# Radiological and endocrinological evaluations with grading of hypothalamic perifocal edema caused by craniopharyngiomas

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## Abstract

**Introduction** Hypophysial and hypothalamic dysfunction caused by craniopharyngioma is a serious problem despite the progress of surgical approaches and techniques. Perifocal edema induced by craniopharyngioma could be speculated as a potential factor resulting in pre- and post-operative hypophysial and hypothalamic dysfunction, as well as, their anatomical involvement.

**Methods** Medical records of 54 patients with craniopharyngioma were retrospectively reviewed. The edema was characterized by a hyperintense area in magnetic resonance imaging, being classified into no edema (group A), only adjacent to the tumor (group B), and extending to the internal capsule or the optic tract (group C). Age, sex, tumor diameter, presence of cyst, hydrocephalus, intracranial pressure (ICP) elevation, visual function impairment, hypopituitarism, diabetes insipidus, memory disturbance, and obesity were investigated.

**Results** The occurrence rate of edema was found more frequently in adults (73.7%) than in children (25.0%). The peritumoral edema grading system had an excellent correlation with the degree of hypothalamic involvement graded by the Puget's system. Pre-operative ICP elevation was significantly detected in group C when compared with the other groups. In adults patients, group C was significantly associated with the occurrence of hydrocephalus both in pre- and post-operatively. Pre- and post-operative hypothalamic dysfunction, including diabetes insipidus, memory disturbance, and obesity, were highest in group C.

**Conclusion** Hypothalamic dysfunctions greatly influence the quality of daily living following craniopharyngioma surgery. The grading of perifocal edema's extension could be a new index suggesting pre- and post-operative hypothalamic dysfunction caused by craniopharyngioma in addition to their anatomical involvement.

**Keywords** Craniopharyngioma · Edema · Hypothalamus · Magnetic resonance imaging · Hyperintensity

## Abbreviations

| | |
|---|---|
| BMI | Body mass index |
| CT | Computed tomography |
| DI | Diabetes insipidus |
| FLAIR | Fluid attenuated inversion recovery |
| GTR | Gross total removal |
| MRI | Magnetic resonance imaging |
| WI | Weighted image |

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## Introduction

It is well known that primary malignant brain tumors, such as high-grade glioma or metastatic brain tumors, are often associated with remarkable brain edema. Meanwhile, primary benign brain tumors, such as pituitary adenoma and craniopharyngioma, usually do not follow the surrounding brain edema. Lanksch evaluated the frequency and the extent of perifocal edema derived from brain tumors and revealed on computed tomography (CT) in 3750 patients [1]. Although perifocal edemas caused by craniopharyngioma were reported

by Higashi et al., the radiological features and endocrinological evaluations have not been investigated in detail [2].

Perifocal edema occurs rarely with craniopharyngioma that extends from the adjacent area surrounding the tumor in the hypothalamus down the internal capsule and the optic tract [2–5]. The edema usually appears on both sides and its shape resembles a moustache on axial images of CT scan and magnetic resonance imaging (MRI). Therefore, Higashi gave the edema the name of moustache sign. Other authors also named it as the optic tract sign [2, 4]. This edema can be found not only in craniopharyngioma but also in other sellar and parasellar tumors [6, 7]. It was speculated that the edema was derived from a compression of the hypothalamus by the tumors. The developing mechanism was considered as follows: the outlet of the interstitial fluid at the area of the hypothalamus is blocked in and along the Virchow–Robin spaces, and the retention of the fluid extends into the internal capsule and the optic tract [8, 9].

It is well known that gross-total removal (GTR) is important to achieve long term survival [10–12]. However, in order to obtain GTR, there is a higher rate of complications that often lead to a difficulty in maintaining normal quality of daily living [13, 14]. The morbidity resulting from radical resection of craniopharyngioma is strongly related to the intimate anatomical relationship with the neurohypophysis, in particular, with the hypothalamus. Post-operative hypophysial and hypothalamic dysfunction (panhypopituitarism, obesity, hyperphagia, diabetes insipidus (DI), and neuropsychological abnormalities) affect the outcome of patients dramatically [15]. It would be very important to evaluate, pre-operatively, the involvement of the hypothalamus with the tumor. The evaluation has been mainly based on pre-operative MRI grading, clinically hypothalamic function and neurosurgeon's operative skills [15, 16]. However, the hypothalamic tumor involvement is sometimes hard to assess accurately. Therefore, another way to evaluate the hypothalamic function is required. Some authors presented hypothalamic hyperintensity in T2-WI/fluid attenuated inversion recovery (FLAIR) on MRI as a prognostic factor for hypothalamic involvement, but hypothalamic hyperintensity varies from the adjacent area to the tumor to the extension toward the internal capsule and the optic tract [17, 18]. The hyperintensity on T2WI/FLAIR was evaluated for its predictive value of the perifocal edema due to the craniopharyngioma and the grade of the edema was compared with the clinical signs and the hypothalamic dysfunction in our series of patients with craniopharyngioma.

