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Hypothalamic obesity following craniopharyngioma surgery: What is the role of hypothalamic T2 signal changes in brain MRI?

Doga Yurddas[1], Rutger A.J. Nievelstein[1,2], Brigitte Bison[3], Marta Fiocco[1,4,5], Wim J.E. Tissing[1], Sanne Hulsmann[1], Julia Beckhaus[6], Carsten Friedrich[6], Eelco W. Hoving[1], Hermann L. Müller[6], Hanneke M. van Santen[1,7]

[1]Princess Maxima Center for Pediatric Oncology, Heidelberglaan 25, 3584 CS Utrecht, The Netherlands;

[2]Department of Radiology and Nuclear Medicine, University Medical Center Utrecht/Wilhelmina Children's Hospital, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands

[3]Diagnostic and Interventional Neuroradiology, Faculty of Medicine, University of Augsburg, Augsburg, Germany

[4]Department of Biomedical Data Science, Leiden University Medical Center, The Netherlands

[5]Mathematical Institute Leiden University, The Netherlands

[6]Department of Pediatrics and Pediatric Hematology/Oncology, University Children's Hospital, Carl von Ossietzky Universität, Klinikum Oldenburg AöR, Rahel-Straus-Strasse 20, 26133 Oldenburg, Germany

[7]Department of Pediatric Endocrinology, University Medical Center Utrecht/Wilhelmina Children's Hospital, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands.

Running Title: Role of Hypothalamic T2 SI changes in cCP-surgery Associated Obesity

Corresponding Author:

Prof. Hanneke M. van Santen

Department of Supportive Care/ Pediatric Endocrinology, Princess Maxima Center, Utrecht, The Netherlands,

Phone: 088 972 7272

Email: h.m.vansanten-3@prinsesmaximacenter.nl

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ABSTRACT

Background

Despite hypothalamus-sparing surgical techniques, hypothalamic obesity remains common in childhood craniopharyngioma (cCP) survivors. Emerging evidence suggests a role for hypothalamic inflammation (HI) in obesity development. This study aimed to quantitatively assess post-operative T2 signal intensity (SI) changes, suggestive of inflammation and edema, using MRI and investigate its association with clinical outcomes, including BMI changes, over a one-year period.

Methods

We retrospectively analyzed two cCP cohorts. Diagnostic and post-operative MRIs were evaluated for changes in hypothalamic T2 SI on FLAIR. We assessed clinical and radiological predictors of post-operative T2 SI and examined correlations between ΔT2SI and ΔBMI z-score from pre-operative to 3 months after surgery. A multivariable model was used to evaluate factors influencing BMI z-score change. In a subgroup (n=40), we compared post-operative T2 SI between patients with and without hypothalamic syndrome at 6 months.

Results

Both left ($p<0.001$) and right ($p<0.05$) hypothalamic T2 SI increased post-operatively. Higher post-operative T2 SI was associated with increased pre-operative T2 SI, age, less cystic tumors, and higher post-operative Müller grades. ΔT2SI correlated with ΔBMI z-score at 3 months (r=0.56, 95% CI:0.29–0.74). ΔT2SI (left) was significantly associated with ΔBMI z-score (β=1.02, SE=0.35) after adjusting for baseline variables. Patients with hypothalamic syndrome (n=17) had higher post-operative T2 SI than those without (n=23, $p<0.01$).

Conclusion

Our data suggests that hypothalamic T2 SI increase is associated with the BMI increase and hypothalamic dysfunction after cCP surgery. These insights enhance our understanding of the pathophysiology underlying post-operative hypothalamic obesity and may inform future preventive and therapeutic strategies.

Keywords: BMI, craniopharyngioma, hypothalamic inflammation, MRI, hypothalamic obesity, T2 signal intensity

Key points:

- Hypothalamic T2 signal intensity (SI), suggestive of inflammation or edema, rises after cCP surgery.
- High hypothalamic post-operative T2 SI is linked to older age, less cystic tumors, and higher Müller grade.
- High hypothalamic post-operative T2 SI correlates with BMI increase and presence of hypothalamic syndrome presence after surgery.

Importance of the study

This study quantitatively assesses post-operative T2 signal hyperintensity changes on MRI, possibly reflecting presence of hypothalamic inflammation or edema, after childhood craniopharyngioma (cCP) surgery. We found that increased T2 signal intensity changes

correlates with post-operative BMI increase and the presence of hypothalamic syndrome. These results suggest that hypothalamic inflammation or edema contributes to acquired hypothalamic dysfunction, including obesity in cCP patients. This work advances understanding of factors influencing hypothalamic and BMI changes after surgery and may guide future treatment strategies for hypothalamic obesity.

