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Pediatric craniopharyngiomas: classification and treatment according to the degree of hypothalamic involvement

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Object. The current treatment of craniopharyngiomas is evolving into one of a multimodal approach in which the aim is disease control and improved preservation of quality of life (QOL). To date, an appropriate classification system with which to individualize treatment is absent. The objectives of this study were to identify preoperative prognostic factors in patients with craniopharyngiomas and to develop a risk-based treatment algorithm.

Methods. The authors reviewed data obtained in a retrospective cohort of 66 children (mean age 7.4 years, mean follow-up period 7 years) who underwent resection between 1984 and 2001. Postoperative recurrence rates, vision status, and endocrine function were consistent with those reported in the literature. The postoperative morbidity was related to hypothalamic dysfunction. The preoperative magnetic resonance imaging grade, clinically assessed hypothalamic function, and the sugeon's operative experience ($p = 0.007$, $p = 0.047$, $p = 0.035$, respectively) significantly predicted poor outcome. Preoperative hypothalamic grading was used in a prospective cohort of 22 children (mean age 8 years, mean follow-up period 1.2 years) treated between 2002 and 2004 to stratify patients according to whether they underwent gross-total resection (GTR) (20%), complete resection avoiding the hypothalamus (40%), or subtotal resection (STR) (40%). In cases in which residual disease was present, the patient underwent radiotherapy. There have been no new cases of postoperative hyperphagia, morbid obesity, or behavioral dysfunction in this prospective cohort.

Conclusions. For many children with craniopharyngiomas, the cost of resection is hypothalamic dysfunction and a poor QOL. By using a preoperative classification system to grade hypothalamic involvement and stratify treatment, the authors were able to minimize devastating morbidity. This was achieved by identifying subgroups in which complete resection or STR, performed by an experienced craniopharyngioma surgeon and with postoperative radiotherapy when necessary, yielded better overall results than the traditional GTR.

Key Words • craniopharyngioma • hypothalamus • surgery • quality of life • pediatric neurosurgery

Historically their benign histological characteristics and accessible but challenging location made craniopharyngiomas an ideal tumor for the new techniques of microsurgery. This enticed most pediatric neurosurgeons to attempt to "cure" the disease by undertaking a GTR.[11,18,21,22,47] The investigators at some centers, however, resisted this trend and reported studies in which they found that partial resection and postoperative radiotherapy yielded disease control rates at least as good as GTR but with improved outcomes in QOL.[10,13,24,31,33,34,45]

For years, the outcomes of craniopharyngioma treatment have been evaluated in terms of mortality rates, vision status, and endocrine function but not in terms of QOL. The complications of GTR are often incompatible with a normal life.[4,5,10,16] The morbidity resulting from radical resection arises from the intimate anatomical relationship of craniopharyngiomas with the neurohypophysis and, in particular, the hypothalamus. When assessed in the context of QOL, hypophysial and hypothalamic dysfunction (panhypopituitarism, obesity, hyperphagia, obsessive food-seeking behavior, and neuropsychological disorders) dramatically affect the outcome of children and their families. Few studies have been conducted to address these QOL outcomes or to modify the treatment of craniopharyngiomas accordingly.[10,16,25]

Many authors have noted the need to individualize the treatment protocols to each child's presentation.[13,16,24,30] To

Abbreviations used in this paper: BMI = body mass index; GTR = gross-total resection; HRT = hormone replacement therapy; HUI2 = Health Utility Index Mark 2; MR = magnetic resonance; QOL = quality of life; SD = standard deviation; STR = subtotal resection.

this end, however, we have lacked both the appropriate classification systems and clinical indicators of outcome. Like many other pediatric services that for decades promoted radical resection, we have reviewed our surgical series and concluded that an imaging-documented cure was often associated with a poor QOL in those treated. In the present study we conducted a retrospective analysis to identify preoperative prognostic factors that would allow clinical stratification of patients. This stratification was then applied prospectively to another cohort of patients.

Clinical Material and Methods

Study Design and Objectives

This study consists of two patient cohorts: a retrospective cohort of children treated for craniopharyngioma at Hôpital Necker–Enfants Malades between 1984 and 2001, and a prospective cohort of children treated between 2002 and 2004.

The objectives of the retrospective study were to review the clinical features at presentation, the treatment received, and the cases in which morbidity and death occurred. In particular the clinical and imaging involvements of the hypophysial–hypothalamic axis were noted. These data were used to identify possible prognostic factors.

For the prospective study, the objective was to stratify the treatment based on the prognostic factors identified in the retrospective component and to review prospectively any deficits and causes of death.

Inclusion and Exclusion Criteria

In the retrospective cohort of patients, we reviewed data obtained in all children with craniopharyngiomas treated at Hôpital Necker–Enfants Malades. Patients were excluded either because they had previously undergone surgery in another unit or there were no pre- and postoperative MR imaging studies available.

Clinical Evaluation

The patient's clinical (including BMI Z score), psychological, vision, and endocrine statuses were evaluated pre- and postoperatively.

Imaging Findings

The preoperative MR images were independently graded by a neuroradiologist (N.B.), who classified the tumor according to the degree of hypothalamic involvement as follows: Grade 0, no hypothalamic involvement; Grade 1, the tumor abuting or displacing the hypothalamus; and Grade 2, hypothalamic involvement (the hypothalamus is no longer identifiable) (Fig. 1).

