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Treatment of Craniopharyngioma in Adults: Systematic Analysis of a 25-year Experience

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Background and Aims. Craniopharyngioma is a rare and mostly benign epithelial tumor of the central nervous system, mostly affecting children. Considering that most of the published series of craniopharyngioma are based on pediatric populations, studies in adults gain importance based mainly on the reduced number of cases and the possible differences emerging from a mostly different histological type. We undertook this study to establish the pattern of presentation, morphological features and specific characteristics of craniopharyngioma in an adult Mexican population, as well as discussing the long-term outcome and how it may be influenced by surgical, anatomic and clinical factors.

Methods. A total of 153 adult patients (16 years or older) underwent transcranial and transsphenoidal surgery between January 1985 and December 2009, all with histological confirmation of craniopharyngioma. Hypothalamic involvement, surgical complications, rate of tumor resection and endocrinological outcome were evaluated.

Results. Seventy nine males (51.6%) and 74 females (48.4%) were included. Mean age at diagnosis was 32.4 years (range: 16–77 years). Mean initial tumor volume was 28.44 mL (range: 0.18–100.44 mL). Partial or complete hypothalamic involvement (Samii Grades III, IV and V) was found in 90.2%. The overall rate of new endocrinopathies was 37.25% after surgery (95% CI = 33.9–41.2).

Conclusions. Gross total removal of craniopharyngiomas with large hypothalamic involvement was related to poor neuroendocrine outcome in adults. Partial removal should be indicated, associated with adjuvant therapy, in order to improve postoperative neuroendocrine status.

Key Words: Craniopharyngioma, Adult, Pituitary neoplasms, Hypopituitarism, Surgery.

Introduction

Craniopharyngioma (CP) is a rare and mostly benign epithelial tumor of the central nervous system. Its annual incidence ranges from 0.13–2/100,000 persons with no variance by gender or race. CPs are thought to result from disembryogenic deffects of the pituitary stalk or gland, thus explaining their most common locations in the sellar and suprasellar regions (1,2). Distribution by age is bimodal. The highest peak of presentation is in children aged 5–9 years where it represents the most common nonglial intracranial tumor and, secondly, a less numerous adult group, presenting by the fifth decade of life (3). There are two different histological phenotypes seen in CP. Although the adamantinomatous type is more prevalent in children, the squamous papillary form is more frequently seen in adults (4,5).

Despite their benign histological nature, CPs have a tendency to invade an important number of neural, vascular and neuroendocrine structures that are difficult to access surgically without associated hormonal complications.

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Preoperative demonstration of large tumoral invasion of the hypothalamus, infundibulohypophyseal tract and sellar regions may contribute to poor endocrinological outcome after surgical resection (6–8).

Considering that most published series of CPs are based on pediatric populations, studies in adults gain importance based mainly on the reduced number of cases and the possible differences emerging from a mostly different histological type. In addition, data from Carmel (9) and Banna (10,11) showed different patterns of clinical presentation between children and adults. Pediatric population presents more frequently with endocrine dysfunction, progressive visual impairment and symptoms of increased intracranial pressure. On the other hand, adults tend to initiate their clinical presentation with visual loss.

Materials and Methods

In order to establish the pattern of presentation, morphological features and specific characteristics of CP in adults we reviewed 153 cases of patients who were treated surgically and discuss their endocrinological outcome and how it may be influenced by surgical, anatomic and clinical factors.

Patient Population and Center Characteristics

We conducted this retrospective study at the National Institute of Neurology and Neurosurgery Manuel Velasco Suarez, a national referral center located in Mexico City. The hospital is one of the National Health Institutes and its area of influence reaches throughout all the country. The treated population consists mainly of patients without social security and with low to middle-low incomes.

We reviewed our experience with 153 patients treated surgically in our center between January 1985 and December 2009, all with histological confirmation of CP. For this purpose, we conducted a database search from the registries of our Department of Neuropathology where the pathological diagnosis of CP (either adamantinomatous or papillary types) was conclusive by light microscopic evaluation of hematoxylin- and eosin-stained surgical specimens.

We obtained patients' clinical information from their records and reviewed their radiological and hormonal studies. Patients <15 years old at the time of diagnosis and those with incomplete files or not subsequently followed-up at our center were excluded from the study. Demographic information, presenting symptoms, location/extension of tumor and pre- and postoperative follow-up hormonal results were reviewed.