## Methods

### Characteristics of study patients

Fifty-four patients with craniopharyngiomas were included in this retrospective study. Between 2000 and 2018, all patients underwent MRI scans at Kanazawa University Hospital, and had a post-operative follow-up for at least 6 months. The diagnosis of craniopharyngioma was based on histopathological confirmation [19]. Patients were enrolled in this study with the approval of the Institutional Review Board of Kanazawa University. Patient demographics, including age, sex, tumor histology, and symptoms, including headache, nausea, vomiting due to intracranial pressure (ICP) elevation, visual function impairment, symptoms due to hypopituitarism (e.g., general malaise), and polydipsia and polyuria due to DI were obtained from clinical records.

Basically, in order to achieve GTR, surgery was performed. Surgical procedures were determined by tumor size, direction of extension, and surgeon's preference. At the beginning of this study, the more common approaches were transcranial approaches including translamina terminalis, pterional, transcallosal, and orbitozygomatic. However, more recently, almost all cases were treated with endoscopic extended endonasal transsphenoidal approach.

### Neuroradiological evaluation

In this study, perifocal edema in the hypothalamus caused by craniopharyngioma was assessed as hyperintense areas on MRI by at least two neurosurgeons (Y.H., Y.S.) and one neuroradiologist (K.K.). MR images were obtained using a Signa HDx 3T (GE Medical Systems, Milwaukee, WI). For T2-WI, the following parameters were used: repetition time, 2500–3500 ms; echo time, 98–104 ms; flip angle, 90°; field of view, $14 \times 14$ cm; matrix, $288 \times 224$ or $256 \times 192$; section thickness, 2.0–3.0 mm; and spacing, 0.5 mm. For FLAIR: repetition time, 8000 ms; echo time, 110–144 ms; inversion time 2000–2750 ms, field of view $20 \times 20$ cm, matrix $256–288 \times 160–230$, section thickness, 5.0 mm; and spacing, 1.5 mm. Based on the extent of the pre-operative perifocal edema caused by craniopharyngiomas, patients in this study were divided into the following three groups: A—no edema was detected; B—edema restricted to the nearby area of the tumor in the hypothalamus; and C—edema extended toward the internal capsule and the optic tract.

The preoperative MR images in each patient were independently distributed by Puget's grading, which was prescribed by the degree of hypothalamic involvement

[15]: Grade 0, no hypothalamic involvement; Grade 1, the tumor abutting or displacing the hypothalamus; Grade 2, hypothalamic involvement (the hypothalamus is no longer identifiable).

Cystic craniopharyngiomas are considered as the cystic portion of a tumor and, predominantly, account for at least 60% of the tumors. This diagnosis was based on MRI [20]. Hydrocephalus is defined as the progressive ventricular enlargement and related symptoms, such as memory disturbance, gait disturbance, urinary incontinence, headache, and reduced level of alertness.

## Endocrinological evaluation

A pre-operative endocrinological assessment was undertaken in each patient at hospital admission, including the measurement of plasma levels of the following hormones secreted from the pituitary gland and their targeted organs: growth hormone, insulin-like growth factor-I, prolactin, adrenocorticotropic hormone, cortisol, thyroid-stimulating hormone, triiodothyronine, thyroxine, luteinizing hormone and follicle-stimulating hormone. After removal of the tumors, loading tests for corticotropin-releasing hormone, thyrotropin-releasing hormone and luteinizing hormone-releasing hormone were performed for reserve capacity of each hormone tested pre-operatively. Hypopituitarism was defined as a requirement for hormonal replacement. Regular endocrinological follow-up assessments were performed post-operatively at 3, 6 months, and annually thereafter.

At the pre-operative endocrinological evaluation, DI was considered for complaints of polydipsia and polyuria, and 1-deamino-8-ᴅ-arginine vasopressin (DDAVP or desmopressin, synthetic forms of ADH) was required in order to control urine volume. Post-operatively, in this study, central-type DI was diagnosed if the following two conditions were met: total urine volume per day > 2500 mL and a urine specific gravity of < 1.005 [21]. In the pre- and post-operative assessment of DI long-lasting after discharge, low levels of urine osmolality that did not increase with hyper saline loading, were evaluated by endocrinologists. After discharge, DI was considered cured if patients self-judged that they did not require DDAVP or desmopressin and had not experienced polydipsia and polyuria on a daily basis.