INTRODUCTION

Childhood craniopharyngioma (cCP) is a low-grade intracranial tumor with a high survival rate approaching 92%(1, 2, 3). However, it presents a complex challenge due to potential hypothalamic damage resulting from either the disease or its treatment(4, 5). Despite the favourable survival rates, survivors often suffer from disturbed hunger-satiety and thirst feelings(6), decreased energy expenditure(7), behavioural problems(8), disturbances of circadian rhythm(9), temperature dysregulation(10), and pituitary dysfunction, together referred to as hypothalamic syndrome (HS)(11). Hypothalamic obesity is a common complication after cCP therapy, occurring in up to 75% of survivors(12). The mechanism behind this is the damage to the hypothalamus, disrupting satiety and hunger signals, leading to hyperphagia in addition to reduced energy expenditure, altered lipolysis, insulin overproduction, and increased lipogenesis. Subsequently, the risk for development of the metabolic syndrome and related comorbidities, including the likelihood of premature mortality, is significantly elevated(13, 14, 15).

Several neuroimaging studies found that structural defects in medial hypothalamic nuclei are linked to increased risk of obesity, with treatment-resistant, uncontrollable appetite, and rapid weight gain(16). While hypothalamus-sparing surgery, potentially combined with radiotherapy, presents strong evidence in reducing comorbidities without raising tumor recurrence, the severe obesity following cCP remains a significant concern(17, 18, 19). Therefore, identifying the risk factors in patients with cCP that may contribute to obesity is crucial for implementing early and efficient interventions.

One of the key risk factors in the development of hypothalamic dysfunction and subsequent obesity may be the brain's inflammatory response, primary to the tumor mass effect or secondary, triggered by the neurosurgical intervention, involving delayed molecular cascades that promote inflammation, neuronal death, and edema(20). Additionally, for cystic cCP

specifically, the cyst fluid of the tumor, containing pro-inflammatory properties, may contribute to inflammation when spilled into the surgical field(21). Inflammation in an area as susceptible as the hypothalamus may cause resistance of the hypothalamic neurons to satiety-signalling hormones such as leptin and insulin(22).

Emerging evidence suggests a link between hypothalamic inflammation (HI) and obesity in both rodents and humans(23). In rodent studies, HI induced by a high-fat diet has been shown to lead to reactive astrocytosis and astrogliosis, increased cytokine expression, neural dysregulation, and neurodegeneration of the mediobasal hypothalamus (MBH)(23, 24, 25). These changes lead to insulin and leptin resistance with subsequent impairment in satiety feeling, regulation of energy homeostasis, and food-related reward networks contributing to hypothalamic obesity(26). In humans, MRI studies have identified MBH inflammation and gliosis, detected as T2 signal intensity (SI) increase. Later, this T2 SI increase was associated with higher levels of adiposity in non-craniopharyngioma cohorts(25, 27, 28). Lateralization of the human hypothalamus in metabolic activity was mentioned in several studies. Studies have shown that inflammation and gliosis on the left MBH had stronger associations with obesity(23, 25, 27). These findings of left MBH inflammation and gliosis align with evidence suggesting that hypothalamic white matter connections are lateralized in humans, and that parasympathetic output, which plays a role in glucose regulation, is primarily dominant on the left side of the brain(29).

Several previous studies have identified risk factors for post-operative weight gain in patients with cCP, such as hypothalamic involvement of the tumor and extent of the neurosurgical resection. However, in many cases, it remains difficult to predict which patients will develop hypothalamic obesity, which might be partly explained by the degree of HI. No study has thus far evaluated the presence or change in T2 SI as a marker for the presence of HI in patients after cCP surgery in relation to changes in hypothalamic function during the first post-

operative year. Therefore, by combining data from two well-defined cCP cohorts (Dutch and German), we aimed to investigate the presence of pre- and post-operative T2 SI changes in cCP patients on MRI and its association with post-operative BMI changes and presence of hypothalamic syndrome(11).

MATERIALS AND METHODS

Patients

The study consisted of a retrospective analysis of the cCP Dutch cohort from the Princess Máxima Center for Pediatric Oncology, all patients diagnosed between 2018 and 2023, and the German cohort derived from the German KRANIOPHARYNGEOM 2019 Registry, all patients diagnosed between 2019 and 2023. The inclusion criteria were a histologically confirmed adamantinomatous craniopharyngioma (ACP) diagnosed before the age of 18 years.