Radiological Evaluation

Location and extent of the tumor were evaluated on available films of computed tomography (CT), magnetic resonance imaging (MRI) and/or radiology reports. Tumor volume was calculated using the formula

$$4/3\ pi\ (a^{*}b^{*}c)$$

where *a, b* and *c* equal half-diameters in millimeters on axial, coronal and sagittal planes (12).

Endocrinological Evaluation

Neuroendocrine evaluation was carried out during the pre- and postoperative periods. During the preoperative period, basal levels of pituitary-dependent hormonal axes were drawn within 1 week of surgery. Postoperative determinations included a first hormonal test upon arrival to the Neurosurgical Recovery Unit or within the 3 days following surgery and a second one during the first outpatient visit after being discharged from hospitalization (average 1–3 months postsurgery).

All hormonal determinations were done in our center by radioimmunoassay (years 1994–2000), immunofluorescence (2000–2005), immunoradiometric assay (IRMA) and chemiluminiscence immunoassay methods (2005 present).

Pituitary-thyroid axis evaluation included determination of plasma levels of free thyroxine (FT_4), FT_4 index (FT_4I), free triiodothyronine (FT_3), T_3-uptake (T_3U), total T_3 (TT_3), free T_3 index (FT_3I) and thyroid-stimulating hormone (TSH). Pituitary-gonadal axis was evaluated by quantifying levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone and estradiol, along with the clinical evaluation of amenorrhea. Evaluation of pituitary-adrenal axis was based on serum cortisol determination. Prolactin (PRL) levels were determined as part of the protocol.

Assessment of posterior pituitary function, GH and IGF-1 levels were not constantly found across the reviewed records and thus were not included in the analysis.

Diagnosis of Endocrinopathies and Reference Values

Pre- and postoperative hypopituitarism were both defined by the development of any new mono- or polyhormonal anterior endocrinopathy according to accepted values and reference ranges (13).

The hypothalamus-pituitary-adrenal axis (HPA axis) was evaluated by morning cortisol levels. Levels >18 μg/dL were taken as normal. Undetermined diagnosis was done within the range of 3–18 μg/dL. Adrenal insufficiency was diagnosed by values <3 μg/dL (14).

We evaluated the hypothalamic-pituitary-thyroid axis (HPT axis) by free thyroxine (FT_4) measurement. Hypothyroidism was diagnosed on the basis of levels <11 pmol/L (15).

Hypogonadism was diagnosed in women with estradiol levels <100 pmol/L along with history of amenhorrea. Hypogonadism in men was diagnosed by testosterone levels <12 nmol/L. Evaluations of hypothalamic-pituitary-gonadal axis (HPG axis) in both males and females took into account inappropriate low levels of LH and FSH (16).

Surgical Technique

Several transcranial and transsphenoidal surgical techniques were used according to tumor grading. Election of side of

craniotomy was based on lateral extension of the tumor. Extent of resection was evaluated after correlating intraoperative impression of resection confirmed by postoperative neuroradiological volumetric quantification of tumor removal. Gross total resection (GTR) was defined as lack of residual tumor by visual inspection intraoperatively and no residual mass or enhancement suspicious for tumor on postoperative imaging. Near total resection (NTR) was defined with volumetric diminishment of 90% or more. Subtotal resection (STR) was defined in cases of 60−90% of tumor removal. Partial resection (PR) was defined as postoperative volumetric diminishment <60% (17).

Statistical Analysis

Statistical analyses were performed using SPSS v.16.0 (SPSS Inc., Chicago, IL); $p < 0.05$ was accepted as significant. Descriptive data were presented as means with standard deviations or medians with ranges depending on the expected distributions. Mann-Whitney *U* test and paired-sample Wilcoxon signed rank tests were used to compare nonparametric variables between groups. Pearson's χ^2 test was used to analyze for differences in categorical factors. All odds ratios on multivariate analysis reflect the risk of having endocrine complications compared to reference groups.

In order to establish the possible correlations emerging from age, tumor size and extent of hypothalamic involvement as independent factors of postoperative neuroendocrine dysfunction, univariate comparisons of rates of morbidities with patients stratified by these variables were done. In order to better understand the effect of surgery on single hormonal axes, special subanalyses were done considering tumor size, extent of hypothalamic involvement and extent of resection.