Hypothalamic dysfunction, including hyperphagia, memory deficits, emotionally labile behavior, and sleep–awake cycle disruption, was recorded. Body mass index (BMI kg/m²) was calculated before and after operation, and follow-up thereafter. Obesity was defined by a BMI > 30 kg/m² [17].

## Statistical analysis

Post hoc analysis was used to compare ages of patients at presentation (pediatrics vs. adults), sex distribution,

maximum diameter of the adenomas, presence of intratumoral cyst occupying more than 60% volume of tumor, occurrence of each symptom; ICP elevation, visual function impairment, presence of hydrocephalus, hypopituitarism, DI, cognitive function disturbance, and obesity among the three groups in this study. Spearman's rank correlation coefficient was used to compare the extension grades of the perifocal edema and the anatomical hypothalamic grading (Puget's grading system). Statistical analyses were performed using Excel 2016 (Microsoft, Redmond, Washington, USA). A p-value < 0.05 was considered as statistically significant.

# Results

## Comparisons of patients' demographics among the groups

All 54 patients with craniopharyngioma enrolled in this study undertook MRI both pre- and post-operatively for radiological evaluation. This study consisted of 31 males and 23 female patients, with the age at diagnosis ranging from 4 months to 83 years old (mean age, $43.5 \pm 25.2$ years). Sixteen of these patients (29.6%) were 18 years or less old at the diagnosis, and they were classified as pediatric patients and other 38 patients (70.4%) whose age was more than 18 years old were as adult patients. The pediatric patients were $8.3 \pm 6.7$ years old on average and included 10 males and 6 females. Furthermore, all patients underwent surgical procedures (transcranial in 20 patients, transsphenoidal in 27 patients, both in 4 patients, biopsy with cyst puncture in 2 patients, and only biopsy in 1 patient), and histological diagnoses were confirmed as follows: adamantinomatous type in 41 patients (75.9%) and squamous-papillary type in 13 patients (24.1%). Pre-operative symptoms observed were visual function disturbance (n = 48, 88.9%, 15 children and 33 adults), ICP elevation (n = 9, 16.7%, 5 children and 4 adults), symptoms derived from hypopituitarism (n = 17, 31.5%, 6 children and 11 adults), DI (n = 7, 13.0%, all adults), cognition disturbance (n = 7, 13.0%, only adults) and obesity (n = 14, 25.9%, 2 children and 12 adults) (Table 1).

As described in the "Methods" section, these 54 patients were divided into three groups (A–C) based on the extent of perifocal edema caused by craniopharyngioma assessed with T2WI/FLAIR on MRI. Group A consisted of 22 patients (40.7%), group B included 14 patients (25.9%) and group C had 18 patients (33.3%). The age at presentation, sex distribution, and tumor histology were compared among the groups (Table 1). Representative cases from each group are shown on Fig. 1. The adult–child ratio and the sex distribution of each group were 10 adults and 12 children, 13 males and 9 females in group A; 13 adults and 1 children, 10 males

**Table 1** Comparisons of patients' demographics across all groups

| Groups | A | B | C | Total (%) | p value | B+C | |
|---|---|---|---|---|---|---|---|
| Number (%) | 22 (40.7) | 14 (25.9) | 18 (33.3) | 54 (100) | | | |
| Children | 12 | 1 | 3 | 16 (29.6) | n.e. | 4 (25.0) | p < 0.01** |
| Adults | 10 | 13 | 15 | 38 (70.4) | 0.287 | 28 (73.7)** | |
| Sex (male/female) | 13:9 | 10:4 | 8:10 | 31:23 | 0.316 | | |
| Diameter (mm) | 29.7 ± 7.7 | 27.8 ± 7.6 | 33.3 ± 8.7 | 30.8 ± 8.6 | 0.157 | | |

