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ORIGINAL ARTICLE

Magnetic resonance imaging as predictor of functional outcome in craniopharyngiomas

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Abstract Quality of life of craniopharyngioma patients can be severely impaired by derangement of hypothalamic function. A classification, taking into account preoperative hypothalamic damage, evaluated by magnetic resonance imaging (MRI), and correlating it with postoperative weight change is still missing in the literature. The aim of our study is to identify objective radiological criteria as preoperative prognostic factors for hypothalamic damage. Pre- and post-operative MRI and clinical data of 47 patients, treated at our Institution for craniopharyngioma, were retrospectively analyzed, based on radiological variables, identified as prognostic factor for hypothalamic involvement. Main factors associated with postoperative obesity were hypothalamic hyperintensity in T2-weighted/FLAIR imaging ($p < 0.033$), mammillary body involvement according to Müller classification ($p < 0.020$), unidentifiable pituitary stalk ($p < 0.001$), dislocated chiasm ($p < 0.038$), either not visible infundibular recess ($p < 0.019$) or unrecognizable supra-optic recess ($p < 0.004$), and retrochiasmatic tumor extension ($p < 0.019$). Accordingly, postoperative hypothalamic syndrome was associated with peritumoral edema in T2-weighted/FLAIR images ($p < 0.003$), unidentifiable hypothalamus ($p < 0.024$), hypothalamic compression ($p < 0.006$), fornix displacement ($p < 0.032$), and unrecognizable supra-optic recess ($p < 0.031$). Ultimately, variables identified as predictive factors of postoperative hypothalamic syndrome were the degree of hypothalamic involvement according to the classification described by Sainte-Rose and Puget ($p < 0.002$; grade 0 vs 2 $p < 0.001$), Van Gompel ($p < 0.002$; grade 0 vs 1, $p < 0.027$; and grade 0 vs 2, $p < 0.002$), and Muller ($p < 0.006$; grade 0 vs 1, $p < 0.05$; and grade 0 vs 2, $p < 0.004$). The identification of these predictive factors will help to define and score the preoperative hypothalamic involvement in craniopharyngioma patients.

Keywords Craniopharyngioma · MRI · Hypothalamus · Clinical outcome

Introduction

Craniopharyngiomas are classified as histologically benign tumors (WHO Grade 1 tumors) [1]. Nevertheless, the infiltrative behavior of the lesion may hamper its definitive treatment and often implies unfavorable and long-term sequelae after surgical removal [2].

Outcomes of craniopharyngioma treatment have been evaluated in terms of mortality rates, visual status, and endocrine function, but few studies have been conducted to address the derangement of hypothalamic function [3, 4].

It has become increasingly evident that the quality of life (QOL) following craniopharyngioma surgery is severely decreased by hyperphagia, obesity, and behavioral dysfunction, both in adult and in children [4–7].

At present, there are no adequate classifications available in the literature. A detailed and appropriate classification system which takes into account the preoperative hypothalamic impairment, evaluated by MRI, correlating it

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with postoperative weight change, has seldom been adopted in surgical series on craniopharyngiomas [8].

A topographical classification of craniopharyngiomas based on description of tumor relationships to the diencephalic structures through objective criteria could predict the potential risks of injury associated with surgical resection.

The aim of this study is to identify objective radiological criteria as preoperative prognostic factors of hypothalamic damage.

Methods

The study consists of a retrospective analysis of 47 patients with previously untreated craniopharyngioma who underwent surgery at the Department of Neurosurgery of San Raffaele Hospital, between 1996 and 2013. The diagnosis of craniopharyngioma was based on histopathological confirmation [9].

Follow-up information was retrospectively obtained by reviewing the records of each patient's regular follow-up visit and by contacting the patients and their families.

A complete endocrine evaluation was performed preoperatively in each patient at hospital admission and at 3, 6 months, and annually thereafter, according to criteria we have described in a previous report [2].

Body mass index (BMI kg/m^2) was calculated before, after surgery, and at follow-up. Obesity was defined by a BMI $>$ 30 kg/m^2. BMI in the pediatric cohort has been calculated as BMI SDS.

Hypothalamic dysfunction, including hyperphagia, memory deficits, thermoregulatory abnormalities, emotionally labile behavior, and sleep–wake cycle disruption, was recorded.

To complete pre- and post-operative clinical evaluation, patients were routinely submitted to an ophthalmological examination, including visual acuity and visual field computerized perimetry which were performed before and after surgery. Early postoperative results were based on an evaluation 2–3 months after surgery.

Selection of surgical approach was tailored on each case, according to criteria we have described in previous reports [10–13].

When indicated, patients underwent radiation treatment after surgery.

Fractionated radiotherapy was given in 25–27 fractions of 2 Gy each for a total dose ranging from 50 to 54 Gy.

Since 1993, Leksell Gamma Knife Radiosurgery was available in our department. Patients with craniopharyngioma were treated with a prescription dose ranging from 15 to 18 Gy. The choice between the two radiation modalities was primarily dictated by the location and the size of residual or recurrent tumor after surgery [11].

Neuroradiological evaluation

We considered anatomical structures involved by craniopharyngioma assigning a value to each parameter, scoring the degree in which the structure was involved. Tumor size was estimated by measuring the maximum antero-posterior, vertical, and horizontal diameters. The presence of hydrocephalus and the relationships of the tumor to optic chiasm, third ventricle, and sellar region were recorded in all cases.

Only the parameters that showed statistically significant association have been reported.

Structures, which were finally taken into consideration, were pituitary stalk, optic chiasm, anterior aspect and floor of the third ventricle, hypothalamus and mammillary bodies.

Lesions were topographically classified according to their relationship with the diaphragma sellae, ventricular walls and floor and the optic chiasm, as infra- and supradiaphragmatic, intra-/extra-/para-ventricular, pre-, and retrochiasmatic lesions, respectively.

Hypothalamic invasion was scored according to the three different classification systems proposed by Sainte-Rose and Puget, Van Gompel, and Muller [4, 14–17],

Neuroradiological follow-up examinations were used to assess surgical results in order to define extent of resection, quantification of tumor seeding in case of subtotal and partial tumor excision, as well as tumor recurrence. Images were systematically reviewed by a team of experienced neuroradiologists, routinely involved in the radiological evaluation of skull base pathologies.

Statistical analysis

Continuous data were examined for homogeneity of variance and are expressed as mean ± SEM. The Student's t-tests were used to compare continuous variables within groups. Boxplots and p values are given for illustration. The generalized exact Fisher's test was used for the comparison of a categorical variable among groups. Crosstabs and p values are given for illustration.