Analyses of local control (LC) and overall survival (OS) were estimated using the Kaplan-Meier method. Log-rank test was used for comparisons between treatment groups. For survival and local control analyses, we used the date of the first surgical procedure as time zero.

Results

Patient Demographic Characteristics

All 153 patients were 16 years or older at the time of diagnosis. Distribution according to gender was 79 males (51.6%) and 74 females (48.4%). Mean age at diagnosis was 32.4 years (range: 16−77 years). Distribution curve showed a bimodal presentation pattern with two significant peaks: first at 19.1 years (±3.1) and second at 43.8 years (±8.7). Twelve patients received previous treatment at different centers prior to attending our Institute. There were no statistically significant differences between these patients and those with primary tumors in terms of demographic data, tumor size and location ($p > 0.05$, Mann-Whitney *U* test).

All patients had pathological diagnosis of CP; histological type was adamantinomatous in 128 cases (83.6%) and papillary in 25 (16.3%). We found significant differences concerning histological type and age of presentation; adamantinomatous type was more prevalent during the first peak of presentation (98% of cases between 16−25 years), with only four cases of papillary type diagnosed in patients <25 years of age. By the second peak of presentation there was a significantly higher proportion of papillary type that gradually increased over the age of 40. All cases diagnosed in patients >60 years of age were papillary ($n = 4$).

Presenting Symptoms and Preoperative Clinical Status

Symptoms at presentation and preoperative status are shown in Table 1. Most cases presented with insidious symptoms (visual field defects in 66.6% and primary hormonal deficit in 12.4%), whereas a small percentage began with acute or subacute symptomatology: intracranial hypertension in 11.7% and psychiatric alterations including depression (1.3%), emotional instability (0.6%) and hostility (0.6%).

Mean time between onset and diagnosis was closely related to the type of symptom. On average, first medical visit was 22 months after the beginning of symptoms. Hormonal alteration as the first sign of disease was found in 12.4% (19 patients) and was detected considerably later at an average of 41.2 months after onset.

Radiological Findings

Ninety eight patients had available MRI films and 55 cases were analyzed by using CT films and/or radiology reports. Mean initial volume of tumors was 28.44 mL (range: 0.18−100.44 mL). Average dimensions were 38.44 mm (±15.4 mm), 34 mm (±12.5 mm) and 30.76 mm (±14.4 mm) on sagittal, axial and coronal planes, respectively. Calcifications were found in 113 cases (73.85%). Tumors were staged by their vertical projection into the floor of the third ventricle according to Samii's criteria (18). Results were summarized in Table 2. As such, a grade I CP was defined by a purely intrasellar and/or infradiaphragmatic lesion. Grade II was defined by invasion of suprasellar cisterns with or without intrasellar tumor. Grade III was

Table 1. Clinical presentation

Initial symptom	Number of cases (%)	Average time from onset to initial evaluation (months)
Chiasmatic syndrome	102 (66.6)	34.5
Primary hormonal alteration	19 (12.4)	41.2
Headache/papilledema/intracranial hypertension	18 (11.7)	5.2
Psychiatric manifestations	14 (9.1)	4.6

Table 2. Vertical tumor extension

Grade/vertical extension	Number of cases	%
Grade II/suprasellar cistern	15	9.8
Grade III/inferior half 3rd ventricle	84	54.9
Grade IV/superior half 3rd ventricle	45	29.4
Grade V/septum pellucidum or lateral ventricles	9	5.9

defined as lesions involving the lower half of the third ventricle. Grade IV was defined as those located in the upper half of the third ventricle, and grade V was classified as those reaching the septum pellucidum or lateral ventricles. Hypothalamic invasion was defined according to the *Hôpital Necker–Enfants Malades* classification as Grade 0 for no hypothalamic involvement; Grade 1 for hypothalamus displaced by the tumor and Grade 2 for hypothalamic involvement (19). Samii's Grades III, IV and V were found in 138 patients (90.19%). Grades 1 and 2 of hypothalamic involvement for these patients were found in 47 and 91 cases, respectively (Figure 1).

A considerable number of patients had large lesions including giant CPs (20), i.e., >4 cm on its largest axis ($n = 96$, 62.7%).

When comparing both histological types (adamantinomatous and papillary) in terms of tumor size, we found slightly larger lesions in the adamantinomatous group; however, our results revealed a nonsignificant trend over this observation ($p = 0.8$). Calcifications were notoriously more frequent—but nonexclusive—in adamantinomatous type (110/113 cases).