*n.e.* not evaluated

*p* Values were obtained from comparisons among groups in children, adults, and total
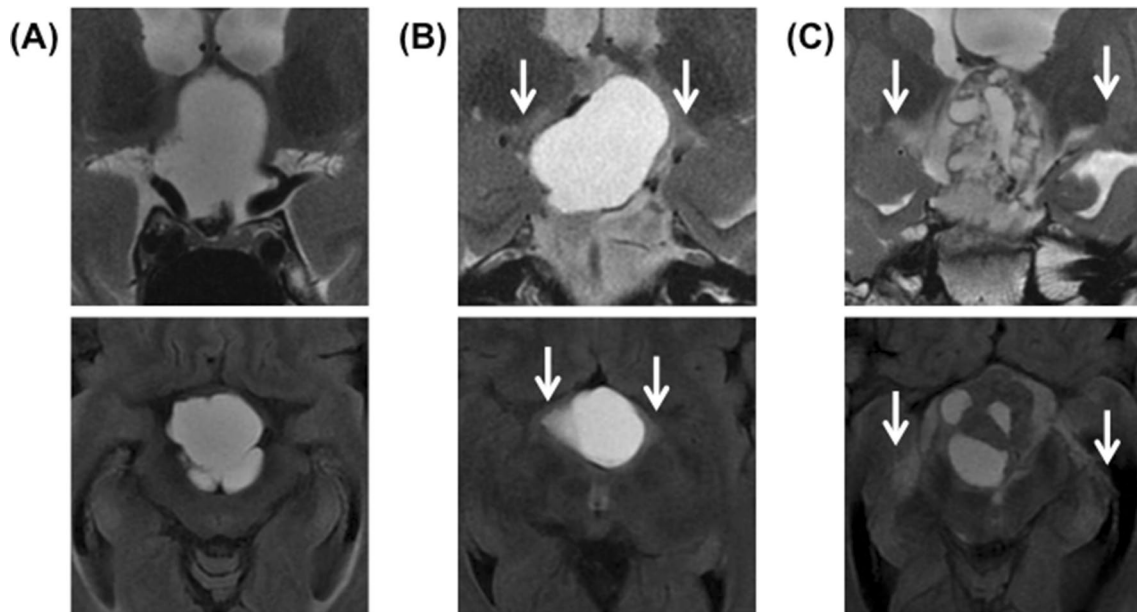
**p < 0.01



**Fig. 1** Representative images of hypothalamic perifocal edema caused by craniopharyngioma on MRI in each group (**a–c**). Each type of edema (indicated with an arrow) is shown by axial image on fluid attenuated imaging recovery (lower lane) and coronal image on T2 weighted imaging (upper lane). **a** No edema is found around the tumor. **b** Focal edema is detected only adjacent to the tumor in the hypothalamus. **c** Perifocal edema extends toward the internal capsule and the optic tract

and 4 females in group B; 15 adults and 3 children, 8 males and 10 females in group C. The existence of perifocal edema (groups B and C) in adults (28 out of 38 patients, 73.7%) was significantly higher when compared with children (4 out of 16 patients, 25.0%, p < 0.001). The maximum diameter of the tumors (mean ± SD) in each group was 29.7 ± 7.7 mm in group A, 27.8 ± 7.6 mm in group B, and 33.3 ± 8.7 mm in group C. Sex distribution and diameters of the tumors were not statistically different among groups (sex; p = 0.316, maximum diameter; p = 0.157) (Table 1).

## Evaluation of hypothalamic involvement and perifocal edema on MRI among the groups

Puget's grading system was compared with the three-groups system (group A–C) described above (Table 2).

Representative cases from each grade are also shown (Fig. 2). In pediatric patients (n = 16), 12 were included in group A and there were 4 patients in each grade. Therefore, no apparent correlation was found between Puget's grading system and our grouping (Table 2a). However, in adults patients (n = 38), the correlation between Puget's grading system and our grouping was much greater compared with the pediatric population (p < 0.001, ρ = 0.683, Table 2b). Overall, the Puget's grading system was correlated with our grouping based on the extent of perifocal edema (p < 0.001, ρ = 0.569, Table 2c).

The hypothalamus was decompressed in all the cases except in two cases treated with biopsy only. In those cases, perifocal edema was subsided after removal of the tumor.

**Table 2** Comparisons of hypothalamic involvement using Puget's grading system and perifocal edema on MRI among groups

| Puget's grade | a Children Groups | | | b Adults Groups | | | c Total Groups | | |
|---|---|---|---|---|---|---|---|---|---|
| | A | B | C | A | B | C | A | B | C |
| 0 (n=12) | 4 | 0 | 0 | 7 | 1 | 0 | 11 | 1 | 0 |
| 1 (n=20) | 4 | 1 | 0 | 2 | 9 | 4 | 6 | 10 | 4 |
| 2 (n=22) | 4 | 0 | 3 | 1 | 3 | 11 | 5 | 3 | 14 |
| Total (n=54) | 12 | 1 | 3 | 10 | 13 | 15 | 22 | 14 | 18 |
| | n.e. | | | p<0.01**, ρ=0.683 | | | p<0.01**, ρ=0.569 | | |

*n.e.* not evaluated

*p* Values were obtained from comparisons among groups in children, adults, and total