All patients underwent computed tomography scanning of the head the day following surgery and brain MR imaging at 3 months, 6 months, and annually thereafter.

The lesions on the postoperative MR images were graded as follows: Grade 0, no hypothalamic damage; Grade 1, negligible hypothalamic damage or residual tumor displacing the hypothalamus; and Grade 2, significant hypothalamic damage (floor of the third ventricle not identifiable) (Fig. 1).

In addition, the presence of hydrocephalus and the relationships of the tumor to the optic chiasm, ventricles, and sellar region were noted. Any residual postoperative tumor was documented. We categorized the presence of tumor recurrence or progression as the reappearance of or increase in, respectively, contrast enhancement on the postoperative MR image as assessed by the independent neuroradiologist.

Treatment Strategies

In the retrospective cohort, surgery was undertaken with the aim of GTR. In patients with acute visual loss or acute intracranial hypertension, emergency decompression was achieved by tumor resection alone or initial decompression (ventriculoperitoneal shunt placement or cyst drainage) followed by tumor resection.

In the prospective cohort, the patients' treatment was stratified according to the treatment algorithm, which was developed using the results of the retrospective study (Fig. 2).

In both arms of the study, details of the surgical procedure and postoperative adjuvant therapy were recorded.

In all patients, the diagnosis of craniopharyngioma was histologically confirmed by the same independent neuropathologist.

Functional Outcome Scale

The HUI2,[40] which defines patient health status within seven categories (sensation, mobility, emotion, cognition, self-care, pain, and fertility), was used to evaluate the QOL. Because the study included only children, the fertility category was omitted. This test was performed by a phone interview with parents and/or patients as appropriate by a single neurosurgeon (S.P.), rather than by the treating neurosurgeon. In addition, the patients were evaluated, if possible, with IQ scores, the Wechsler Intelligence Scale for Children, and the McCarthy Scale.

Statistical Analysis

Statistical analysis was performed using SPSS software version 10 for Windows (SPSS Inc.). We compared categorical data using chi-square and Fisher exact tests. A probability value less than 0.05 was considered significant.

Results

Retrospective Cohort

Clinical Features. Between 1984 and 2002, 103 patients were treated at Hôpital Necker–Enfants Malades, of whom 66 (42 boys and 24 girls) fulfilled the inclusion criteria. The median follow-up duration was 7 years (range 1–19 years). The median patient age at diagnosis was 7.4 years (range 1–16 years). The duration of symptomatology prior to diagnosis ranged from 1 day to 3 years. Thirty-eight (58%) of the children presented acutely, requiring emergency intervention (50% for intracranial hypertension and 50% for visual impairment). The clinical features on admission are summarized in Table 1 (with the prospective cohort included for ease of comparison). Symptoms of intracranial hypertension were present in 68%, whereas visual symptoms were documented in 44%. Motor deficits and seizures were less common presentations (12 and 4.5%, respectively). Endocrinological signs were evident in 36% (growth retardation in 27%, diabetes insipidus in 9%); however, in 80%