Preoperative factors and outcomes according to the different morphological characteristics and classification system were compared.

All calculations were performed using SPSS 16 software version (SPSS 16 Inc.). A p value <0.05 was considered statistically significant, and all reported probability values are 2-tailed.

Results

Clinical features

The clinical characteristics of the 47 patients are summarized in Table 1.

Childhood cases represented 21.3 % of all cases (10/47 patients). Excluding age, no significant difference between childhood and adult cases was observed for any of the variables.

Visual function was impaired before surgery in 32 patients (68.1 %). Twelve (25.5 %) had a visual field defect only, whereas the remaining 20 patients (42.6 %) had also impaired visual acuity.

Hypothalamic dysfunction was found in 16 patients (34 %). Particularly, in 6 cases, hyperphagia was the only clinical hypothalamic manifestation, whereas in 4 hyperphagia was not found. Of these latter, 3 cases were not associated with hydrocephalus: one patient showed drowsiness, depression, and asthenia; another one lethargy, anorexia, memory impairment, and irritability; and the last one showed disturbances of consciousness. In the case associated with hydrocephalus but not with hyperphagia, short-term memory and attention deficiency, change of mood, apathy, and disorientation were recorded.

The mean BMI before surgery was 24.5 ± 0.9 (range 14–37.5).

Surgical results

Among 7 patients (14.9 %) with hydrocephalus, 4 underwent ventricular drainage before tumor resection.

A transsphenoidal approach was used in 10 patients (21.3 %) and a transcranial approach in 37 patients (78.7 %). Among transcranial approaches, fronto-orbito-zygomatic (FOZ) approach was performed in 30 patients (81.1 %) and pterional approach in 7 patients (18.9 %). In a single case, the interhemispheric transcallosal-transventricular approach was adopted after the pterional approach to remove residual intraventricular tumors at the foramen of Monro.

Histological analysis confirmed the presence of craniopharyngioma in all cases. Thirty-nine of 46 (84.8 %) were classified as adamantinomatous subtype and 7/46 tumors (15.2 %) as papillary.

Radical resection, as evidenced by the first postoperative MRI, was achieved in 37 cases (78.7 %), subtotal in 9 (19.1 %), and partial in only one (2.1 %).

There were no perioperative deaths. Long-term complication occurred in 12 of the 46 surviving patients (25.5 %), whereas minor non-endocrine adverse events occurred in 21 patients (44.7 %).

Analysis of data collection referred only to the patients for whom a complete clinical assessment was available at the end of the follow-up.

Particularly, visual function of 44 patients, for whom it was possible to obtain information, improved after surgery in 24/44 patients (54.5 %), remained unchanged in 16/44 patients (34.0 %), and deteriorated in the remaining 4/44 patients (9.1 %). Among 14 of 15 patients with preoperative normal visual examinations, 12 patients (85.7 %) retained normal function, whereas the remaining 2 patients (14.3 %) developed a slight permanent visual field defect without any impairment of visual acuity.

Among 45 patients, 34 (75.6 %) had no hyperphagia before surgery, with or without obesity, and 21 (46.7 %) retained a normal weight (BMI < 29), whereas the remaining 13 (28.9 %) experienced postoperative weight gain. Of the 11 patients with preoperative obesity, only 1 (4.5 %) regained a normal weight. Preoperative hyperphagia had significant association with postoperative obesity ($p < 0.004$).

Among pediatric cases mean pediatric preoperative BMI was 20.5 (median: 18.7; range 14–34) with a mean Z-Score of -0.04 (median: 0.03; range -2.36 to 2.09); patients scored within a mean percentile of 50 % (median: 51 %; range 1–98 %). At the last follow-up examination, mean pediatric BMI was 29.1 (median: 29.7; range 19.8–42.4) with a mean Z-Score of 1.5 (median: 1.84; range -0.62 to 2.75); patients scored within a mean percentile of 82.2 % (median: 96 %; range 27–98 %).

Of 45 patients, 30 (66.7 %) had no clinical manifestations of hypothalamic syndrome before surgery and 18 (40 %) retained a normal function, whereas the remaining 12 (26.7 %) experienced postoperative hypothalamic syndrome. Of the 14 patients with preoperative hypothalamic syndrome, only 1 (5.3 %) regained a normal function. Preoperative clinical manifestations of hypothalamic syndrome had significant association with permanent postoperative hypothalamic syndrome ($p < 0.001$).

Among the 9 patients with residual tumor, radiation therapy was performed in 5 cases (55.6 %); three patients received fractionated radiotherapy and 2 were treated by single-dose GKS; radiotherapy was advised but not performed in 4 patients (44.4 %) because of early symptomatic recurrence of the tumor needing another surgical procedure (3 cases); and in one case it was refused.

In 3 patients (33.3 %), residual tumor was completely removed by the second surgical procedure (in one case through a transsphenoidal approach and in the other two through a transcranial approach).

Tumor recurrence or regrowth was detected in 7 (15.6 %) of the 45 patients on MRI follow-up with a median neuroradiological follow-up duration of 45 months (IQR 13–73 months), in 4 (11.1 %) of the 36 patients in

Table 1 Clinical and neuroradiological characteristics of the 47 patients who underwent surgery for craniopharyngioma