Patients were excluded if no MRI was available, or if MRI images were not suitable for the measurements needed to reliably detect the presence of T2 SI changes (due to the presence of artefacts, MR slice thickness > 5mm, and/or non-identifiable anatomical landmarks due to distortion related to the craniopharyngioma), or if there was a lack of pre- and/or post-operative clinical information.

Clinical Data Collection

Follow-up information was collected retrospectively by reviewing the patient records of each patient's regular follow-up visit or by data extraction from existing databases. All available endocrine data were collected. BMI was recorded pre-operatively and at 3- and 12-months intervals post-operatively. BMI in the pediatric cohort was calculated as BMI SDS according to the WHO definitions(30).

Hypothalamic criteria for HS as defined by van Santen et al., including hyperphagia, behavioural problems, sleep disorders, temperature regulation disorders, and pituitary dysfunction, were collected before surgery and at 6- and 12-months intervals after surgery [16].

Neuroradiological Evaluation

Patients were treated and followed according to local treatment guidelines. In the majority of cases, MRI protocols included T1-weighted, T2-weighted, and T2 FLAIR sequences, obtained both at diagnosis and within the first two weeks following surgery. Additionally, in 88 patients, the scan protocol included Diffusion Weighted Imaging (DWI). All MRI scans were collected and evaluated by a clinician-researcher blinded to clinical information, under the supervision of two experienced neuroradiologists (RAJ.N. and B.B.). For quality assurance, the two experienced neuroradiologists assessed the scans of every tenth patient from each cohort (Dutch and German) independently. Discrepancies were resolved through consensus discussion.

Tumor volume was estimated using the ellipsoid formula based on three perpendicular dimensions. Craniocaudal and anteroposterior measurements were obtained from sagittal MRI slices, while left–right dimensions were measured on both axial and coronal planes. Tumor composition was classified as predominantly solid, predominantly cystic, or mixed. Additionally, the presence of a cystic component comprising more than 50% of the tumor volume was recorded as a binary variable (yes/no).

Hypothalamic involvement of the cCP was scored pre- and post-operatively according to the Müller grading system, as described by Müller et al.(31, 32). The tumor was graded according to the degree of hypothalamic involvement/surgical lesions: grade 0, no hypothalamic involvement/lesion; grade 1, hypothalamic involvement/lesion of the anterior hypothalamus

not involving the mammillary bodies (MB) and the hypothalamic area beyond MB; and grade 2, hypothalamic involvement/lesion of the anterior and posterior hypothalamic area, i.e. involving the MB and the area beyond MB.

In addition to Müller grading, the eagle sign, a MRI based tool for predicting the pre-operative topographical correlations between cCP and hypothalamus, was assessed according to the following anatomical landmarks; third ventricle floor (TVF), MB and cerebral peduncles and subsequently divided into 4 variants of eagle sign accordingly; Group A being the upward sign, Group B the downward sign, Group C the anterior upward sign and Group D the unidentifiable sign (assigned according to the position of TVF and MB)(33).

Moreover, the presence of diffusion restriction on Diffusion Weighted Imaging (DWI) and Apparent Diffusion Coefficient (ADC) were explored to reveal tissue ischemia versus inflammation/vasogenic edema on the intra- and/or first post-operative MRI.

To assess inflammation, hypothalamic T2 signal intensity (SI) was quantified by measuring the mean SI of regions of interests (ROIs) on FLAIR sequences. To control for inter-individual and scan-related variability, the mediobasal hypothalamus (MBH) was compared to ipsilateral reference regions: the amygdala (AMY) and putamen (PUT). Two ratios were calculated per hemisphere: (1) MBH/PUT and (2) AMY/PUT. The MBH/PUT ratio was used to quantify hypothalamic T2 SI, while the AMY/PUT ratio served as a control.

For the T2 SI measurements, axial and coronal slices through the hypothalamus were reviewed for each subject. The MBH was visually inspected for artifacts or abnormalities. ROIs were defined bilaterally in the MBH, AMY, and PUT. In **Figure 1A**, the ROIs used for MBH and PUT are shown. MBH ROIs were placed posterior to the optic chiasm, anterior to the mammillary bodies, adjacent to the third ventricle, and superior to the median eminence,

as described in the literature(23, 25). The visual T2 hyperintense zones in MBH were targeted for the measurements if present.

Mean T2 SI, standard deviation, and ROI area were measured using PACS workstation software (IDS7, Sectra AB, Linköping, Sweden) and RadiAnt DICOM Viewer 2025.1 (Medixant, Poznań, Poland).