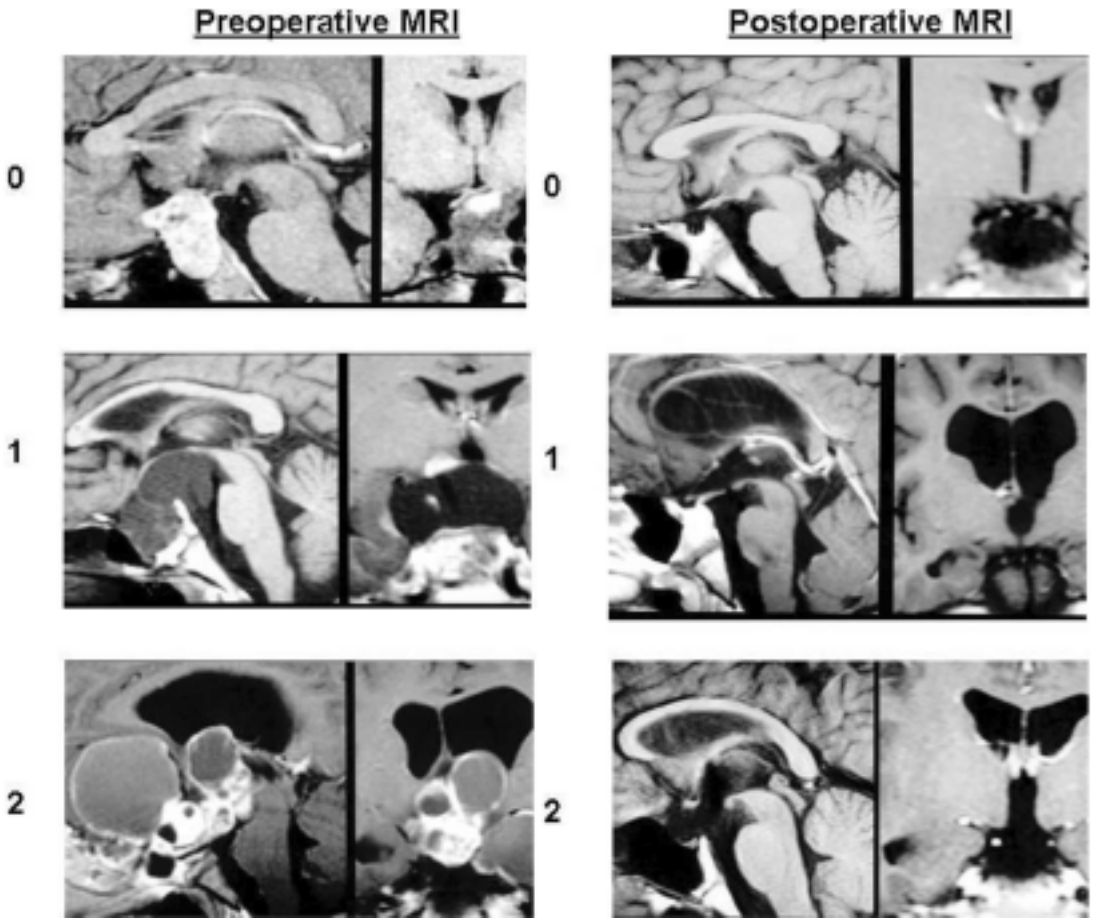

FIG. 1. Preoperative *(left column)* and postoperative *(right column)* MR imaging classification of pediatric craniopharyngiomas. *Upper Left:* Grade 0, no hypothalamic involvement. *Center Left:* Grade 1, hypothalamus displaced by the tumor. *Lower Left:* Grade 2, hypothalamic involvement. *Upper Right:* Grade 0, no hypothalamic damage. *Center Right:* Grade 1, minimal hypothalamic damage. *Lower Right:* Grade 2, severe hypothalamic damage.

of the children we found biochemical evidence of endocrine dysfunction). The median admission height and weight were +0.8 SD (range −6 to +4 SD) and +2 (range −6 to +16), respectively (norms were previously established for the French population and these values represent SDs of those norms. See Rolland-Cachera and colleagues[29]). The median BMI Z score was 1.15 (range −5 to +8). There were symptoms and signs of hypophysial–hypothalamic dysfunction in 18 patients (27%) as summarized in Table 2.

Preoperative Imaging Features. The majority of the tumors had solid and cystic components; 10% presented as purely cystic lesions. Hydrocephalus was present in 53% of the patients, and giant tumors (defined as having the longest axis of > 5 cm) represented 20% of the lesions. Anatomically the tumors involved the following regions: prechiasmatic, 20 patients (30%); retrochiasmatic, 60 (91%); intraventricular, 45 (68%); and intrasellar, 46 (70%). In this cohort, 14 patients (21%) harbored a Grade 0 tumor, 24 (36%) a Grade 1 tumor, and 28 (42%) a Grade 2 tumor.

Treatment Strategies

Surgery. Thirty-six children (55%) underwent emergency cyst drainage (Ommaya reservoir placement in 33 and endoscopic fenestrations in three) prior to definitive resection. Resection was undertaken via three routes: the transcallosal–transventricular in 14 (21%), frontopterional in 34 (52%), and subfrontal (uni- or bilateral) in 18 (27%). The intention to treat was for GTR; however, in many cases this was not achieved. The excision was total, subtotal, or partial in 33 (50%), 24 (36%), and nine (14%) patients, respectively, based both on the operative report and MR imaging study. The series incorporates the work of six surgeons over a 10-year period. One surgeon (C.S.R.) performed 44% of the operations and the remaining surgeons (including A.P.K., M.Z., D.R., and G.C.) together performed fewer than four of these particular surgeries per year. Compared with the higher-volume surgeon, those treating fewer cases had results that were associated with increased morbidity.

As in other pediatric series, the histological type was adamantinomatous craniopharyngioma, except in one case in which it was both adamantinomatous and squamous craniopharyngioma.

Radiotherapy. In total, 23 (35%) of the patients underwent some form of radiotherapy during their clinical course. In eight patients with STR or recurrence, conventional radiotherapy was conducted. The median age of these patients was 7.5 years (range 4–16 years) and the radiation doses ranged from 50 to 55 Gy. Twelve patients in whom there