Variable	Children	Adults	Total
No. of patients	10 (21.3)	37 (78.8)	47
Mean age (years) at surgery (±SEM)	11 ± 1	41 ± 2	34 ± 2
Female sex	5 (50)	18 (48.6)	23 (48.9)
Endocrine symptoms	8/9 (88.9)	31 (83.8)	39/46 (84.8)
Adrenal function deficit	3 (30)	18 (48.6)	21 (44.7)
Thyroid function deficit	2 (20)	19 (51.4)	21 (44.7)
Gonadal function deficit	NA	29 (78.4)	29/37 (78.4)
GH deficit	6/9 (66.7)	7/24 (29.2)	13/33 (39.4)
Growth deficit	7 (70)	NA	7/10 (70)
Hyperprolactinemia	1/8 (12.5)	17 (45.9)	18/45 (40)
Diabetes insipidus	2 (30)	12 (32.4)	15 (31.9)
Visual deficit	6 (60)	26 (70.3)	32 (68.1)
Headache	6/8 (75)	20/32 (62.5)	26/40 (65)
Hyperphagia	3 (30)	9 (24.3)	12 (25.5)
Hypothalamic syndrome	3 (30)	13 (35.1)	16 (34)
Transsphenoidal approach	3 (30)	7 (18.9)	10 (21.3)
Neuroradiological characteristic			Total
Pituitary stalk and sella turcica			
Sellar invasion			21 (44.7)
Pituitary stalk identification			17 (36.2)
Chiasm			
Identification			37 (78.7)
dislocation			39 (83)
Anterior III ventricle cavity			
Infundibular recess identification			9 (19.1)
Supra-optic recess identification			20 (42.6)
III ventricle floor			
No involvement			8 (17)
Dislocation			23 (48.9)
Infiltration			16 (34)
Hypothalamus			
Identification			33 (70.2)
Compression			38 (80.9)
Irregular contrast enhancement			18 (38.3)
Peritumoral T2-weighted of FLAIR hyperintensity[a]			27/43 (62.8)
Mammillary bodies			
No involvement			22 (46.8)
Dislocation			16 (34)
Unrecognizable structures			9 (19.1)
Others			
Fornix dislocation			6 (12.8)
Monro involvement			12 (25.5)
Calcifications[b]			19/42 (45.2)
Hydrocephalus			7 (14.9)
Mean size (mm) ± SEM			27 ± 1.5
(Range)			(10–52)

Values given as number of patients (%) unless indicated as number of patients/valid cases (valid %)

NA not applicable

[a] Information on T2-weighted hyperintensity was missing in 4 patients

[b] Information on tumor calcification was missing in 5 patients

which gross total resection was previously confirmed and in 3 (33.3 %) of the 9 patients in which resection was incomplete.

Data on postoperative obesity and hypothalamic syndrome were retrospectively collected in 45. Obesity was observed in 23 (51.1 %) of the cases; symptoms and signs of hypothalamic dysfunction were observed in 26 patients (57.8 %). Height and weight measurements were available for 35 patients at the last BMI follow-up (median 40 and IQR 18–90 months). At the last BMI follow-up, the mean BMI was 29.9 ± 0.9 (range 19.8–42.4) kg/m^2.

Neuroradiological characteristics

The main neuroradiological characteristics are summarized in Table 1.

Infradiaphragmatic tumors accounted for 17 cases (36.2 %), eight of them showing an incompetent diaphragm sellae; among the remaining 9 with a competent diaphragm, 2 were purely intrasellar and 7 intrasuprasellar. Supradiaphragmatic tumors accounted for 30 cases (63.8 %), among which 13 were purely extraventricular, while the remaining 17 showed an intra/extra-ventricular extension. Pure paraventricular tumors were only three (6.4 %).

The tumors were classified according to the relative position to the optic chiasm. Nine (19.1 %) were prechiasmatic, and 38 were retrochiasmatic (80.9 %), among which 8 were subdiaphragmatic and 30 were supradiaphragmatic.

According to the classification proposed by Sainte-Rose and Puget, 9 patients did not show any hypothalamic involvement in MRI examination, 23 showed a compressed/displaced hypothalamus, and 15 a severe hypothalamic involvement. Van Gompel classification was applied in 43 patients; based on the paramagnetic signal on T2-weighted images, 17 patients did not show any invasion of the hypothalamus, while 14 showed a clear T2 hyperintensity suggesting a hypothalamic involvement.

According to the classification suggested by Muller, 9 patients did not present any diencephalic involvement, while 22 and 16 showed an anterior and a posterior hypothalamic involvement, respectively.

Significant difference in the presence of calcifications and hydrocephalus was observed between childhood and adult cases ($p < 0.015$, $p < 0.029$, respectively). In 42 patients for whom the report of the CT scan was available, calcifications were observed in 7 of 8 (87.5 %) children and 12 of 34 (35.3 %) adults. Among 10 children, 4 (40 %) showed obstructive hydrocephalus, while among the adult population, only 3 of 34 (8.1 %) showed this finding.

Correlations between neuroimaging characteristics, visual function and excessive hunger/abnormally large intake of food at presentation

The presence of preoperative disturbance in visual field or visual acuity was statistically associated with the following neuroradiological characteristics: chiasm dislocation ($p < 0.001$); hypothalamic identification ($p < 0.020$); the degree of third ventricle floor involvement ($p < 0.013$; grade 0 vs 1, $p < 0.027$; 0 vs 2 $p < 0.014$); and the degree of hypothalamic involvement according to Sainte-Rose and Puget [15] ($p < 0.025$: grade 0 vs 2, $p < 0.026$) (Table 2).

At presentation, excessive hunger and abnormally large intake of food were less frequent, in patients with a visible pituitary stalk ($p < 0.002$) and supra-optic recess ($p < 0.047$) on preoperative MRI.

Other characteristics associated with hyperphagia at presentation were the presence of peritumoral edema evaluated with T2-weighted or FLAIR imaging ($p < 0.033$), the degree of mammillary body involvement ($p < 0.020$; in particular between the grade 0 and grade 2, $p < 0.020$), and the degree of hypothalamic tumor involvement according to Muller classification [14] ($p < 0.011$; grade 0 vs 2, $p < 0.015$) (Table 2).

Correlations between neuroimaging characteristics and symptoms/signs of hypothalamic syndrome at presentation

Hypothalamic syndrome was associated with the following neuroradiological findings: unidentifiable pituitary stalk ($p < 0.001$), dislocated chiasm ($p < 0.038$), either infundibular recess ($p < 0.019$) or unrecognizable supra-optic recess ($p < 0.004$); a hypothalamic involvement in which anatomical structures were compressed ($p < 0.019$), unidentifiable ($p < 0.045$), or affected by peritumoral edema in T2-weighted or FLAIR imaging ($p < 0.003$); and the degree of mammillary body involvement ($p < 0.002$; grade 0 vs 2, $p < 0.001$).

According to the growth patterns described by Wang [18], retrochiasmatic tumors, as compared with the prechiasmatic ones, were associated with hypothalamic syndrome ($p < 0.019$). Other significant correlations were found with the degree of hypothalamic involvement according to Sainte-Rose and Puget ($p < 0.008$; grade 0 vs 2 $p < 0.007$) [15], to Van Gompel ($p < 0.006$; grade 0 vs 1, $p < 0.048$; and grade 0 vs 2, $p < 0.005$) [17] and to Muller classification ($p < 0.003$; grade 0 vs 2, $p < 0.003$; and grade 1 vs 2, $p < 0.049$) [14] (Table 3).