Statistical Analysis

Categorical data was summarized as contingency tables with frequencies and percentages. For continuous data, mean, median, and standard deviation are presented. A paired t-test was used to compare the means of the pre- and post-operative T2 SI values. A Wilcoxon signed-rank test was used to compare the means of the control ratio (AMY/PUT ratios) due to the non-normality of the data. A p-value <0.05 was considered statistically significant.

To investigate whether T2 SI ratios were associated with other radiological variables or clinical characteristics, univariable and multivariable linear regression models were estimated.

To explore the relationship between the T2 SI in the hypothalamic region and clinical outcomes following craniopharyngioma surgeries, a correlation between delta BMI z-score and delta T2 SI was estimated; to assess if the correlation was significantly different from zero, Pearson's correlation test was employed.

A univariable linear regression model for post-operative MBH/PUT T2 SI ratio was estimated with independent variables: pre-operative MBH/PUT T2 SI ratio, pre-operative Müller score, post-operative Müller score, cystic tumor parts greater than 50%, eagle sign B-D, hypothalamic infarct, peri-operative administration of dexamethasone, tumor volume, extent of resection, age at diagnosis, and sex. Secondly, a multivariable linear regression model for the post-operative MBH/PUT T2 SI ratio was estimated, with following variables included:

post-operative Müller grade 2, cystic tumor part >50%, eagle sign group B-D, age at diagnosis, and pre-operative MBH/PUT T2 SI ratio.

A multivariable linear regression model for the change of BMI at 3 months after surgery was estimated with the variables: Δ MBH/PUT T2 SI (left), BMI z-score at diagnosis, post-operative Müller grading, cystic tumor parts greater than 50%, and age at diagnosis as independent variables.

To assess the difference between the mean post-operative MBH/PUT T2 SI ratio between patients who developed hypothalamic syndrome at 6 months and at 1 year follow-up visit, a t-test was used.

All statistical analyses were performed in the R software environment version 2024.4.2.764(34)

Ethics

Patients and parents were asked for informed consent for the use of clinical data for research. Only data from patients and parents who had given informed consent were used for this study. The study was approved by the Oldenburg Medical Ethical Committee (KRANIOPHARYNGEOM Registry 2019: Medical Ethics Committee of the Carl von Ossietzky Universität Oldenburg (2023-005); Clinical Trial No: NCT04158284). The Dutch IRB provided a waiver for ethics approval (MEC-2016-739).

All data were pseudonymized.

RESULTS

Patient Characteristics

A total of 107 patients with cCP were included in the study (40 Dutch and 67 German), with a median age at diagnosis of 8 years, including 42 females and 65 males. Patient characteristics

are shown in **Table 1**. The mean BMI z-score increased by 1.05 (SD=1.06) within the first 3 months post-surgery (n=69) and subsequently decreased to 0.706 (SD=1.91) by the end of the first post-operative year (n=67). In only 15 patients, the tumor had been completely resected, while 88 patients had an incomplete resection. One patient did not receive surgical removal but only a cyst fenestration, and the remaining 3 patients had missing data on the degree of surgical resection. Fifteen patients received peri-operative dexamethasone, and radiotherapy was given to 23 patients after a mean of 6 months following surgery.. Not all sequences, image planes, diagnostic and post-operative MR images, or clinical information were available for all patients due to the retrospective nature of our study.

Imaging Characteristics

Of 107 patients, 4 patients presented with pre-operative hypothalamic involvement, Müller grade 0(4%), 24 had Müller grade 1(22%), and 79 had Müller grade 2(74%). Post-operative Müller grading of the surgical lesion showed grade 0(%10) in 11 patients, grade 1(%44) in 47 patients, and grade 2(%46) in 49 patients. The mean tumor volume was 31.4 (SD=38.2) cm^3 before the first resection. Tumor compositions revealed that less than a quarter of the tumors were predominantly cystic (22.8%, n=23/101), while the remaining tumors consisted of a mix of both solid and cystic components (n=78/101). More than three-quarters of the tumors contained cystic components in more than half of their volume (83.2%, n=84/101).