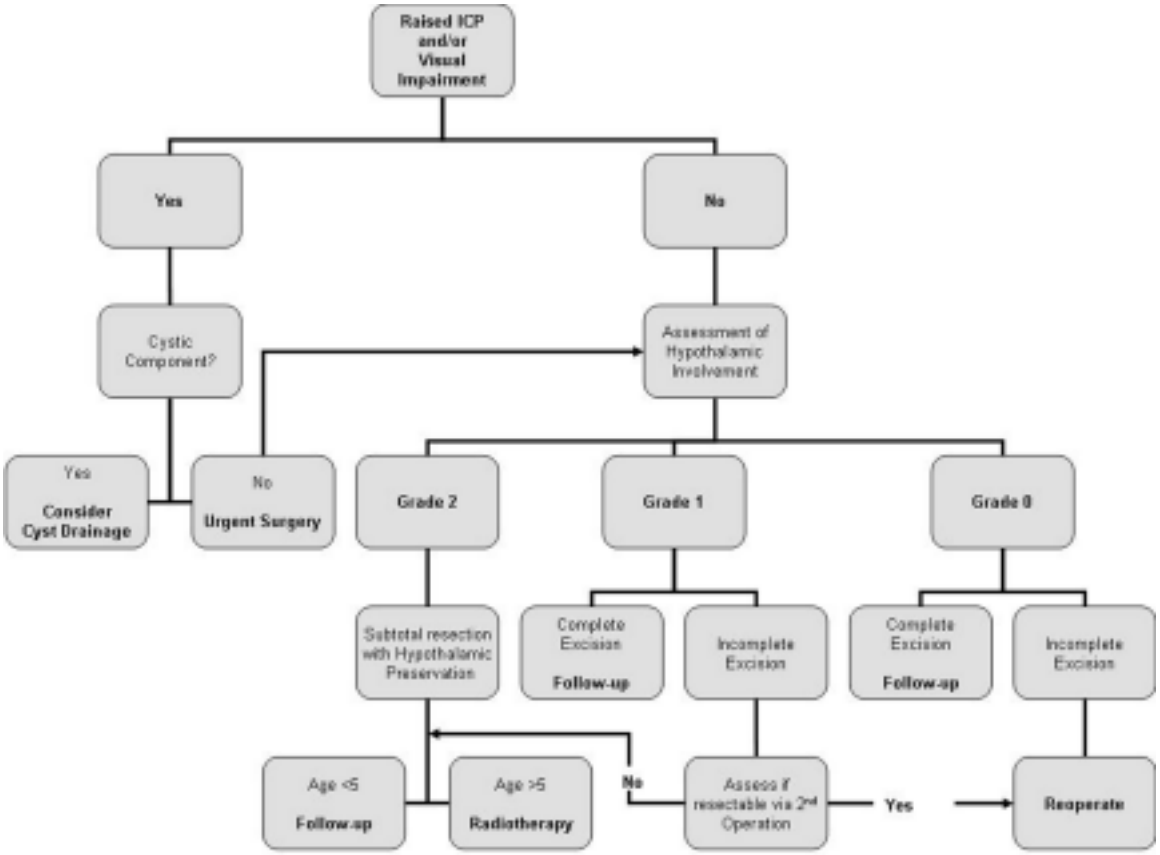

FIG. 2. Flow chart demonstrating the risk-based treatment algorithm for pediatric craniopharyngiomas. ICP = intracranial pressure. Age is given in years.

was a small postoperative residual tumor underwent stereotactic Gamma Knife surgery when the tumor enlarged (median age of these patients 8.2 years, median dose 10 Gy [maximum 7 Gy to visual pathways]). Three patients with purely cystic lesions underwent Re-based brachytherapy.

Chemotherapy. Five patients with cystic craniopharyngiomas were treated with intracavity bleomycin-based chemotherapy. A recurrence developed in all of these patients and major complications were documented in two (chemical meningitis in one and Korsakoff syndrome in one).

Outcomes After Treatment

Death. Four patients died, two of severe endocrine disturbances (one at 3 months and one at 10 months) and two of disease progression (one at 27 months and one at 33 months).

Postoperative Morbidity Events. There were two cases involving major morbidity. In one case the patient became hemiplegic secondary to vasospasm of the terminal carotid artery. In the other case a middle cerebral artery infarction developed as a result of operative trauma at the carotid bifurcation. Less severe related deficits were seizures (seven cases), facial spasm (two cases [one transient]), subdural fluid collections requiring temporary drainage (nine cases, all involving giant tumors), extradural hematoma (one case), and wound complications (six cases). One patient experienced a transient memory disturbance after undergoing surgery via a pterional approach.

Vision Outcome. Visual function improved in 68% of cases and deteriorated in 21%. The results of visual acuity and visual field testing are summarized in Tables 3 and 4, respectively. We noted an improvement in outcome between the initial postoperative and the last follow-up examinations. The outcome of a patient's vision status did not correlate with initial tumor volume, extent of resection, use of radiotherapy, or tumor recurrence.

Endocrine Outcome. During the 1st postoperative week, diabetes insipidus developed in 95.5% of the patients; it was permanent in all except one patient. There were two patients in whom HRT was not required. These two patients had undergone cyst drainage and irradiation (Re-based brachytherapy in one and stereotactic radiotherapy in the other). One patient died in the immediate postoperative period before we could establish the precise postoperative endocrine status. We found no relationship between endocrine outcome and patient or tumor characteristics.

Neurological Outcome. As previously noted, two patients sustained permanent hemiplegia. All patients with a preoperative motor deficit recovered normal function.

Morphometric Status. At the last follow-up examination, the median height was +1 SD (−6 to +4 SD) and the median weight was +4 SD (−4 to +20 SD). In the cohort, 63 patients required growth HRT. The median postoperative BMI Z score was +2.5 SD (−1.5 to +6 SD). Sixty percent of the patients were above the 98th percentile for

TABLE 1

*Characteristics of patients in the retrospective and prospective cohorts**

Characteristic	Value (%)	
	Retrospective	Prospective
no. of cases	66	22
age (yrs)		
median	7.4	8
range	1–16	2.8–14
M/F ratio	1.75:1	1.45:1
clinical features at presentation		
intracranial hypertension	45 (68)	13 (59)
visual impairment	29 (44)	10 (45)
blindness	10 (15)	4 (18)
hemiparesis	8 (12)	0
seizures	3 (4.5)	1
polyuria/polydipsia	6 (9)	2
growth retardation	18 (27)	8 (36)
radiological features		
preop hydrocephalus	35 (53)	10 (45)
preop MRI grade		
0	14 (21)	4 (20)
1	24 (36)	9 (40)
2	28 (42)	9 (40)
postop MRI grade		
0	21 (32)	9 (39)
1	20 (30)	10 (46)
2	25 (38)	3 (15)
hypothalamic features		
BMI Z score (SD)		
preop	+1	−0.2
postop	+2.5	+1.3
HUI2		
preop	NA	0.95
postop	0.8	0.95

* Values are numbers of patients unless otherwise specified. Abbreviation: NA = not available.

weight, and of these 37.5% were morbidly obese based on established criteria.