The analysis revealed that an unidentifiable pituitary stalk was associated with higher preoperative BMI (mean BMI = 26.04 ± 1.15 SEM) in comparison to patients in

Table 2 Statistically significant correlations in 47 patients between neuroimaging characteristics, visual function and excessive hunger/abnormally large intake of food at presentation

Characteristic	Normal visual function	Visual symptoms and sign	*p* value
Chiasm dislocation			0.001
No	7 (87.5)	1 (12.5)[b]	
Yes	8 (20.5)	31 (79.5)	
Hypothalamus identification			0.02
No	1 (7.1)	13 (92.9)	
Yes	13 (42.4)	19 (57.6)	
III ventricle floor			0.013
No involvement (grade 0)	6 (75)	2 (25)	0.027 (0 vs 1)
Dislocation (grade 1)	6 (26.1)	17 (73.9)	NS (1 vs 2)
Infiltration (grade 2)	3 (18.8)	13 (81.2)	0.014 (2 vs 0)
Puget hypothalamic involvement degree			0025
No involvement (grade 0)	5 (55.6)	4 (44.4)	NS (0 vs 1)
Intermediate (grade 1)	9 (39.1)	14 (60.9)	NS (1 vs 2)
Severe (grade 2)	1 (6.7)	14 (93.3)	0026 (2 vs1)

Characteristic	No hyperphagia	Hyperphagia	*p* value
Pituitary stalk identification			0.002
No	18 (60)	12 (40)	
Yes	17 (100)	0	
Supra-optic recess identification			0.047
No	17 (63)	10 (37)	
Yes	18 (90)	2 (10)	
Peritumoral edema in T2-weighted or FLAIR imaging[a]			0.033
No	15 (93.8)	1 (6.2)	
Yes	17 (63)	10 (37)	
Mammillary body involvement			0.02
No involvement (grade 0)	20 (90.9)	2 (9.1)	NS (0 vs 1)
Dislocation (grade 1)	11 (68.8)	5 (31.2)	NS (1 vs 2)
Unrecognizable structures (grade 2)	4 (44.4)	5 (55.6)	0.02 (1 vs 2)
Muller hypothalamic involvement degree			0.011
No involvement (grade 0)	9 (100)	0	NS (0 vs 1)
Anterior (grade 1)	18 (81.8)	4 (28.2)	NS (1 vs 2)
Anterior and posterior (grade 2)	8 (50)	8 (50)	0015 (2 vs 0)

Value given as number of patients (%) unless otherwise indicated

NS not significant

[a] Information on T2/FLAIR hyperintensity was missing in 5 patients

[b] One case was known for multiple sclerosis together with craniopharyngioma

whom it was recognizable (mean BMI = 21.95 ± 1.09 SEM) (*t* test, $p < 0.021$). In patients whose tumor displaced the chiasm, the preoperative BMI was higher (mean BMI = 25.42 ± 0.97 SEM) compared to the cases where the dislocation had not occurred (mean BMI = 20.48 ± 1.22 SEM) (*t* test, $p < 0.025$). Finally, through the analysis of T2-weighted or FLAIR, we found that patients with peritumoral hypothalamic edema had a higher BMI (mean BMI = 26.28 ± 1.18 SEM) compared to those where it was absent (mean BMI = 22.61 ± 1.28 SEM) (*t* test, $p < 0.042$) (Fig. 1a–c).

Correlations between neuroimaging characteristics, postoperative obesity and manifestation of hypothalamic syndrome

Hypothalamic involvement was the neuroradiological evidence associated with obesity (BMI > 30 kg/m2) at the

Table 3 Statistically significant correlations between neuroimaging characteristics and symptoms/signs of hypothalamic syndrome at presentation in 47 patients

Characteristic	No hypothalamic syndrome	Hypothalamic syndrome	*p* value
Pituitary stalk identification			0.000
No	14 (46.7)	16 (53.3)	
Yes	17 (100)	0	
Chiasm dislocation			0.038
no	8 (100)	0	
Yes	23 (59)	16 (41)	
Infundibular recess identification			0.019
No	22 (57.9)	16 (42.1)	
Yes	9 (100)	0	
Supra-optic recess identification			0.004
No	13 (48.1)	14 (51.9)	
Yes	18 (90)	2 (10)	
Hypothalamic compression			0.019
No	9 (100)	0	
Yes	22 (57.9)	16 (42.1)	
Hypothalamic identification			0.045
No	6 (42.9)	8 (57.1)	
Yes	25 (75.8)	8 (24.2)	
Peritumoral edema in T2-weighted or FLAIR imaging[a]			0.003
No	15 (93.8)	1 (6.2)	
Yes	13 (48.1)	14 (51.9)	
Mammillary body involvement			0.002
No involvement (grade 0)	19 (86.4)	3 (13.6)	NS (0 vs 1)
Dislocation (grade 1)	10 (62.5)	6 (37.5)	NS (1 vs 2)
Unrecognizable structures (grade 2)	2 (22.2)	7 (77.8)	0001 (2 vs 0)
Wang growth pattern			0.019
Prechiasmatic	9 (100)	0	
Retrochiasmatic	22 (57.9)	16 (42.1)	
Puget hypothalamic involvement			0.008
No involvement (grade 0)	9 (100)	0	NS (0 vs 1)
Intermediate (grade 1)	16 (69.9)	7 (30.4)	NS (1 vs 2)
Severe (grade 2)	6 (40)	9 (60)	0007 (2 vs 0)
Van Gompel hypothalamic involvement			0.006
No involvement (grade 0)	12 (100)	0	0.048 (0 vs 1)
Intermediate (grade 1)	10 (58.8)	7 (41.2)	NS (1 vs 2)
Severe (grade 2)	6 (42.9)	8 (57.1)	0.005 (2 vs 0)
Muller hypothalamic involvement			0.003
No involvement (grade 0)	9 (100)	0	NS (0 vs 1)
Anterior (grade 1)	16 (72.7)	6 (27.3)	0.049 (1 vs 2)
Anterior and posterior (grade 2)	6 (37.5)	10 (62.5)	0.003 (2 vs 0)

Value given as number of patients (%) unless otherwise indicated

NS not significant

[a] Information on T2/FLAIR hyperintensity was missing in 5 patients

long-term follow-up. We found significant associations with the compression of the hypothalamic structures ($p < 0.022$), the presence of peritumoral hypothalamic edema on T2-weighted or FLAIR images ($p < 0.008$), and the degree of hypothalamic involvement described by Sainte-Rose and Puget ($p < 0.027$), Van Gompel