Changes in T2 SI in the Hypothalamic Region

MBH ROIs ranged from 3.1–12.5 mm^2 (2–4 mm diameter), while AMY and PUT ROIs ranged from 7–38.4 mm^2 (3–7 mm diameter) for T2 SI measurements. The mean pre-operative T2 SI MBH/PUT ratios for the left(n=61) and right(n=62) hemispheres were 1.23 (0.205) and 1.24 (0.247), respectively. Post-operatively, the mean ratios were 1.37 (SD=0.185) for the left hemisphere and 1.32 (SD=0.207) for the right hemisphere. As shown

in **Figure 1B**, the left mean MBH/PUT T2 SI ratio increased significantly ($p<0.001$) from pre-operative to post-operative MRI ;with a mean difference of 0.14. Similarly, the right-sided mean MBH/PUT T2 SI ratio showed a significant ($p<0.05$) though smaller mean increase of 0.08. This increase in T2 SI was limited to the MBH as the AMY/PUT ratio did not change significantly for the left or right hemispheres following surgery ($p>0.05$).

Associations between the post-operative hypothalamic(MBH/PUT) T2 SI ratio and other radiological variables and clinical information were analysed. First, univariate (**Table 2**) and then multivariable linear regression models were estimated for the bilateral sum of post-operative T2 MBH/PUT SI ratios. In the univariate analysis, post-operative Müller grade 1 (β=0.28 (0.12), CI:0.04–0.53, p=0.02, n=84) and Müller grade 2 (β=0.38 (0.12), CI:0.12–0.62, p=0.003, n=84) were statistically significantly associated with a higher post-operative T2 SI ratio. In contrast, pre-operative Müller grade 1 (p=0.17, CI:-0.12–0.67, n=84) and Müller grade 2(p=0.059, CI:-0.01–0.75) showed no such association (**Figures 2A and 2B**). Additionally, high post-operative T2 SI was associated with increased pre-operative T2 SI (β=0.27 (0.09), CI:0.08–0.46, p=0.005, n=84) and older age at diagnosis (β=0.02 (0.008), CI:0.0006–0.03, p=0.04, n=84). Tumors that consisted of more than 50% cystic component were negatively associated with high post-operative T2 SI (β=-0.20 (0.09), CI:-0.04–-0.01,p=0.03, n=79, **Figure 2C**). Eagle signs B and D, grouped together (β=0.17 (0.07), CI:0.02–0.31, p=0.02, n=84), were associated with higher post-operative T2 SI. In patients who received dexamethasone peri-operatively (n=11), the T2 SI ratio was observed to be lower, but this difference was not statistically significant (β=-0.02 (0.1), CI:-0.24– 0.19, p=0.81, n=73, **Figure 2D**). In **Figure 2**, it is shown how different variables are related to pre- and post-operative T2 SI ratios.

Next, we investigated factors associated with post-operative hypothalamic(MBH/PUT ratio) T2 SI using a multivariable linear regression model. The model included post-operative

Müller grade 2, cystic tumor part >50%, eagle sign group B-D, and corrected for age at diagnosis and pre-operative hypothalamic T2 SI ratio (n=60). Results showed that higher pre-operative T2 SI (β=0.24 (0.10), CI:0.03–0.45, p=0.02) was significantly associated with increased post-operative T2 SI. While, cystic tumor part >50% (β =-0.19 (0.11), CI:-0.42–0.04, p=0.1), eagle sign B-D (β=0.10 (0.1), CI:-0.09–0.31, p=0.2), Müller grade 2(β=-0.03 (0.7), CI:-0.22–0.15, p=0.1) and age at diagnosis(β=-0.01 (0.009), CI:-0.02–0.02, p=0.3) were not significantly associated.

Post-operative Changes in T2 SI and BMI

A positive correlation was observed between the bilateral sum of left and right ΔT2 SI ratio and ΔBMI z-score at three months after surgery (r=0.56, CI:0.29–0.74, p=0.0002, n=39). When analysing each hemisphere separately, both the left (r=0.5, CI:0.22–0.70, p=0.001) and right (r=0.42, CI:0.12–0.65, p=0.007) MBH/PUT ratios showed a positive correlation with BMI increase at three months, with a stronger effect observed on the left side **(Figure 3)**. In addition, the bilateral sum of post-operative T2 SI ratio was significantly correlated with BMI changes three months after surgery (r=0.30, CI:0.03–0.52, p=0.029, n=54). This correlation was not seen one year after surgery, because neither the bilateral sum of ΔT2 SI ratios(n=37, r=0.28, CI:-0.04–0.55, p=0.08), nor the bilateral sum of post-operative T2 SI ratios(n=51, r=0.22, CI:-0.04–0.47, p=0.1) were linked to changes in BMI z-score.