Using the Fisher exact test, we found a significant relationship between the postoperative BMI Z score and the preoperative imaging grade as well as between the postoperative imaging grade and the experience of the surgeon (Tables 5 and 6).

Hyperphagia. Postoperatively, hyperphagia developed in 46 (70%) of the patients, and in 12 (18%) the hyperphagia was uncontrollable regardless of any medical and nonmedical attempts. The children with uncontrolled hyperphagia also exhibited behavioral problems leading to social exclusion.

TABLE 2

Symptoms and signs of hypophysial–hypothalamic dysfunction at presentation in retrospective cases

Symptoms & Signs	No. of Patients (%)
total no. of cases	66
polyuria/polydipsia	6 (9)
precocious puberty	1 (1.5)
neuropsychological disorder	2 (3)
short stature	13 (20)
hyperphagia	14 (21)
obesity	20 (30)
diencephalic syndrome	3 (4.5)

TABLE 3

*Visual acuity outcome after attempted GTR in the retrospective cohort**

Visual Acuity	% of Patients	
	Early Postop Period	Last FU
normal	40	56
bilat moderate deficiency	10	6
unilat blindness	17	22
total blindness	20	16

* FU = follow up.

Thermoregulation. Temperature intolerance was common. Twenty patients (30%) felt overly warm and nine (14%) felt cold. One child was readmitted several times with unexplained hyperthermia, and one child became poikilothermic.

Neuropsychological Outcome. Eleven children experienced memory disturbance, which was severe in four cases. Appetite perturbation consistently resulted in behavioral change in 14 patients, in five of whom it led to major behavioral disturbances. Typically, frustration at food restriction led patients to rage attacks and uncontrolled violence, although apathy and hypersomnolence were also observed. There was a statistically significant relationship between behavioral disturbances and tumor grade (preoperative $p = 0.01$, postoperative $p = 0.002$; Fisher exact test).

Health Status Classification. In the 45 patients available for interview, the mean HUI2 score was 0.8 (range 0–1). There was no statistical correlation between the HUI2 score and patient characteristics, tumor characteristics, the extent of resection, the use of radiotherapy, or the number of tumor recurrences. There was, however, a significant correlation between the MR imaging tumor grade and the HUI2 score both pre- and postoperatively ($p = 0.001$ and $p = 0.003$, respectively; Table 7) and between the postoperative HUI2 score and behavioral dysfunction ($p = 0.003$; Table 8).

Social Outcome. Of the 45 patients, 34 (76%) exhibited normal development, good social integration, and progressed well in school and subsequently professionally; two blind children required special schooling; four children were integrated into specialized institutions for major memory deficiencies; and five children were socially isolated due to major behavioral dysfunction.

TABLE 4

*Visual field outcome after attempted GTR in the retrospective cohort**

Visual Field	% of Patients	
	Early Postop Period	Last FU
normal	35	42
LHH	17	17
UH	4	6
BTH	15	11
quadrantanopia	9	4
not assessable	20	20

* BTH = bitemporal hemianopia; LHH = lateral homonymous hemianopia; UH = unilateral hemianopia.

TABLE 5

*Factors affecting the postoperative BMI Z score**

Variable	p Value
patient age & sex	NS
hydrocephalus	NS
tumor volume	NS
location in relation to chiasm	NS
MRI tumor grade	
preop	0.007
postop	0.001
extent of resection	NS
surgical route	NS
radiotherapy	NS
surgeon's expertise	0.035

* Significance was assessed using the Fisher exact test. Abbreviation: NS = not significant.

Postoperative Imaging Studies. The postoperative hypothalamic damage was Grade 0 in 21 (32%), Grade 1 in 20 (30%), and Grade 2 in 25 patients (38%) (Table 1). Compared with the preoperative scores, 77% of the Grade 0 lesions remained Grade 0. In the cases involving a preoperative grade of 1, 50% remained unchanged, 20% became Grade 0, and 30% deteriorated to Grade 2. In the cases involving preoperative Grade 2 hypothalamic damage, 60% were unchanged whereas in 40% the floor of the third ventricle became visible, suggesting an overappreciation of hypothalamic involvement on the preoperative MR image.

Tumor Recurrence. Tumor recurrence was documented in 35 patients (53%), in six of whom there was a second and in one a third recurrence. The mean time to tumor recurrence was 6.4 years. Although the rate of recurrence was influenced by the extent of resection (recurrence rate 36% after total resection and 54% after STR), the intergroup difference was not significant. In the 12 patients who underwent stereotactic radiosurgery to treat an enlarging postsurgical recurrence, there were three further recurrences at a mean of 1.5 years. These three patients harbored an initial predominantly cystic tumor. In no patient who underwent conventional radiotherapy for an enlarging recurrence was there disease relapse during the study period (mean follow-up duration 10 years). There were five patients in whom an STR was achieved who subsequently underwent postoperative radiotherapy. None of these five patients suffered a relapse at a mean follow-up duration of 9 years. The lesions in the five patients treated with intracystic bleomycin-based chemotherapy recurred, as did those in two of the three patients who underwent brachytherapy.