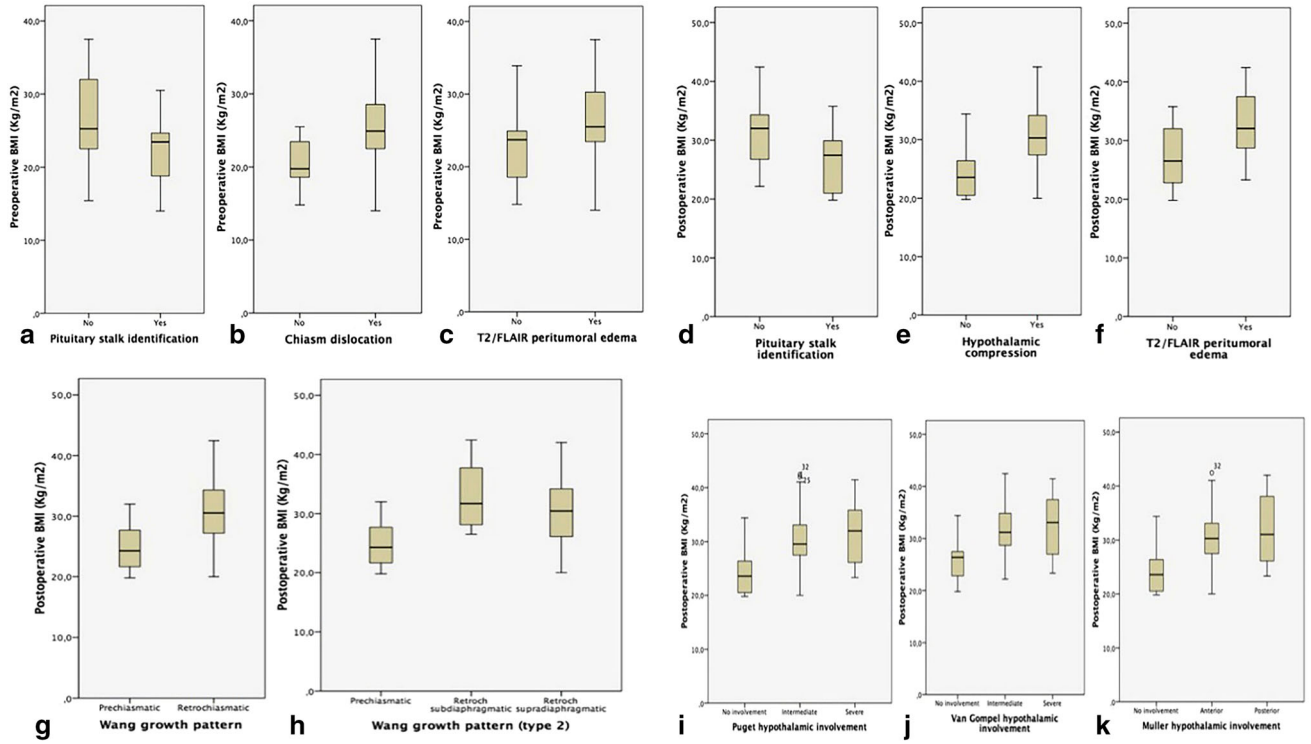

Fig. 1 **a–c** Preoperative body mass index in relation to presurgical pituitary stalk identification, chiasm dislocation, and peritumoral hypothalamic edema at T2/FLAIR-weighted images of 47 patients treated for craniopharyngioma. The *horizontal line* in the middle of the box depicts the median. Edges of box mark the 25th and 75th percentile. *Whiskers* indicate the range of values that fall within 1.5 box-length. **d–f** Body mass index at the last evaluation in relation to presurgical pituitary stalk identification, hypothalamic compression, peritumoral hypothalamic edema at T2/FLAIR-weighted images of patients treated for craniopharyngioma. **g, h** Body mass index at the last evaluation in relation to presurgical growth pattern (described by Wang) of patients treated for craniopharyngioma. **i–k** Body mass index at the last evaluation in relation to presurgical degree of hypothalamic involvement (described by Puget, Van Gompel and Muller) of patients treated for craniopharyngioma

($p < 0.008$), and Muller ($p < 0.041$). In all three classification systems, there was a significant difference between the involvements classified as severe or absent: Sainte-Rose and Puget grade 2 versus 0 ($p < 0.023$); Van Gompel grade 2 versus 0 ($p < 0.009$); and Muller grade 2 versus 0 ($p < 0.04$). In addition, according to Van Gompel's classification, a significant difference was also found with an intermediate degree of hypothalamic involvement (grade 0 vs 1, $p < 0.035$) (Table 4).

Postoperative hypothalamic syndrome was associated with the following neuroradiological findings: unrecognizable supra-optic recess ($p < 0.031$); a hypothalamus compression ($p < 0.006$), hypothalamus unidentifiable ($p < 0.024$), or with peritumoral edema in T2-weighted or FLAIR images ($p < 0.003$); and displacement of the fornix ($p < 0.032$).

Retrochiasmatic growth pattern was significantly associated with hypothalamic syndrome compared to the prechiasmatic growth pattern ($p < 0.024$). Other significant correlations were found with the degree of hypothalamic involvement according to the classification by Sainte-Rose and Puget ($p < 0.002$; grade 0 vs 2 $p < 0.001$), Van Gompel ($p < 0.002$; grade 0 vs 1, $p < 0.027$; and grade 0 vs 2, $p < 0.002$), and Muller ($p < 0.006$; grade 0 vs 1, $p < 0.05$; and grade 0 vs 2, $p < 0.004$) (Table 5).

The detailed statistical analysis with the independent *t* test results is shown in Table 6 and represented through box and whiskers plot in Fig. 1. Case examples of the most relevant parameters demonstrated to be predictive of hypothalamic dysfunction are shown in Fig. 2.

Discussion

Outcomes of craniopharyngioma treatment have been previously evaluated in terms of mortality, vision status, and endocrine function, but few studies have been addressed to the derangement of hypothalamic function [3, 4, 11]. It has become increasingly evident that QOL following craniopharyngioma surgery can be influenced by uncontrollable hyperphagia, obesity, and behavioral dysfunction, due to hypothalamic dysfunction [4–7].