In univariate analyses, post-operative Müller grade 1 (β=1.01(0.38), CI:0.23–1.78, p=0.01) and grade 2 (β=1.12(0.38), CI:0.36–1.88, p=0.004) were both associated with BMI z-score change three months after surgery(n=69). The post-operative Müller grade 1 (β=1.45(0.7), CI:0.06–2.85, p=0.04) and grade 2(β=1.93(0.7), CI:0.53–3.33, p=0.007) were also associated with BMI change one year(n=67) after surgery. However, pre-operative Müller scores were not significantly associated with the observed changes in BMI z-score after three months for both grade 1 (β=-0.06(0.66), CI:-1.38–1.25, p=0.9) nor grade 2 (β=0.35(0.63), CI:-0.90–1.61,

p=0.5). As well as not at the one-year follow-up for grade 1 (β=-0.42(1.03), CI:-2.49–1.64, p=0.68), nor grade 2 (β=0.61(0.98), CI:-1.34–2.57, p=0.53) after surgery.

Moreover, the eagle sign was absent in 9 patients, indicating that in these patients there was no contact between the third ventricle floor (TVF) and the cCP. Among the remaining patients (n=85), 4 were in eagle sign group A, 20 in group B, 25 in group C, and 36 in group D. When groups B and D were combined, a significant association was observed between combined groups and an increase in BMI z-scores at both time points, three months (β=0.63(0.26), CI:0.11–1.16, p=0.01, n=53) and one year (β=1.04(0.48), CI:0.07–2.01, p=0.03, n=52) following surgery, compared to groups A and C. Furthermore, patients exhibiting restricted diffusion in the hypothalamus (indicative of ischemic damage) on immediate post-operative (<2 weeks) diffusion-weighted imaging (DWI) also developed increased BMI z-scores one year after initial surgery (β=1.45(0.62), CI:0.19–2.71, p=0.02, n=52), but not at 3 months(β=0.28(0.34), CI:-0.4–0.96, p=0.4, n=61). Additionally, the presence of vasogenic edema on DWI was not found to be significantly associated with change in BMI z-scores at 3 months (β=0.08(0.31), CI:-0.54–0.7, p=0.79, n=61), nor at 1 year (β=0.24(0.67), CI:-1.11–1.6, p=0.72, n=57) after surgery. Among the 67 patients with available BMI data, 11 received postoperative radiotherapy within the first year, and no significant difference(p=0.40) nor association(p=0.51) with first-year BMI change was observed.

Using multivariable linear regression analysis (**Table 3**), the change in T2 SI on the left (hemisphere) MBH/PUT ratio (β=1.4, SE=0.68, CI:0.009–2.80, p=0.04) was significantly associated with the change in BMI z-score three months after surgery, after adjusting for post-operative Müller grade 2, tumor composition (cystic tumor part >50%), BMI z-score at diagnosis, and age at diagnosis.

Post-operative T2 SI and Presence of the Hypothalamic Syndrome

Presence of the hypothalamic syndrome, as defined by van Santen et al.(11) was recorded in 40 patients at the 6-month follow-up visit of the patients. Post-operative T2 SI ratios were compared between patients with (M=2.94, n=17, 42.5%) and without hypothalamic syndrome (M=2.60, n=23, 57.5%) and were significantly higher in the group of patients with hypothalamic syndrome (p=0.004, n=40) (see Supplementary Figure 1A). At one year follow-up (n=37), there was no statistically significant difference in T2 SI ratios between patients with or without hypothalamic syndrome (see Supplementary Figure 1B).

DISCUSSION

Despite advances in hypothalamus-sparing surgery, hypothalamic dysfunction and the development of obesity remain important clinical issues following cCP treatment.(17, 35). In this combined Dutch–German cohort, we found that increases in post-operative T2 signal intensity in the MBH were associated with early BMI changes at three months and with hypothalamic syndrome at six months after the surgery. To our knowledge, this is the first study to relate post-operative T2 signal changes to post-operative hypothalamic function. Our findings may contribute to clarify post-operative hypothalamic dysfunction and potentially guide strategies to prevent and treat it.

Measuring the mean T2 SI of the MBH allowed us to quantify post-operative changes in this region. Although T2 hyperintensity is not specific and may reflect inflammation, edema, or gliosis, MBH T2 measurements are sensitive to subtle CNS tissue changes(36). Prior studies have correlated hypothalamic inflammation, measured as increased MBH T2 SI ratios to BMI in tumor-free cohorts(25, 27, 28). Our findings align with these studies and suggest that post-operative BMI changes may result from impaired satiety and energy balance, caused by hypothalamic inflammation.