We found no relationship between tumor volume or the presence of hydrocephalus and recurrence. Importantly, growth HRT was not correlated with tumor recurrence. Recurrences were managed by surgery (21 cases), radiotherapy (five cases), radiosurgery (eight cases), and Re-based brachytherapy (one case). After a second recurrence, four patients underwent surgery and one radiosurgery. For the patient in whom the tumor recurred three times, surgery was complicated by hypothalamic syndrome and recurring subdural collections, and the patient eventually died.

TABLE 6

*Relationship of the MR imaging hypothalamic grade, pre- and postoperatively to the BMI Z score**

MRI Grade	Postop BMI Z Score (in SD ± SD)	p Value
preop grade		
0	1 ± 1.6	0.007
1	2.4 ± 1.6	
2	2.8 ± 1.8	
postop grade		
0	1.2 ± 1.4	0.001
1	2.6 ± 1.5	
2	3.1 ± 1.9	

* Values are presented as the SD ± SD. The BMI Z score is itself representive of an SD of the norm.

TABLE 7

Relationship of the MR imaging hypothalamic grade, pre- and postoperatively, to the HUI2 score

MRI Grade	Postop HUI2 Score (± SD)	p Value
preop grade		
0	0.92 ± 0.08	0.001
1	0.86 ± 0.11	
2	0.51 ± 0.31	
postop grade		
0	0.82 ± 0.24	0.003
1	0.80 ± 0.14	
2	0.52 ± 0.35	

Prospective Cohort

Patient Characteristics and Clinical Observations. Between 2002 and 2004, 22 patients (13 boys and nine girls) were treated for craniopharyngioma at Hôpital Necker–Enfants Malades and all were enrolled in the prospective study. The mean age of these patients was 8 years (range 2.4–14 years, median 7.9 years), yielding a population comparable to that in the retrospective cohort. The duration of symptomatology prior to presentation ranged from 1 month to 3.2 years. The clinical features at presentation, summarized in Table 1, were similar to those observed in patients in the retrospective arm. The median BMI Z score was −0.2 SD (−1.8 to +3.3 SD), and there were three obese, hyperphagic children at referral.

TABLE 8

Factors associated with the postoperative HUI2 score

Variable	p Value
patient age & sex	NS
hydrocephalus	0.014
tumor volume	NS
location in relation to chiasm	NS
MRI tumor grade	
preop	0.001
postop	0.003
extent of resection	NS
surgical approach	NS
radiotherapy	NS
recurrence	NS
surgeon's expertise	NS
hyperphagia	0.047
neuropsychological dysfunction	0.003

Preoperative Imaging Features. Assessment of the preoperative MR images revealed a strikingly similar distribution of hypothalamic involvement as documented in patients in the retrospective study (Table 1).

Treatment Strategies

Surgery. All children underwent surgery, but the surgical goals were tailored to the treatment algorithm (Fig. 2). Six children (27%) required emergency cyst drainage once visual impairment or intracranial hypertension was discovered prior to definitive surgery (five endoscopically guided, one stereotactically guided). This resulted in visual improvement in two cases, resolution of intracranial hypertension in four, and continued visual deterioration necessitating emergency tumor resection in one case (a child with a prefixed chiasm), despite drainage. A single operation was performed in 15 cases (68%), two were performed in six (27%), and three were performed in one. Based on intraoperative findings and postoperative MR imaging findings, GTR was achieved in only five patients (23%), STR was achieved in the majority (16 [73%] cases), and partial resection was achieved in one child only.

Radiotherapy. Any residual tumor was absent in 17 patients. Of these, 10 underwent adjuvant radiotherapy involving a conformal (seven patients) and/or proton beam (five patients) technique. Postoperative MR imaging demonstrated normal results in five patients, despite a reported STR. In these patients it was decided to delay the decision for radiotherapy and to continue with regular (3 monthly) surveillance. Two foreign patients were lost to follow up.

Outcomes After Treatment

Follow-Up Duration. The mean follow-up period in this cohort was 13.8 months (median 13.9 months).

Death and Morbidity Events. There were no deaths in this cohort. There were, however, two cases of postoperative subdural fluid collection requiring temporary drainage, and there was one case of rhinorrhea.

Vision Outcome. Apart from the one patient with refractory preoperative visual deterioration, the ophthalmological status was either improved or unchanged in all patients. In particular, three children in whom only light perception was noted on admission recovered useful vision.

Endocrine Outcome. To date, all of the children have panhypopituitarism and remain on HRT.

Morphometric Features and Hyperphagia. The median postoperative BMI Z score was +1.3 SD (−1.7 to +4.5 SD), which is dramatically different from that in the retrospective series (+2.5 SD, ranging from −1.5 to +6 SD). The weight of six patients (27%), however, was still above the 98th percentile. A degree of appetite dysregulation remains in eight children but to a lesser degree than that observed in the retrospective cohort, and at an intensity manageable by the family and not significantly impacting each child's behavior.

Health Status Classification. The postoperative HUI2 score was 0.95, identical to the preoperative score. To date, none of the children has experienced QOL-related deterioration since treatment.

Postoperative Imaging Studies. Examination of the postoperative MR imaging grades of hypothalamic integrity showed that only three patients (14%) had hypothalamic damage (Grade 2) compared with 38% in the retrospective cohort.