Furthermore, while these observations have been made mostly in children, adult patients have been

Table 4 Correlation between the hypothalamic involvement and the presence of postoperative obesity in 45 patients treated for craniopharyngioma

Characteristic	No postoperative obesity	Postoperative obesity	*p* value
Hypothalamic compression			0.022
No	7 (87.5)	1 (12.5)	
Yes	15 (40.5)	22 (59.5)	
Peritumoral edema in T2-weighted or FLAIR imaging[a]			0.008
No	11 (73.3)	4 (26.7)	
Yes	7 (26.9)	19 (73.1)	
Puget hypothalamic involvement			0.027
No involvement (grade 0)	7 (87.5)	1 (12.5)	NS (0 vs 1)
Intermediate (grade 1)	11 (47.8)	12 (52.2)	NS (1 vs 2)
Severe (grade 2)	4 (28.6)	10 (71.4)	0023 (2 vs 0)
Van Gompel hypothalamic involvement[b]			0.008
No involvement (grade 0)	9 (81.8)	2 (18.2)	0.035 (0 vs 1)
Intermediate (grade 1)	6 (35.3)	11 (64.7)	NS (1 vs 2)
Severe (grade 2)	3 (23.1)	10 (76.9)	0.009 (2 vs 0)
Muller hypothalamic involvement			0.041
No involvement (grade 0)	7 (87.5)	1 (12.5)	NS (0 vs 1)
Anterior (grade 1)	10 (45.5)	12 (54.5)	NS (1 vs 2)
Anterior and posterior (grade 2)	5 (33.3)	10 (66.7)	0.04 (2 vs 0)

Value given as number of patients (%) unless otherwise indicated

[a] Information on T2/FLAIR hyperintensity was missing in 4 patients

[b] Information on Van Gompel classification was missing in 4 patients

underrepresented regarding these important perioperative morbidities [17]. In our study, we did not find any significant difference in clinical and radiological characteristics between adults and children, except for the higher frequency of tumor calcification ($p < 0.015$) and hydrocephalus ($p < 0.029$) in the pediatric cases. Therefore, pooling the results of the two groups together for the statistical analysis has to be considered appropriate.

Craniopharyngiomas topographical classifications

The high variability of the relationships of craniopharyngiomas with the surrounding structures has resulted in numerous topographical classifications [19–22]. Nevertheless, a detailed classification on the diencephalic involvement in craniopharyngiomas with suprasellar extension, which is thought to predict hypothalamic function, is still missing in the literature [23].

A majority of craniopharyngiomas have a suprasellar component at presentation, while purely intrasellar ones are the least common variety [18, 24]. In our series, purely intrasellar craniopharyngiomas account only for 4.3 % of cases. The major part of prechiasmatic tumors (19.1 % in our series) presented only an intrasellar subdiaphragmatic portion (80.9 %), as compared to retrochiasmatic cases, among which the 21.1 % are limited to the sellar cavity.

Even in case of a competent diaphragm sellae, primarily subdiaphragmatic craniopharyngioma may secondarily extend to the suprasellar area, causing upward displacement of the third ventricular floor [18, 25]. In particular we found that, among 31.9 % of subdiaphragmatic tumors, 14.9 % showed a competent diaphragm sellae and 17 % an incompetent one.

In case of primarily supradiaphragmatic craniopharyngiomas (63.8 % in our series), the topographical relationship with the third ventricle and hypothalamus can be more complex; the tumor can indeed be purely extraventricular, intra/extra-ventricular, or completely intraventricular [25]. Among the supradiaphragmatic tumors of our series, 43.3 % of craniopharyngiomas were purely extraventricular, 56.7 % intra/extra-ventricular, and there were no case of purely intraventricular tumors.

The type of craniopharyngioma-induced deformation of the third ventricle walls influences the functional state of the hypothalamus [23].

De Vile et al. [3] showed that postoperatively assessed hypothalamic damage positively correlated with weight gain during follow-up. After this study, many authors analyzed the weight increase in relation to the preoperative hypothalamic impairment to find prognostic factors [14–17, 26, 27].

Meuric et al. and Sainte-Rose and Puget [15, 16, 27] introduced the concept of grading hypothalamic

Table 5 Correlation between neuroradiological characteristics and manifestation of hypothalamic syndrome after surgery in 45 patients treated for craniopharyngioma

Characteristic	No hypothalamic syndrome	Hypothalamic syndrome	*p* value
Supra-optic recess identification			0.031
No	7 (26.9)	19 (73.1)	
Yes	12 (63.7)	7 (36.8)	
Hypothalamic identification			0.024
No	2 (15.4)	11 (84.6)	
Yes	17 (53.1)	15 (46.9)	
Hypothalamic compression			0.006
No	7 (87.5)	1 (12.5)	
Yes	12 (32.4)	25 (67.6)	
Peritumoral edema in T2-weighted or FLAIR imaging[a]			0003
No	11 (73.3)	4 (26.7)	
Yes	6 (23.1)	20 (76.9)	
Fornix dislocation			0.032
No	19 (48.7)	20 (51.3)	
Yes	0	6 (100)	
Wang growth pattern			0.024
Prechiasmatic	7 (77.8)	2 (22.2)	
Retrochiasmatic	12 (33.3)	24 (66.7)	
Puget hypothalamic involvement			0.002
No involvement (grade 0)	7 (87.5)	1 (12.5)	NS (0 vs 1)
Intermediate (grade 1)	10 (43.5)	13 (56.5)	NS (1 vs 2)
Severe (grade 2)	2 (14.3)	12 (46.2)	0.001 (2 vs 0)
Van Gompel hypothalamic involvement[b]			0.002
No involvement (grade 0)	9 (81.8)	2 (18.2)	0.027 (0 vs 1)
Intermediate (grade 1)	6 (35.3)	11 (64.7)	NS (1 vs 2)
Severe (grade 2)	2 (15.4)	11 (84.6)	0.004 (2 vs 0)
Muller hypothalamic involvement			0.006
No involvement (grade 0)	7 (87.5)	1 (12.5)	0.05 (0 vs 1)
Anterior (grade 1)	9 (40.9)	13 (59.1)	NS (1 vs 2)
Anterior and posterior (grade 2)	3 (20)	12 (80)	0.004 (2 vs 0)

Value given as number of patients (%) unless otherwise indicated

[a] Information on T2/FLAIR hyperintensity was missing in 4 patients

[b] Information on Van Gompel classification was missing in 4 patients

involvement with a radiological score ranging from 1 to 3, later modified to the 0–2 system. After that, Van Gompel et al. [17] reported that hypothalamic signal changes in T2-weighed MR images as well as irregular contrast enhancement predicted the hypothalamic involvement. On the other hand, Müller et al. [14] found that the risk of hypothalamic damage increases in case of tumors extended beyond the mammillary bodies.