Surgical Approach, Tumor Size and Extent of Resection

Surgical approaches were elected according to location and extension of tumors. All surgeries were performed by members of our neurosurgical staff. Transcranial approaches were the primary modality of treatment during the first two thirds of the studied period and thus were the most frequently used (84% of the total) (21). During the last third of the study, transsphenoidal routes were introduced (microscopic transseptal and purely endoscopic), representing 16% of the total.

There were two cases (1.3%) of stereotactic-guided biopsy with placement of Ommaya reservoirs as unique modality of treatment. Concerning extent of tumor removal in the other 151 patients, 30 clinical records lacked sufficient information on the postoperative report and/or did not have subsequent radiological images to quantify postoperative tumoral volume diminishment; thus, they were excluded from this analysis. Extent of tumor removal could be established in only 121 complete files: GTR was achieved in 46 patients (30.46%), NTR in 33 (21.85%), STR in 23 (15.23%) and PR in 19 (12.58%).

Surgical Complications

In this series the most common postoperative complication was CSF leak, occurring in 16.3% of cases. Less frequent complications were hematoma (11.7%), third nerve palsy (5.2%), stroke (1.3%) and blindness (0.6%). We established a positive relationship between tumor size and surgical complications; however, this difference did not achieve statistical significance.

Recurrence and Follow-up: Overall Survival (OS) and Local Control (LC)

OS was defined as the time from initial surgery to the most recent follow-up visit, or time zero to death from any cause. LC was defined as the time from initial surgery to tumor recurrence requiring reintervention.

LC at 5, 10, 15 and 20 years for the entire cohort was 78, 72, 70 and 65%, respectively. We found the extent of surgical removal was closely associated with rates of recurrence. Tumor relapse was significantly less frequent after GTR (5/46, 10.86%) than after NTR or STR (23/56, 41.07%) ($p < 0.01$).

OS at 5, 10, 15 and 20 years for the entire cohort was 96.5, 93, 89.5 and 87%, respectively. In order to determine the effect of different degrees of surgical removal on OS rates, we conducted separate OS analyses for group GTR/NTR vs. lesser grades of tumor removal STR/PR. We found significantly higher OS rates at 5, 10, 15 and 20 years for group STR/PR (conservative resection) when compared to GTR/NTR (radical resection) group (Figure 2).

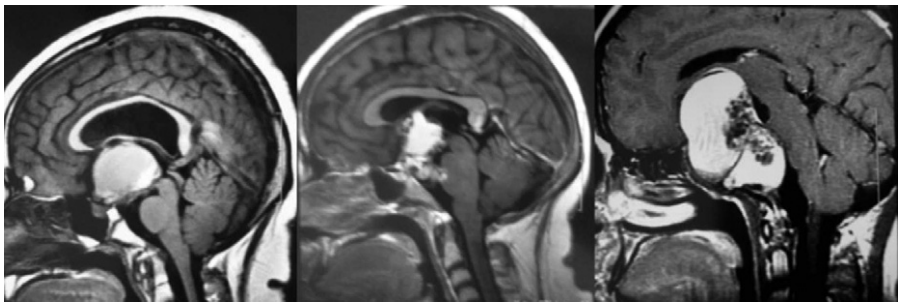

Figure 1. T1 Sagittal planes of MRI showing craniopharyngiomas with large hypothalamic involvement (from left to right: Samii Grades III, IV and V). Grade III tumors involve the lower half of the third ventricle, grade IV lesions are located in the upper half of the third ventricle, and grade V reach the septum pellucidum or lateral ventricles.

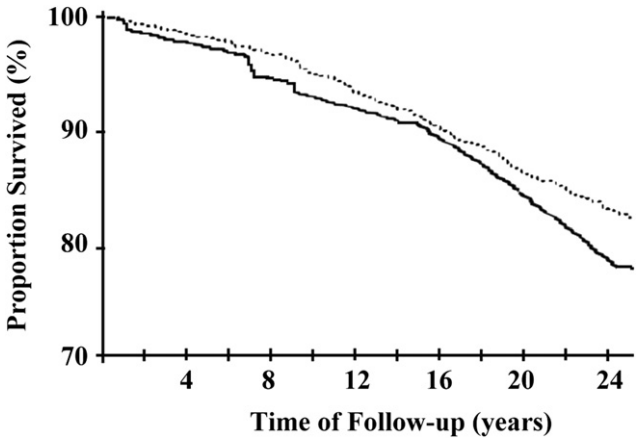

Figure 2. Survival curves for patients with CP after radical resection (Group GTR/NTR) (bold continuous line) and conservative resection (Group STR/PR) (thin dotted line). Relative risk of death associated with postoperative new endocrinopathies vs. postoperative normal hormone levels was 1.78 (95 % CI, 1.18−2.68); $p < 0.01$.