Tumor Recurrence. The disease status in the five cases in which total resection was achieved remains stable with no evidence of recurrence. In the short-term follow-up period, we have observed no evidence of postirradiation progression. Longer-term follow-up data will be necessary, however, to judge the outcome. In five patients with more than 1 year of postirradiation follow up, we have observed a decrease in the residual lesion in three cases and no change in two.

Discussion

Background of Childhood Craniopharyngioma

The optimal management of childhood craniopharyngiomas continues to evolve. Widely promoted to be the gold standard for many years, GTR is still advocated by its proponents despite high morbidity particularly relating to hypothalamic injury.[12,18,41,47] Since the 1970s, a strategy involving less aggressive surgery combined with radiotherapy has consistently been shown to be effective.[10,13,15,24,31,33,34,43,45] The significantly reduced QOL associated with GTR is now recognized. Thus, as more and more centers favor multimodal therapy, the gold standard is now swinging away from radical surgery to less aggressive surgery.[16]

Nevertheless, childhood craniopharyngiomas are histologically benign, and we know that a proportion of them can be resected without significant morbidity. We also know from the literature that radiotherapy is not a perfect solution because of concerns over long-term sequelae as well as the recurrence rates of the tumor ranging between 0 and 50% (Table 9). Furthermore, the radiotherapy-induced changes could create further challenges for surgical management, potentially increasing morbidity. To balance these two risks, we have hypothesized that the challenge is to identify those patients in whom GTR is possible without the risk of significant postoperative morbidity. The aim of our study was to identify preoperative criteria allowing us to define a treatment strategy aimed at disease control with minimal hypothalamic injury and to then test this hypothesis in a prospective fashion.

Craniopharyngioma-Related Morbidity

Due to their location, craniopharyngiomas pose a triple challenge. First, the challenge of vision-related morbidity has been successfully addressed by improving surgical techniques and developing specialized centers allowing for the concentration of expertise. This has brought craniopharyngiomas to the broader audience of the medical community so that more timely referrals, when vision is salvageable, are made.

Second, endocrine-related morbidity has been significantly improved by advances in hormone therapy. There is, however, the threat of postoperative death due to endocrine disturbance. Despite remarkable improvements, HRT—which is almost universally required in these children—cannot pretend to reproduce the complexity of normal physiology. It can be said that endocrine dysfunction remains a challenge for the future.

Third, hypothalamic dysfunction continues to pose a

TABLE 9

*Summary of long-term results of irradiation for craniopharyngiomas in children published in the literature**

Authors & Year	Study Period	No. of Cases	No. of Procedures	XRT		Tumor Recur (%)	FU	Complication	% Survival	
				Type	Dose (Gy)				5 yrs	10 yrs
Shapiro et al., 1979	1953–1974	60	29 (7 op & XRT, 22 cyst drainage & XRT)	deep x-ray	40–55	0	10 yrs	none	—	—
						50	—	—	—	—
Richmond et al., 1980	1956–1974	32	20 (12 op & XRT, 8 cyst drainage & XRT)	—	—	50	—	—	—	—
						0	—	—	—	100
Thomsett et al., 1980	1966–1978	42	17 op & XRT	external	45–57	18	52 mos	none	100	—
Carmel et al., 1982	1952–1977	43	43	—	—	21	—	—	—	—
Danoff et al., 1982	1961–1978	19	19 (5 for recur)	supervoltage	55–65	16	10 yrs	none	69	66
Sung, 1982	1950–1975	98	21 (8 op & XRT, 13 cyst drainage & XRT)	—	—	25	—	—	—	—
						15	—	—	—	—
Cavazzuti et al., 1983	1959–1982	95	26 op & XRT	4-mV photon	50–56.7	0	10 yrs	3 brain calcifications, 2 cataracts, 4 deafness	100	—
Hoogenhout et al., 1984	1960–1978	13	13 op & XRT	3 external	50–56	11	5 yrs	none	—	62
						25	10 yrs	—	—	—
Wen et al., 1988	1961–1986	52	27 (20 op & XRT, 7 XRT only)	external Co	49–70	26	10 yrs	1 otitis media & meningitis (involved field)	100	—
Weiss et al., 1989	1965–1986	31	12 (5 op & XRT, 7 for recur)	external	44–57	20	89 mos	none	—	—
						0	33 mos	—	—	—
Fischer et al., 1990	1972–1981	37	37 (14 op & XRT, 21 cyst drainage & XRT, 10 XRT only)	4-mV photon	50–56.7	14	10.5 yrs	1 glioma (8 yrs)	85	75
						22	—	—	—	—
Flickinger et al., 1990	1971–1985	21	21 (19 op & XRT, 2 XRT only)	megavoltage	51–70	14	14 yrs	2 optic necrosis, 1 brain necrosis, 1 optic & brain necrosis	89	82
Hetelekidis et al., 1993	1970–1990	61	8	—	—	26	—	—	96	91
De Vile et al., 1996	1973–1994	75	38 (16 op & XRT, 22 for recur)	external	40–60	28	10 yrs	none	—	88
Zuccaro et al., 1996	1988–1994	48	35 op & XRT	—	—	50	—	—	—	—
Habrand et al., 1999	1969–1992	37	37 (18 op & XRT, 19 for recur)	megavoltage	45–56	24	10 yrs	1 glioma (9 yrs)	91	65
Merchant et al., 2002	1984–1997	—	23 (15 op & XRT, 8 for recur)	EBRT & 3P32	20–55	13	4–62 mos	none	—	—
Varlotto et al., 2002	1971–1992	24	24 (22 op & XRT, 2 XRT only)	EBRT	>55	0	12 yrs	pontine infarct (12 yrs), optic necrosis (2 yrs), hemiparesis (3.5 yrs), 2 visual field defects (3 & 5 yrs), thalamic infarct (4.5 yrs), memory loss (2.5 yrs)	100	92
Stripp et al., 2004	1974-2001	76	40 (18 op & XRT, 22 for recur)	external	44–56	16	10 yrs	1 cerebral infarct (4.7 yrs)	—	83
					<55	10	10 yrs	none	—	—
						46	20 yrs	none	—	—