**p<0.01



**Fig. 2** Representative images of hypothalamic involvement by craniopharyngioma on MRI scan assessed with Puget's grading system. **a** No hypothalamic involvement is found, **b** the tumor abuts or displaces the hypothalamus, **c** hypothalamus is involved by the tumor (the hypothalamus is no longer identifiable)

## Comparisons of preoperative clinical features among the groups

The occurrence rate of cystic craniopharyngioma in this study was 32 out of 54 patients (59.3%), with 16 out of 16 pediatric patients (100%) and 16 out of 38 adult patients (42.1%). The rates of cystic craniopharyngioma in each group were 17 out of 22 patients (77.3%) in group A, 8 out of 14 (57.1%) in group B, and 7 out of 17 (38.9%) in group C. The statistical difference between the occurrence rates of the cyst formation and the extent of the grades of perifocal edema was found only between group A and group C (p=0.048). In adult patients, no significant difference was found among groups (p=0.310, Table 3a).

The occurrence rate of pre-operative ICP elevation in this study was 15 out of 54 patients (27.8%), with 6 out of 16 pediatric patients (37.5%) and 9 out of 38 adult patients (23.7%). The rates of ICP elevation in each group were 4 out of 22 patients (18.2%) in group A, 2 out of 14 (14.3%) in group B, and 9 out of 18 (50.0%) in group C. The occurrence rate in group C was significantly higher than in the other two groups, both in total and in the adult population (p=0.034 and p=0.016, Table 3b).

The occurrence rate of pre-operative visual function impairment in this study was 48 out of 54 patients (88.9%), with 15 out of 16 pediatric patients (93.8%) and 33 out of 38 adult patients (86.8%). The rates of visual function impairment in each group were 20 out of 22 patients (90.9%) in group A, 12 out of 14 patients (85.7%) in group B, and 16 out of 18 patients (88.9%) in group C. A statistical difference was not detected between the occurrence rates of the visual function impairment and the extent of the grades of perifocal edema among these three groups (p=0.393, Table 3c).

**Table 3** Comparisons of pre-operative clinical features among groups: (a) with or without intratumoral cyst on MRI; (b) with or without symptoms due to intracranial pressure elevation; (c) with or without visual function impairment

|  | Groups | A | B | C | Total (%) | p value |
|---|---|---|---|---|---|---|
| **a** | | | | | | |
| Children | w/ | 12 | 1 | 3 | 16 (100) | n.e. |
|  | w/o | 0 | 0 | 0 | 0 (0) | |
| Adults | w/ | 5 | 7 | 4 | 16 (42) | 0.31 |
|  | w/o | 5 | 6 | 11 | 22 (58) | |
| Total | w/ | 17 | 8 | 7 | 32 (59) | 0.048* |
|  | w/o | 5 | 6 | 11 | 22 (41) | |
| **b** | | | | | | |
| Children | w/ | 4 | 0 | 2 | 6 (38) | n.e. |
|  | w/o | 8 | 1 | 1 | 10 (63) | |
| Adults | w/ | 0 | 2 | 7 | 9 (24) | 0.016* |
|  | w/o | 10 | 11 | 8 | 29 (76) | |
| Total | w/ | 4 | 2 | 9 | 15 (28) | 0.034* |
|  | w/o | 18 | 12 | 9 | 39 (72) | |
| **c** | | | | | | |
| Children | w/ | 11 | 1 | 3 | 15 (94) | n.e. |
|  | w/o | 1 | 0 | 0 | 1 (6) | |
| Adults | w/ | 9 | 11 | 13 | 33 (87) | 0.638 |
|  | w/o | 1 | 2 | 2 | 5 (13) | |
| Total | w/ | 20 | 12 | 16 | 48 (59) | 0.393 |
|  | w/o | 2 | 2 | 2 | 6 (11) | |

*n.e.* not evaluated

*p* Values were obtained from comparisons among groups in children, adults, and total

*p < 0.05

## Comparisons of pre- and post-operative states of clinical features among the groups

The occurrence of pre- and post-operative hydrocephalus was 18 (33.3%) and 12 (22.2%) out of 54 patients, respectively. The occurrence rate in group C was significantly higher among groups both pre- and post-operatively, and was followed by group B and afterwards by group A (p = 0.040 and p = 0.023, respectively). Although three cases of hydrocephalus were recognized pre-operatively, no case was found post-operatively in children. In adults, group C was significantly associated with the occurrence of hydrocephalus both pre- and post-operatively (p = 0.048 and p = 0.023, Table 4a).