We found no differences for OS and LC in terms of age of presentation for most of the cohort; however, we found a positive trend for older patients and analyzed this further. A significant relationship was found when comparing rates of recurrence among histological types. Recurrence was more frequent among adamantinomatous type: 4/5 cases for GTR and 22/23 cases for NTR/STR ($p < 0.05$).

Endocrine Outcome

Effects of surgery on overall anterior pituitary function are summarized in Table 3. The overall rate of new endocrinopathies for all patients undergoing surgery was 21.03%. Although hypogonadism was the most common preoperative endocrine alteration (108 patients; 70.5%), we found no significant association between postoperative hormonal levels and the extent of resection for HPG axis ($p < 0.87$, Mann-Whitney *U* test).

Hormonal deficiencies of HPT and HPA axes were both the most clinically significant, thus they were analyzed separately. Preoperative hypothyroidism was found in 68 patients (44.4%). In order to determine the effect of varying degrees of tumor resection in a euthyroid population, cases of hypothyroidism were excluded on subanalysis. We found a significant decrease of TSH, TT_3, FT_3I and FT_4 below preoperative levels according to the first and second PO determinations ($p < 0.0001$) in both groups (GTR and NTR) when compared with lower rates of resection (Figure 3). No statistical correlations as independent predictors of morbidity were established with hypothalamic involvement and preoperative hormone levels when the extent of resection was controlled for. Despite an apparent trend to improve thyroid axis function between the first and second PO determinations, this observation did not achieve statistical significance. We also examined the correlations between PO determinations of thyroid hormones and other variables such as preoperative chief complaints and radiographic findings, and there were no significant data supporting these associations.

Table 3. Anterior pituitary-dependent hormonal deficiencies before and after surgery

Hormonal deficiency	Preoperative: cases (%)	Postoperative: cases (%)
Hypothyroidism	68 (44.4%)	103 (67.0)
Hypocortisolism	60 (39.2%)	108 (70.5)
Hypogonadism	108 (70.5%)	122 (79.7)

Preoperative hypocortisolism was found in 60 patients (39.2%). Patients with normal preoperative cortisol levels were analyzed according to the extent of resection. Serum cortisol levels according to the first and second PO determinations were significantly lower ($p < 0.01$) in subjects belonging to GTR and NTR groups when compared to STR and PR. As was demonstrated on the thyroid axis, there were no significant correlations between cortisol levels and the symptom/radiographic profiles.

Uni- and Multivariate Analysis

We tested several variables as potential predictors of outcome in terms of OS, LC and hypopituitarism. For this purpose, we organized variables into two groups: patient related (age, gender, presenting symptoms and preoperative hormonal deficiencies) and tumor related (location, size, hypothalamic involvement and histological type).

In univariate analyses, age <55 years was not a predictor for OS, LC or hypopituitarism ($p = 0.3$, 0.6, 0.12, respectively); however, we found age would be a significant predictor for postoperative hypopituitarism only in patients >55 years (OR 1.4 per decade over 55 years, CI = 1.3−2, $p < 0.001$). Gender, presenting symptoms and preoperative hormonal deficiencies were not significant predictors for any of the outcome variables ($p = 0.5$, 0.3 and 0.6, respectively).

Univariate analysis of tumor-related variables as outcome predictors did not show significant relationships for both location and size in terms of LC ($p = 0.3$ and 0.4, respectively) and postoperative hypopituitarism ($p = 0.3$ and 0.5, respectively). We found no relationship between both variables and OS ($p = 0.9$ and 0.4, respectively). Histological type was not associated as outcome predictor for OS or postoperative endocrinopathy ($p = 0.6$ and 0.9, respectively); however, a positive relationship was established in terms of local control for adamantinomatous type ($p < 0.05$).