* EBRT = external-beam radiotherapy; recur = recurrence; XRT = radiotherapy; — = not specified.

challenge. In time it has become increasingly evident that the QOL following craniopharyngioma surgery is severely diminished by uncontrollable hyperphagia, obesity, and behavioral dysfunction.[9,24,25,27] The relationship between food intake and severe obesity after hypothalamic damage is well known and has been described in experimental models and in association with hypothalamic tumors and injuries in humans.[1] Since 1940, it has been established that the anteromedial and lateral hypothalamic areas control satiety and food intake, respectively. In experimental models, destruction of the anteromedial nuclei leads to hyperphagia and obesity, associated with a loss of circadian rhythm for meals, whereas destruction of the lateral hypothalamic areas leads to death by food refusal. It has also been identified that the hypothalamus has a role in cognitive and behavioral functions.[7,23,32]

Retrospective Cohort

The results of our retrospective cohort are consistent with those obtained in other contemporary published series. The tumor recurrence rate of 36% after complete resection is similar to that found in the literature.[3,13,20] The improvement rate in vision of 68% and deterioration rate in vision

of 21% are also comparable with rates in the literature.[3,6,15,20,39,43,44] This study confirmed our impression that emergency decompression of cystic components can be used in cases of acute visual deterioration, improving vision in 64% of the patients. The results of endocrine status (90% of diabetes insipidus and 95% of panhypopituitarism) are in keeping with previous pediatric reports.[2,4,18,35,48]

Quality of Life Outcome

In the retrospective arm, whereas 76% of the patients were well integrated socially, the remaining 24% had a difficult existence with major memory disturbances and/or major behavioral dysfunction in keeping with hypothalamic disturbance. This hypothalamic dysfunction generated by the tumor itself was already evident at presentation in 30% of the cases. Radical surgery dramatically increased the severity of the hypothalamic damage. The degree of postoperative hypothalamic damage, categorized into three groups using the postoperative MR imaging, significantly correlated with patient outcome (for example, BMI score [Table 6] and HUI2 [Table 7]). Moreover, this postoperative MR imaging appearance of the lesion, following attempted GTR, can be predicted by examining the preoperative MR images. Even though this grading correlates with the outcome variables, however, this stratification is not perfect, as illustrated in the cases in which the preoperative assessment indicating a loss of hypothalamic integrity was disproven by the postoperative MR imaging–documented reappearance of the floor of the third ventricle (Table 1). It is our belief, however, that this imaging classification can potentially be refined by the addition of a clinical assessment of hypothalamic function.

Derived Protocol

It was logical to modify the therapeutic strategy in an attempt to minimize hypothalamic damage and thus potentially improve the postoperative QOL. It has been extensively demonstrated in the literature that the combination of subtotal surgery and radiotherapy produces outcomes at least as good as radical surgery. Indeed, although we can only offer an early assessment of outcome in our prospective cohort, the proposed strategy does appear to be successful.

This treatment strategy, however, carries several risks. It has been widely reported in the literature that radiotherapy is associated with the potential, in up to 5% of cases, for secondary neoplasm.[26] Furthermore, the effectiveness on disease control of undertaking upfront external radiotherapy after incomplete craniopharyngioma resection is not absolute and varies between 80 and 85% in most of the pediatric series (Table 9). Moreover the reported success rates appear to diminish with increasing the duration of follow up. This is of concern in that generally the only available treatment option for postirradiation recurrences is surgery, and surgery at this stage is technically difficult and can result in morbidity at levels currently seen with GTR.

An inherent difficulty for the operating surgeon and, later, for those conducting comparative studies is the precise definition of STR. An STR can encompass a spectrum from a large biopsy specimen to near-complete removal of the lesion. As a result, without definitive guidelines the degree of resection is likely to be influenced by both personal and clinical factors. We propose to define STR as the surgical removal of a tumor without its hypothalamic component.

As for other rare diseases, we should question ourselves on the validity of managing these tumors outside of specialized centers and by experienced craniopharyngioma surgeons. As demonstrated in our study, even in the same center, significant differences can be observed.

Conclusions

In this article we report the evolution of our concepts in the management of children with craniopharyngiomas. Using modern imaging and clinical data, we found it possible to differentiate two groups of patients: one group that would undergo GTR and one that would undergo STR, tailored to preserve as much as possible of the invaded hypothalamus, and combined with postoperative radiotherapy. This should allow for both long-term survival and a good QOL in both patient groups.

Only with long-term prospective data, however, will we be able to accurately evaluate our current opinion on multimodal treatment for craniopharyngiomas in children. Due to the rarity of craniopharyngiomas, it is likely that only collaborative studies and concentration of these tumors in specialized centers will allow us to reach this goal.

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