The occurrence of pre- and post-operative hypopituitarism was 26 (48.1%) and 46 (85.2%) out of 54 patients, respectively. The occurrence rates among the groups were not significantly different both pre- and post-operatively (p = 0.415 and p = 0.200, respectively). However, the post-operative occurrence rate was higher than the pre-operative one (p < 0.001). In addition, the difference in the occurrence rates between children and adults was not obvious both pre- and post-operatively (p = 0.894 and p = 0.366, Table 4b).

The occurrence of pre- and post-operative DI was 8 (14.8%) and 36 (66.7%) out of 54 patients. The post-operative occurrence rates arose significantly both in children and adults (0–56.2% and 21.1–71.1%, p < 0.001, respectively). No children manifested DI pre-operatively and the occurrence rates of pre-op DI in adults were not significantly different among groups (p = 0.232). The occurrence rate of DI in group C was found to be significantly higher both pre- and post-operatively among the groups (p = 0.039 and p = 0.004, Table 4c).

The occurrence of pre- and post-operative memory disturbance was 8 (14.8%) and 11 (20.4%) out of 54 patients. The memory disturbance was not found in children both pre- and post-operatively. However, in adults, the occurrence rates were 8 (22.2%) pre-operatively, and 11 (30.6%) out of 36 patients post-operatively (p = 0.045 and p = 0.011). More, the occurrence of pre- and post-operative memory disturbance in group C (40.0% and 53.3%) was significantly highest followed by group B (15.4% and 23.1%) and group A (0% and 0%) (p = 0.011 and p = 0.016, Table 4d).

The occurrence of pre- and post-operative obesity was 13 (24.1%) and 11 (40.7%) out of 54 patients. The occurrence rate of obesity was found to be significantly higher pre- and post-operatively (p = 0.010 and p = 0.021). The occurrence rates arose from 12.5%, preoperatively, to 25.0%, postoperatively, but not statistically different in

**Table 4** Comparisons of pre- and post-operative states of clinical features among groups: (a) with or without hydrocephalus; (b) with or without hypopituitarism; (c) with or without diabetes insipidus; (d) with or without memory disturbance; (e) with or without obesity

| | | Preoperation A | B | C | Total (%) | p value | Postoperation A | B | C | Total (%) | p value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **a Hydrocephalus** | | | | | | | | | | | |
| Children | w/ | 2 | 0 | 1 | 3 (19) | n.e. | 0 | 0 | 0 | 0 (0) | n.e. |
| | w/o | 10 | 1 | 2 | 13 (81) | | 12 | 1 | 3 | 16 (100) | |
| Adults | w/ | 2 | 4 | 9 | 15 (39) | 0.048* | 1 | 3 | 8 | 12 (32) | 0.023* |
| | w/o | 8 | 9 | 6 | 23 (61) | | 9 | 10 | 7 | 26 (68) | |
| Total | w/ | 4 | 4 | 10 | 18 (33) | 0.040* | 1 | 3 | 8 | 12 (22) | 0.023* |
| | w/o | 18 | 10 | 8 | 36 (67) | | 21 | 11 | 10 | 42 (78) | |
| **b Hypopituitarism** | | | | | | | | | | | |
| Children | w/ | 5 | 1 | 1 | 7 (44) | n.e. | 11 | 1 | 3 | 15 (94) | n.e. |
| | w/o | 7 | 0 | 2 | 9 (56) | | 1 | 0 | 0 | 1 (6) | |
| Adults | w/ | 4 | 5 | 10 | 19 (50) | 0.358 | 8 | 9 | 14 | 31 (82) | 0.267 |
| | w/o | 6 | 8 | 5 | 19 (50) | | 2 | 4 | 1 | 7 (18) | |
| Total | w/ | 9 | 6 | 11 | 26 (48) | 0.415 | 19 | 10 | 17 | 46 (85) | 0.2 |
| | w/o | 13 | 8 | 7 | 28 (52) | | 3 | 4 | 1 | 8 (15) | |
| **c Diabetes insipidus** | | | | | | | | | | | |
| Children | w/ | 0 | 0 | 0 | 0 (0) | n.e. | 5 | 1 | 3 | 9 (56) | n.e. |
| | w/o | 12 | 1 | 3 | 16 (100) | | 7 | 0 | 0 | 7 (44) | |
| Adults | w/ | 1 | 3 | 4 | 8 (21) | 0.232 | 5 | 8 | 14 | 27 (71) | 0.008** |
| | w/o | 9 | 10 | 12 | 30 (79) | | 5 | 5 | 1 | 11 (29) | |
| Total | w/ | 1 | 3 | 4 | 8 (15) | 0.039* | 10 | 9 | 17 | 36 (67) | 0.004** |
| | w/o | 21 | 11 | 15 | 46 (85) | | 12 | 5 | 1 | 18 (33) | |
| **d Memory disturbance** | | | | | | | | | | | |
| Children | w/ | 0 | 0 | 0 | 0 (0) | n.e. | 0 | 0 | 0 | 0 (0) | n.e. |
| | w/o | 12 | 1 | 3 | 16 (100) | | 12 | 1 | 3 | 16 (100) | |
| Adults | w/ | 0 | 2 | 6 | 8 (21) | 0.045* | 0 | 3 | 8 | 11 (29) | 0.011* |
| | w/o | 10 | 11 | 9 | 30 (79) | | 10 | 10 | 7 | 27 (71) | |
| Total | w/ | 0 | 2 | 6 | 8 (15) | 0.011* | 0 | 3 | 8 | 11 (20) | 0.016* |
| | w/o | 22 | 12 | 12 | 46 (85) | | 22 | 11 | 10 | 43 (80) | |
| **e Obesity** | | | | | | | | | | | |
| Children | w/ | 0 | 0 | 2 | 2 (13) | n.e. | 1 | 0 | 3 | 4 (25) | n.e. |
| | w/o | 12 | 1 | 1 | 14 (87) | | 11 | 1 | 0 | 12 (75) | |
| Adults | w/ | 1 | 6 | 5 | 12 (32) | 0.189 | 2 | 7 | 9 | 18 (48) | 0.024* |
| | w/o | 9 | 7 | 10 | 26 (68) | | 8 | 6 | 6 | 20 (52) | |
| Total | w/ | 0 | 6 | 7 | 13 (24) | 0.010* | 0 | 3 | 8 | 22 (41) | 0.021* |
| | w/o | 22 | 8 | 11 | 41 (76) | | 22 | 11 | 10 | 32 (59) | |