Because both location and size did not show positive relationships as independent outcome factors for local control and postoperative hypopituitarism—as may be expected—we conducted a multivariate analysis using these variables to determine the effect of the extent of resection as conditioning factor for postoperative pituitary

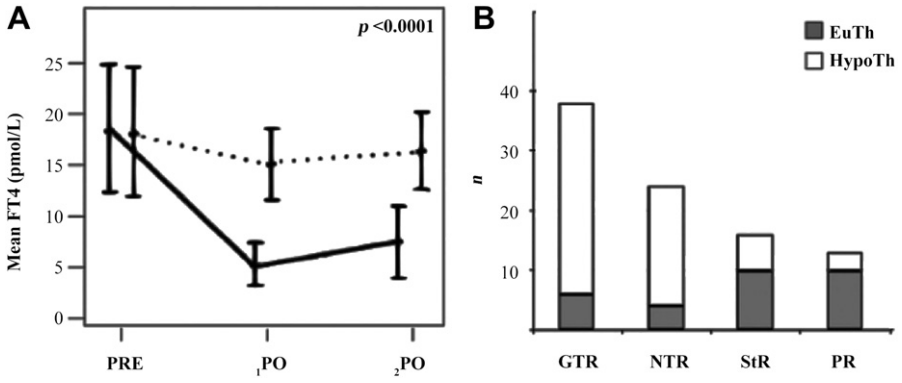

Figure 3. Thyroid axis outcome. (A) Mean plasma FT_4 concentrations and measurements for euthyroidal population (mean ± SD) at each time point: Preoperative (PRE), first postoperative (1PO) and second postoperative (2PO) determinations. Continuous line represents the mean value for both groups GTR and NTR. Dotted line represents the mean value for both groups STR and PR. Significantly decreased hormone levels below reference values were found ($p < 0.0001$) after radical surgeries when compared with lower rates of resection. (B) Comparison of long-term postoperative euthyroid (EuTh) vs. hypothyroidal (HypoTh) patients according to extent of tumor resection.

dysfunction. On multivariate analysis, when comparing GTR vs. NTR, STR and PR (46 vs. 33 vs. 23 vs. 19, χ^2 $p < 0.05$) and grade V vs. less invasive lesions, i.e., Samii grades IV, III and II (51 vs. 31 vs. 29 vs. 25, χ^2 $p < 0.05$), GTR of Grade V tumors increased 1.8 times the risk of postoperative endocrinopathy compared to STR in the same grade of hypothalamic involvement (Figure 4).

Univariate comparisons of rates of morbidities with patients stratified by age, tumor volume and extent of hypothalamic involvement did not reflect significant univariate predictors of neuroendocrine dysfunction for patients aged 55 years or less. Extensive hypothalamic involvement markedly increased the risk of postoperative anterior pituitary dysfunction; however, this factor was not a significant independent predictor of morbidity when the variable of extent of tumor removal was controlled for (OR 1.41, CI = 0.62–2.03, $p < 0.30$).

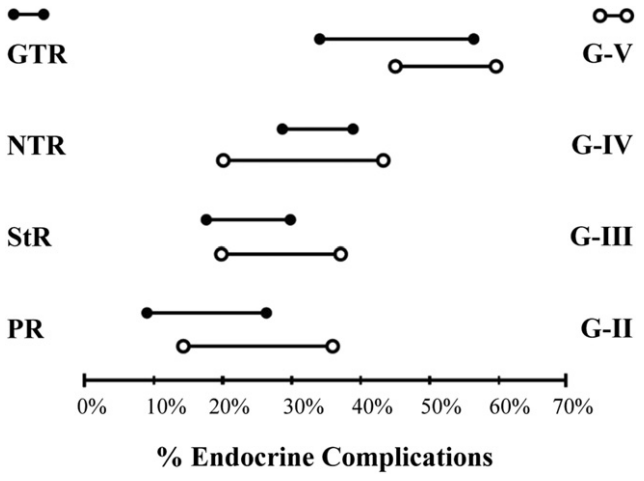

Figure 4. Comparison of 95% CI of rates of endocrinopathy for different grades of tumor resection (filled circles) and different grades of tumor extension (open circles).

Discussion

It has been previously reported that aggressive treatment of CP in adults is associated with excessive multisystem morbidity and increased mortality; however, in our country the information about CP is scarce and limited to series with small numbers (22,23). Consequently, although our data were collected retrospectively, the merits of this large exclusively adult cohort along with its long-term follow up outweigh its limitations.