Interestingly, analysing each hemisphere separately, we observed higher increases in T2 SI and stronger correlations on the left hypothalamus, though each side was positively and significantly correlated with BMI increase. This finding aligns with previous studies demonstrating lateralization of the human hypothalamus, where left-sided compression(37) and gliosis(25) have been associated with obesity. In our study, this association between left-sided T2 SI increase and BMI z-score increase remained statistically significant in a multivariable linear regression model, after adjusting for grade of hypothalamic surgical lesion, age, tumor composition and BMI z-score at diagnosis. Although additional covariates could further explain the underlying mechanisms of BMI increase, our model provides insight into the role of inflammation in the post-operative weight gain in these patients.

The correlation between post-operative T2 SI and BMI increase at three months was significant yet weaker than that for delta T2 SI, possibly because tumor-related hypothalamic changes had already affected BMI before surgery, leading to a more modest post-operative change. Neither delta nor post-operative T2 SI correlated with BMI increase at one year, likely due to multiple factors during the first post-operative year, including endocrine changes, hormone replacement therapy, dietary interventions, and physical activity. Nonetheless, our findings suggest that post-operative hypothalamic inflammation may contribute to the observed clinical hypothalamic dysfunction and early BMI changes.

In addition to inflammation, T2 hyperintensity may reflect perifocal edema, often appearing as the “mustache sign.”(38). While some authors consider the perifocal edema to be indicative of local CP invasiveness(39), others attribute it to fluid retention in dilated Virchow–Robin spaces along the optic tract(40). Although this edema typically resolves within 2–4 weeks after tumor removal, our finding that an immediate post-operative increase in hypothalamic T2 SI correlates with BMI gain at three months suggests that these transient imaging changes may still represent early hypothalamic injury with lasting metabolic effects.(37)(40).

Next to BMI, we correlated the hypothalamic T2 SI to the presence of the hypothalamic syndrome, as the function of the hypothalamus extends beyond energy metabolism. The score was determined according to minor and major criteria of hypothalamic dysfunction, as described by van Santen et al. (11), including signs and symptoms of pituitary dysfunction, sleep, behaviour and temperature dysregulation. Patients who developed hypothalamic syndrome at 6 months follow-up had significantly higher post-operative T2 signal intensity in their MBH, which may again indicate that HI is a contributor to comorbidities seen in CP patients post-operatively. This difference in groups disappeared at 12 months follow-up, which may be due to the lower number of patients with clinical data available at 12 months.

If the increase in T2 SI ratio reflects HI and/or edema, reducing post-operative inflammation and edema may be potentially possible by minimizing surgical manipulation. Because more extensive surgical resection and repeated operations increase the risk of hypothalamic dysfunction, prevention may be achieved by minimizing the number of surgeries and avoiding resection of tumor parts adherent or micro-invasive to the third ventricle walls. Post-operative T2 SI ratio was univariately associated with post-operative Müller grading, indicating that more extensive hypothalamic surgical lesions correspond to higher T2 SI increase. In Müller grade 2 lesions, where the highest T2 SI values were observed, even gentle traction during tumor mobilization may cause micro-trauma to the hypothalamus due to microinvasive tumor extensions. The lack of association between pre-operative Müller grading and post-operative T2 SI suggests that surgery plays a more determinative role than the tumor. Post-operative Müller grading was also associated with BMI changes at three months and one year, supporting a link between advanced hypothalamic surgical lesions, HI/edema, and subsequent weight gain.

Next to limited surgery, peri- and post-operative administration of the anti-inflammatory drug dexamethasone might decrease this inflammatory response. In our cohort, 15 patients received

perioperative dexamethasone; however, no significant association with post-operative T2 SI ratio could be found. A previous study examined the effects of dexamethasone on weight gain following CP surgery and found that dose and duration of perioperative treatment did influence the short-term post-operative weight gain; however, no effect on long-term severe obesity was found(42). Given the small number of patients who received dexamethasone (11/73) and the short duration in which it was given, no definitive conclusions can be drawn. Therefore dexamethasone or the use of other inflammatory reducing compounds may need to be explored further in future prospective studies.

Unexpectedly, we found a negative association between cystic tumors (>50% cystic volume) and high post-operative T2 SI, which may be explained by early-onset inflammation from prior cyst fenestration subsiding by the time of the post-operative scan, or by differences in tumor removal. Cystic tumors may be less adherent to the hypothalamus and somewhat easier to resect, whereas solid, calcified tumors could require more manipulation and carry a higher risk of hypothalamic injury.(43). Beyond the cystic nature of the tumor, we found no association between tumor size and post-operative T2 SI, suggesting that the mechanism behind the inflammation/edemais more complicated than just the mass effect of the tumor. The hypothalamic impact of CP resection seems to depend on the tumor's characteristics (extent and consistency) as well as degree of surgical manipulation.