These data highlight the usefulness of a topographical classification of craniopharyngiomas to predict the potential risks of hypothalamic injury associated with tumor resection; the classification should be based on an accurate description of the tumor relationships to the walls of the third ventricle [15].

Correlations between neuroimaging characteristics and hypothalamic disfunction at presentation

A retrospective analysis of growth of children harboring craniopharyngioma indicated that increased weight was evident even before the diagnosis [28]. In our analysis this finding was noticed not only in the pediatric population but also in adults. Symptoms and signs of hypothalamic dysfunction at presentation were indeed found in 30 % of pediatric and 35.1 % of adults patients. Hyperphagia as a manifestation of hypothalamic damage was present in both groups (30 % of children; 24.3 % of adults).

By analyzing neuroradiological tumor patterns, we observed that an unidentifiable pituitary stalk, the presence

Table 6 Statistical analysis between neuroradiological characteristics and the postoperative BMI at the last evaluation and independent sample *t* test results

Characteristic	No. of patients	Mean BMI ± SEM	*p* value
Pituitary stalk identification			0.016
No	27	31.5 ± 1.1	
Yes	12	26.4 ± 1.5	
Hypothalamic compression			0.022
No	6	24.7 ± 2.1	
Yes	33	30.9 ± 1	
Peritumoral edema in T2-weighted or FLAIR imaging			0.008
No	13	27.3 ± 1.5	
Yes	22	32.7 ± 1.2	
Wang growth pattern			0.017
Prechiasmatic	7	24.9 ± 1.7	
Retrochiasmatic	32	31 ± 1	
Wang growth pattern (type 2)			
Prechiasmatic (0)	7	24.9 ± 1.7	0.012 (0 vs 1)
Retrochiasmatic subdiaphragmatic (1)	8	33 ± 2.1	NS (1 vs 2)
Retrochiasmatic supradiaphragmatic (2)	24	30.4 ± 1.2	0.036 (2 vs 0)
Puget hypothalamic involvement			
No involvement (grade 0)	6	24.7 ± 2.1	0.041 (0 vs 1)
Intermediate (grade 1)	22	30.5 ± 1.2	NS (1 vs 2)
severe (grade 2)	11	31.7 ± 1.8	0.030 (2 vs 0)
Van Gompel hypothalamic involvement			
No involvement (grade 0)	9	26 ± 1.6	0.011 (0 vs 1)
Intermediate (grade 1)	16	32.2 ± 1.4	NS (1 vs 2)
Severe (grade 2)	10	32.4 ± 1.8	0.021 (2 vs 0)
Muller hypothalamic involvement			
No involvement (grade 0)	6	24.7 ± 2.1	0.038 (0 vs 1)
Anterior (grade 1)	21	30.3 ± 1.2	NS (1 vs 2)
Anterior and posterior (grade 2)	12	32 ± 1.9	0.033 (2 vs 0)

of chiasm displacement and a T2/FLAIR peritumoral hypothalamic edema were significantly associated with preoperative hyperphagia and higher BMI, predicting functional hypothalamic damage.

Furthermore, the degree of hypothalamic involvement taking into account the limits of mammillary bodies, as described by Muller [14], was associated with excessive hunger and abnormally food intake at presentation, even without obesity ($p < 0.011$).

Correlations between neuroimaging characteristics and postoperative hypothalamic disfunction

After treatment, hypothalamic obesity (51.1 % in our series with a mean BMI of 29.9 kg/m^2, ranging from 19.8 to 42.4) was documented in 35 to 58 % of patients in other series [17, 29–31]. The degree of preoperative hypothalamic involvement was found to be the major factor influencing weight changes.

Puget et al. found a correlation between the postoperative BMI score and the preoperative imaging grade in a retrospective cohort of 66 children [15]. This finding was subsequently confirmed in a multicenter prospective study on pediatric population, where the only independent risk factor for severe obesity, on multivariate analysis, was the degree of radiological preoperative hypothalamic involvement [14]. In our series, we did not found any significant association between postoperative BMI and preoperative imaging according to the grading system proposed by Puget and Muller, even stratifying the data for the pediatric group.

On the other hand, Van Gompel classification [17] applied in our series showed a good correlation between degree of preoperative hypothalamic involvement and postoperative BMI ($p < 0.022$).