Clinical presentation of CP may vary with size, location and tumor extension. The most common chief complaint, as in two thirds of our patients, is blurred vision in the form of chiasmatic syndrome. Intracranial hypertension has been reported as the second most common clinical manifestation in children (9,11,24,25), along a wide spectrum from mild headache to severely increased intracranial pressure and papilledema. However, in our study, it was only noted in 18/153 patients (11.7%). Interestingly, we found that 9.1% of our patients presented with psychiatric manifestations, a situation that could be explained by the large tumor volume and consequent compression over limbic and frontal structures.

Considering the differences emerging from two different histological types, we found some significant differences in terms of age of presentation and presence of calcifications; adamantinomatous type was more frequently seen by the first peak of presentation and calcifications were notoriously more frequent for this histological type. We found calcifications in three patients with papillary CP. This circumstance is rarely seen; however, it is not new and has been previously reported in other series. Based on our data, we found no significant differences between peaks of presentation and histological types in terms of resectability and surgical/endocrine complications. Even though adamantinomatous type showed higher rates of recurrence in both radical and conservative surgical groups, this

observation did not affect overall survival. Considering the *Hôpital Necker—Enfants Malades* classification of hypothalamic involvement (19), we found >90% of patients included in our series had hypothalamic affection. This result may suggest that tumors were diagnosed at late stages of the disease and could be explained by the long duration of symptoms (Table 1). We tried to explain the diagnostic delay by the lack of social security insurance affiliation among the studied population. However, two previous Mexican studies based exclusively on social security affiliates showed similar results. In 2003, Chávez-López et al. reported their experience with a mixed children/adult series of eight patients with cystic CPs treated between 1998 and 2001. These authors found average tumor dimensions of 30.6 ± 14.2 mm (3.8 mm less than our series) (22). Another study published in 2008 by Robles et al., based on their radiologic experience with eight cases of large craniopharyngiomas in children found similar locations to what had been previously published. However, when quantifying extension, they found large lesions ranging from 2—9 cm (23). Considering these similarities in terms of size and extension, we may hypothesize that, in our country, the knowledge of sellar lesions such as CP as causes of visual alterations (mainly visual field deficits) is not sufficiently spread out among primary care physicians, leading to wrong initial diagnoses and therapeutic strategies.

Based on our data, we found that initial CP volume and extent of hypothalamic involvement did not reflect significant univariate independent predictors of postoperative anterior pituitary dysfunction. However, extensive diencephalic involvement markedly increased the risk of postoperative neuroendocrine dysfunction when associated with higher rates of tumor removal. These data support the idea that lesser extents of resection may be a better choice for the patient's neuroendocrine outcome in adults with CP with large hypothalamic involvement, thus avoiding iatrogenic neuroendocrine complications.

Concerning surgical complications, it is worth mentioning that most CSF leaks presented during our initial experience of endoscopic transsphenoidal surgeries. This complication significantly decreased after refining of skull base reconstruction and closure techniques (nasoseptal flap, middle turbinate vascularized flap and gasket seal techniques) (26—28). Further studies are being carried out in our center to compare outcomes of transcranial and transsphenoidal techniques.

Although we were able to establish significantly higher rates of local control for GTR and NTR during long-term follow up, tumor control was not necessarily related to better overall survival rates. By contrast, higher rates of tumor removal (GTR and NTR group) were significantly associated with lower rates of OS. We could explain this situation by comparing our results with previously published pediatric and combined adult/pediatric series that demonstrated that total resections may lead to an unacceptably high rate of postoperative anterior and posterior pituitary deficiencies (29—33). Because the negative effect of hypopituitarism on life expectancy has been adequately demonstrated (34,35), several therapeutic strategies have arisen, focused on maximal tumor resection and anatomic preservation of critical neuroendocrine structures (32).

These data include the experience of a national referral center during a 25-year follow-up period. During this time, major progress in neuroimaging and preoperative assessment has transformed our own perspective, and currently we always follow a stepwise strategy individualized for each patient. Based on our results, and supported by the available data on CPs in adults, we have created our own treatment algorithm (Figure 5).

We consider that GTR must remain as a feasible choice for patients <55 years of age with pre- or retroinfundibular tumors, independently of tumor size. Transinfundibular and isolated third ventricular lesions must be assessed individually in terms of the relationship and compression over neuroendocrine and vascular structures.