*n.e.* not evaluated

*p* Values were obtained from comparisons among groups in children, adults, and total

*p < 0.05; **p < 0.01

children (p = 0.596, respectively). Subsequently, in adults, the occurrence rates of obesity in group B (53.8%) and group C (60.0%) was significantly higher than group A (20%) post-operatively (p = 0.024), but not pre-operatively (p = 0.189, Table 4e).

# Discussion

In order to prevent recurrence and reduce mortality, optimal treatment of craniopharyngioma is gross total removal. Development of several surgical approaches and instruments continues to improve patients' prognosis [14, 15]. However,

the surgical procedures for GTR still have high morbidity risks, particularly related to hypothalamic injury [10, 16, 22, 23]. As a strategy for the management of craniopharyngioma and to keep quality of daily living, many surgeons consistently maintained the effectiveness of less aggressive surgery combined with radiotherapy [24, 25]. Therefore, pre-operative clinical and radiological evaluation of hypothalamic involvement and post-operative prediction of hypothalamic injury would be important to determine surgical approach and reduce post-operative complications.

Radiological pre-operative involvement of the hypothalamus has been assessed by MRI scan, looking at the anatomical relationship between hypothalamus and tumors [15, 17, 18]. Some authors, including Puget and Van Gompel, presented their own classification system of hypothalamic involvement in order to predict post-operative morbidity related to hypothalamic dysfunction [15, 18]. These systems were defined the anatomical relation of their position as with or without contact, displacement, and involvement [15, 18]. Although available, these classification systems are sometimes not enough to predict hypothalamic dysfunctions post-operatively. Therefore, this study focused on the perifocal edema caused by craniopharyngioma to evaluate the pre-operative involvement and post-operative injury.

The mechanisms of perifocal edema caused by craniopharyngioma were speculated as following: after impairment by compression of microvessels in the blood–brain barrier on the surrounding tissue of the tumor, cholesterin induces direct invasion or spreading of inflammation, resulting in an accumulation of interstitial fluid in the surrounding tissue which culminates in an edema [2]. The pattern of edema extending towards the internal capsule and the optic tract was suspected as follows: first, as the tumor compression is compensated by the suprasellar cistern and the third ventricle, the integrity of the endothelium of the normal brain vasculature adjacent to the tumor is minimally compromised [26]. Second, because the internal capsule and the optic tract are composed of compact, parallel bundles of fibers, it is facilitated to the edema fluid to advance along the fibers. And, the size variability of extracellular spaces within the white matter is formed according to variable crisscross fiber patterns [27].

In all cases presented, except one where only a biopsy was performed, the perifocal edema was subsided regardless of group B and group C and if the hypothalamus was decompressed. Therefore, the mechanisms described above, such as tumor compression and inflammation spreading, were acceptable. The site of the direct invasion of the brain by the tumor was basically left untouched to avoid the hypothalamic injury.

