant impact on the psychosocial situation of children postoperatively.21

IV. Radiation therapy

The role of radiation therapy after subtotal tumor removal of craniopharyngiomas has been advocated by a number of authors.5,6,18,10,24) Long-term results of combined treatment with surgery and radiation demonstrate that survival rates for patients treated with subtotal removal and irradiation are better than for those with subtotal removal alone.24) In surgically difficult cases, a conservative surgical procedure combined with radiation therapy has been recommended due to high risks of surgical complications.6) Some authors dare to affirm that long-term results of combined surgery and radiation are better than results with total resection alone. Still other authors sustain that the proper treatment of primarily cystic tumors in children is drainage and intracavitary injection of radioactive isotopes.24)

The use of radiation therapy for treating craniopharyngiomas has been a matter of debate in neurooncology. An increasing number of reports support the efficacy of radiation therapy; however, the adverse effects of radiation particularly in children cannot be underestimated. Radiosurgery may be indicated if residual tumor is left (total surgical resection is usually not followed by radiation therapy). Brachytherapy is recommended in primarily cystic craniopharyngiomas.

V. Treatment of recurrence

Different treatment modalities are available for recurrences of craniopharyngioma, such as radical tumor resection, subtotal resection combined with radiation therapy, radiation only, brachytherapy, and intracavitary chemotherapy.20) Reoperation after tumor recurrence or after radiation therapy is considerably more difficult than primary operation, and carries a higher morbidity. Scarring from first operations and irradiated areas may create a monumental task for total tumor resection. However, surgery still has been recommended in recurrent craniopharyngioma if gross total removal seems to be possible. Particularly regrowth of solid components of tumor may be surgically approached again. Radiation therapy is reserved for those cases in which it is thought that the tumor cannot be removed completely by surgery.

Outcome

The general survival rate of craniopharyngioma after 10 years is approximately 90%.6) Developments in diagnostic tools and treatment modalities have substantially improved the outcome of these patients by reducing the frequency of neurological, endocrine, and ophthalmologic complications.35) Neuropsychological deficits, including intellectual and memory dysfunction, affective immaturity, and hyperphagia are, however, not uncommon disorders which have a significant impact on the postoperative quality of life, and must therefore be considered in the management decision making.

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References

3) Apuzzo MLJ, Levy ML, Tung H: Surgical strategies and technical methodologies in optimal management of craniopharyngioma and masses affecting the third ventricular chamber. Acta Neurochir Suppl (Wien) 53:


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