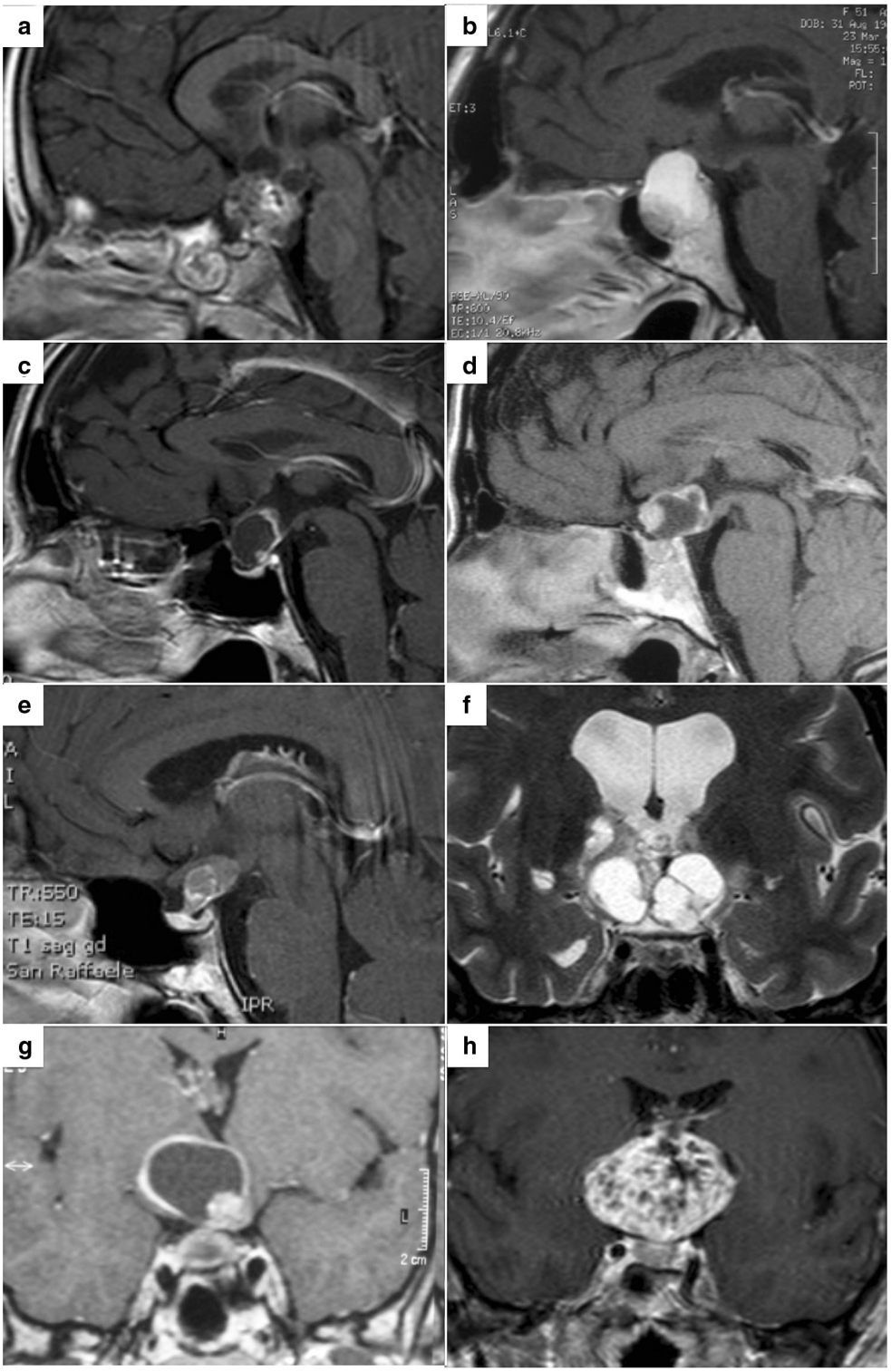

Fig. 2 Case examples of the most relevant parameters demonstrated to be predictive of hypothalamic dysfunction; **a** Mammillary body involvement, **b** dislocated chiasm, **c** unidentifiable pituitary stalk, **d** unrecognizable supra-optic recess, **e** retrochiasmatic tumor extension, **f** hypothalamic T2 hyperintensity, **g** unidentifiable hypothalamus, and **h** fornix displacement

Differently from what observed by Muller et al. [14]. in childhood craniopharyngioma, we did not find differences between mixed anterior/posterior and only anterior hypothalamic involvement in terms of postoperative BMI, although the more severe the hypothalamic involvement, the higher was the rate of postoperative obesity.

The most important factor strongly associated with postoperative obesity (BMI > 30) was peritumoral edema, evaluated by T2- weighted and FLAIR preoperative images ($p < 0.008$).

The degree of peritumoral edema has been suggested as a predictor of complications [17, 32]. Furthermore, Shi et al. discussed the importance of irregular hypothalamic enhancement after Gadolinium administration as suggestive of high-grade invasion and therefore associated with more severe diencephalic involvement [33].

From this perspective, we see some weak points among the classification systems already in use.

Sainte-Rose and Puget's classification was criticized because of the reliance on subjective criteria for differentiation between higher grades [15, 17]. Particularly, the "severe hypothalamic involvement" is assigned to retrochiasmatic tumor with non-identifiable hypothalamus on MRI, without any difference between hypothalamic compression or infiltration and the degree of adherence of the tumor to diencephalic structures [25, 34].

According to Steno et al., primary supradiaphragmatic craniopharyngiomas differ from originally subdiaphragmatic, and are associated with a less favorable prognosis [25, 34]. However, the suprasellar extension of a subdiaphragmatic craniopharyngioma might be still subdiaphragmatic; in this case, the diaphragm covers most of the suprasellar portion, making the tumor less adherent to neurovascular structures. Conversely, in case of subdiaphragmatic tumors with incompetent diaphragm, the lesion directly contacts and adheres to surrounding structures mostly through its retrochiasmatic portion [22, 18].

In our series, tumors with retrochiasmatic growth pattern with incompetent diaphragm were associated with higher postoperative BMI at follow-up as compared with tumors with competent diaphragm and prechiasmatic growth pattern.

Steno et al. [34] and Pascual et al. [35] reported a higher hypothalamic complication rate, in case of tumors with intraventricular extension as compared with purely extraventricular tumors [34]. To preserve the hypothalamic function, it is very important to distinguish between suprasellar extraventricular and suprasellar intra- and extra-ventricular craniopharyngioma. In the first group, the hypothalamus can be simply compressed and not infiltrated [34]. In our series, we did not find any significant difference in the hypothalamic functions comparing intra- and extra-ventricular craniopharyngiomas with purely extraventricular ones.

Final remarks

The treatment of patients with craniopharyngiomas changed during the decades [16]. It has changed from attempting gross total resection in those patients with hypothalamic invasion [22, 36, 37] to a less radical approach [6, 15].

Radical resection is considered the primary therapy of choice, because it is associated with the best outcome in terms of overall and recurrence-free survival [2, 38]. Nevertheless, in the reported series, gross total removal of craniopharyngiomas is extremely variable [2, 3, 6, 14, 21, 22, 29, 37, 39–55] and the rate of firm hypothalamic adherence is reported in the literature up to 26.8 % of cases [36].

For these reasons, the intentional incomplete removal of tumors that are defined as "involving the hypothalamus" cannot be recommended, without defining the relationships of the tumor and the hypothalamus on preoperative images. Hypothalamic hyperintensity in T2-weighted/FLAIR images, mammillary body involvement, unidentifiable pituitary stalk, dislocated chiasm, either infundibular recess or unrecognizable supra-optic recess, and retrochiasmatic tumor extension have proved to be useful to define the hypothalamus invasion [56].

To the best of our knowledge, this is the first study which identifies radiological variables linked to hypothalamus involvement on the preoperative MRI, and correlates them using statistical criteria, with clinical features, long-term outcome, and prognosis.

Conclusion

This study identified objective radiological criteria, as preoperative prognostic factor of hypothalamic damage. The application of these predictive factors will help to precisely define and score hypothalamic involvement and to consequently plan the better treatment strategy in craniopharyngioma patients.

Compliance with Ethical Standards

Conflicts of interest The authors declare that they have no conflict of interest.

Human and animal rights and informed consent All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required. This article does not contain any studies with animals performed by any of the authors. Informed consent was obtained from all individual participants included in the study.

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