First of all, it is worthwhile mentioning the significant dominancy of adults in the occurrence of this perifocal edema when compared to children. In this study, the occurrence rate of the edema (group B and C) in adults (73.7%) was significantly higher when compared with children (25.0%, $p < 0.001$). The reasons for this adult dominancy have not been explored, but Hoffman made a following comment at the end of Higashi's paper [2]: "The tumors have been there for long periods of time. This may be the factor responsible for the perifocal edema. We have not encountered responsible this appearance in children with craniopharyngiomas, even if the tumors have been exceedingly large". Because this study was performed with remarkable advancement of radiological instrument compared to the Hoffman's era, the small edema (coded as group B in our study) might be overlooked. However, it might be certain that the occurrence rate of this perifocal edema in children is uncommon compared with adults.

It has been well known that craniopharyngioma frequently harbors intratumoral cyst, particularly in pediatric patients [28, 29]. Although, it was noticed that even if all pediatric patients had intratumoral cyst, the occurrence of intratumoral cyst was only 25%. Meanwhile, 42% of adults' patients were associated with intratumoral cyst, and the relationship between occurrence rates of cyst formation and the extent of the grades of perifocal edema did not reach any statistical difference among these three groups.

In this study, the occurrence rate of preoperative ICP elevation was significantly higher in group C than in the other two groups. The greater ICP elevation can be associated with the development of a larger extent of edema caused by craniopharyngioma. Tan et al. revealed that stress caused in traumatic brain injury by ICP elevation, leads to apoptosis of neuroendocrine cells in the hypothalamus and the pituitary gland. Moreover, the higher the stress intensity, the higher the apoptosis rate in the hypothalamus and the pituitary gland [30, 31]. Therefore, in patients with craniopharyngioma, dysfunction in the hypothalamus and the pituitary gland could lead to the development of perifocal edema with apoptotic mechanisms during the long-term process of compression. In addition, increased severity of traumatic brain injury aggravates the damage to tight junctions in vascular endothelial cells associated with increasing corticosteroid insufficiency and neuronal apoptosis in the periventricular nucleus of the hypothalamus, leading to the elevated vascular permeability and subsequent perifocal edema [32, 33].

The occurrence rate pre- and post-operative hydrocephalus in group C was significantly higher. Preito described that presence of hydrocephalus as well as topography of craniopharyngioma, tumor consistency, infundibulo-tuberal syndrome, and hypothalamic dysfunction could be a predictor of the severity of tumor attachment to the third ventricle floor, the third ventricle walls, and the pituitary stalk [34]. It could be suggested that severe attachment to the hypothalamus might cause dysfunction due to

malcirculation of interstitial fluid in the area of the hypothalamus, leading to the occurrence of perifocal edema [35].

In this study, hypothalamic dysfunctions, including DI, memory disturbance, and obesity, were obviously correlated with the extent of perifocal edema, both pre- and post-operatively. It was reported that hypothalamic signal changes in T2-WI as well as irregular contrast enhancement predicted the hypothalamic involvement, indicating tumor invasion and hypothalamic injury associated with tumor resection [15, 18, 36]. Mortini et al. observed that peritumoral hypothalamic edema was significantly associated with preoperative hyperphagia and higher BMI, predicting hypothalamic damage [17]. In their study, however, the perifocal edema was evaluated only with presence or absence, not using a grading like here. From the above, the following conclusion has been led that the degree of perifocal edema can be a predictor of further complications [2, 17, 18].

This study had some limitations. First, this study had a retrospective design. Second, the total number of patients (54 patients) was small to provide a high statistical power, particularly in the pediatric population. Third, all cases were not examined using the same MRI instrument. Therefore, radiological evaluation of T2WI/FLAIR hyperintensity might be inconstant. Fourth, surgical procedures were not fixed in our case series. Mainly in the first half, a transcranial approach was applied. In the second half, however, transsphenoidal surgery was performed. This alteration of surgical strategies might influence post-operative functional outcomes.

## Conclusion

Hypothalamic dysfunction can greatly influence the quality of daily living following craniopharyngioma surgery. In this study, it was clearly shown that grading system of perifocal edema, using MRI scan, could be used as a new index in evaluating pre-operatively and predicting post-operatively hypothalamic dysfunction. This includes DI, memory disturbance, and obesity, particularly in adults. In addition, hypothalamic dysfunction was well correlated with the anatomical hypothalamic involvement on MR images. Further studies are required to establish definitive results and a development mechanism, particularly in children.

## Compliance with ethical standards

**Conflict of interest** There is no conflict of interest in this study.

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