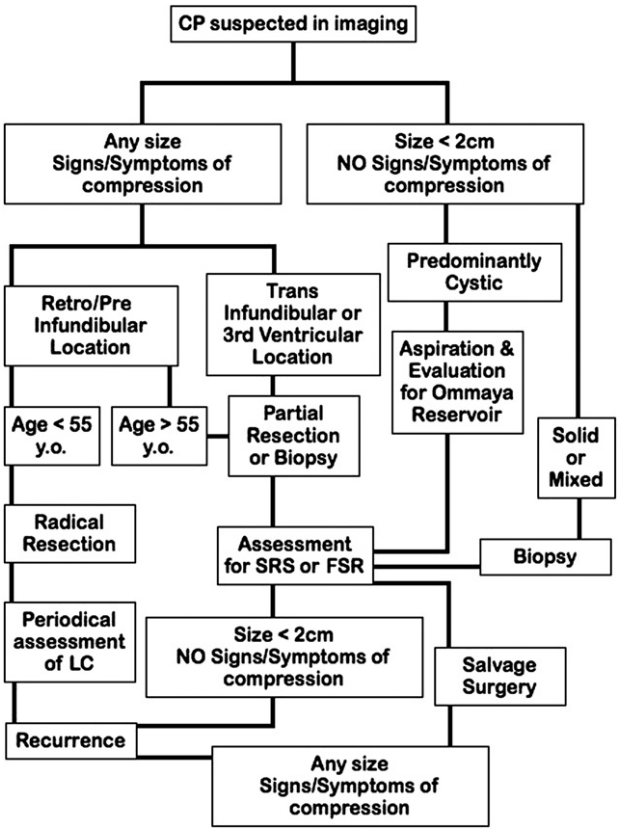

Figure 5. Treatment algorithm. Standardized decision-making algorithm based on our experience and previously published data. Initial evaluation of size, characteristics and location of tumor is essential to determine its relationship with the pituitary stalk. Note the endpoint at radiotherapy evaluation. CP, craniopharyngioma; SRS, stereotactic radiosurgery (single dose); FSR, fractionated stereotactic radiotherapy; LC, local control.

For these cases, stereotactic radiosurgery (SRS) or fractionated stereotactic radiotherapy (FSR) must be considered after biopsy for lesions <2 cm with no compression. Lesions >2 cm in these locations must follow PR or biopsy and postoperative SRS. Cystic CPs must always be considered separately because most compression effects may be alleviated after simple aspiration. Preoperative assessment of these lesions must always consider the feasibility for biopsy and cyst drainage. If solid tumor is unresectable or within the vicinity of critical structures, a conservative approach with PR/biopsy should be considered in order to avoid severe postoperative complications. Because local or systemic chemotherapy has not proved effective in the treatment of CP, it is not conventionally used in our Center as part of the treatment. Previous results in children have shown that subtotal resection with adjuvant SRS can serve as a desirable replacement for GTR when tumor remnants are located on critical structures or disease progression is documented after surgery (33). In this retrospective study involving a large cohort of exclusively adult patients with CPs treated with variable degrees of tumor resection, we were able to demonstrate that this premise may also have value in adult patients. Because the role of SRS and FSR as adjuvant treatments has been well validated in previous studies, it has already become the endpoint of our current treatment algorithm (Figure 5). We strongly recommend its use in those cases of residual tumor after conservative resection and in those with local recurrence; an individual assessment must be carried out to avoid iatrogenic complications associated with radiation. We have opted for a process of consensus decision-making in which the participation and surveillance of neurosurgeons, neuroendocrinologists and radiosurgery specialist results essential before and after radiotherapy treatment. Previous reports in children have advocated for GTR as the gold standard for large CPs with hypothalamic involvement (36–38). However, we believe that despite technical feasibility of complete resection of giant CPs, each individual case must be adequately assessed in order to avoid iatrogenic neuroendocrine complications leading to worse long-term survival.

In conclusion, considering that major complications of CP may emerge from its late diagnosis, diffusion of this condition among the medical community can never be sufficiently stressed, especially if considered as a preventable cause of blindness when opportunely treated.

Current therapeutic strategies of CP must be based on long-term results. In this large series with a 25-year follow-up, radical resection of CP in adults resulted in excellent rates of local control; however, these patients showed worse overall survival rates and more endocrine complications. Multimodal strategies should be considered instead of aggressive surgeries when critical neuroendocrine structures may be at risk, based on an individual and careful preoperative assessment.

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