In addition to T2 SI measurements, patients exhibiting restricted diffusion, indicative of ischemic changes in the hypothalamus on post-operative DWI, also had increased BMI z-scores one year post-operatively. In theory, these ischemic changes may be a consequence of the surgery and/or the tumor's local effects. cCP may create disruption of the blood-brain barrier, which is often seen as the irregular enhancement in the tumor interface on pre-operative MRI. Tumor removal may also affect the surrounding microvasculare perfusion that might lead to ischaemia detectable on DWI, ultimately contributing to hypothalamic

dysfunction. Adjuvant radiotherapy wasn't associated with BMI increase one year after surgery.

The strengths of this study include well-defined cohorts from two experienced institutes and the availability of MRI scans linked to clinical data. However, several limitations must be acknowledged. Despite being large for this rare disease, the cohort size was still limited, warranting caution in interpreting the results and highlighting the need for future prospective studies. Missing scans, sequences, and clinical data reduced the sample size for some analyses. Additionally, as a retrospective study, MRI scans were acquired using different scanners and protocols, so the appropriate planes or sequences were not available for all patients.

Despite these limitations, our data sheds new light on the hypothalamic T2 SI increase after surgery and its possible effect on hypothalamic function during follow-up. Hypothalamic T2 SI increase following surgery for cCP seems to be associated with BMI increase in the first 3 months after adjustment for other radiological and clinical variables and presence of the hypothalamic syndrome. In future studies, our results will have to be confirmed using prospective cohorts with well-defined outcome definitions.In such studies, the underlying cause of the T2 SI increase should be verified as it can be inflammation or edema. If confirmed to be the inflammation, then subsequently, ways to prevent hypothalamic dysfunction may be investigated by reducing this inflammatory response.

CONCLUSION

Our data suggests that hypothalamic T2 SI increase, suggestive of inflammation or edema, is associated with the BMI increase and hypothalamic dysfunction after cCP surgery. These insights enhance our understanding of the pathophysiology underlying post-operative hypothalamic obesity and may inform future preventive and therapeutic strategies.

Required Statements:

Ethics:

The study was approved by the appropriate institutional review board, and all procedures were conducted in accordance with the ethical standards of the responsible committee and the Declaration of Helsinki.

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Conflict of Interest:

No conflict of interest is declared.

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All authors significantly contributed to the experimental design, data collection, analysis, interpretation, and manuscript writing. Each author participated in drafting and revising the manuscript and approved the final version.

- Protocol writing, data collection, data analysis, manuscript drafting: Doga Yurddas
- Protocol writing, quality control as an experienced radiologist, editorial input: Rutger A. Jan Nievelstein
- Protocol writing, quality control as an experienced radiologist: Brigitte Bison
- Protocol writing, statistical analysis, editorial input: Marta Fiocco
- Protocol writing, editorial input: Wim J.E. Tissing

- Clinical data collection (Netherlands), editorial input: Sanne Hulsmann
- Clinical data collection (Germany), editorial input: Julia Beckhaus
- Clinical data collection (Germany), editorial input: Carsten Friedrich
- Protocol writing, editorial input: Eelco W. Hoving
- Protocol writing, head of research team (Germany), editorial input: Hermann L. Müller
- Protocol writing, head of research team (Netherlands), editorial input: Hanneke M. van Santen

Data Availability

Deidentified data supporting this study are available from the corresponding author upon reasonable request. Data may also be provided to the Journal for review during peer review.

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Captions for all illustrations

Tables

Table 1: Patient characteristics. Abbreviations: SD, standard deviation; IQR, interquartile range; BMI, body mass index.

Table 2: Association between variables and post-operative MBH/PUT T2 signal intensity ratio. Post-operative hypothalamic inflammation (HI) was assessed using the MBH/putamen T2 signal ratio. Estimated regression coefficients (B), standard errors (SE), and 95% confidence interval (CI) were derived from univariable linear regression models. The number of patients (n) included in each model is indicated. *P*-values < 0.05 were considered significant. Abbreviations: DWI, diffusion-weighted imaging. * p<0.05, ** p<0.01

Table 3: Effect of variables on change in BMI at 3 months post-surgery.
Multivariable linear regression results (n = 38) showing regression coefficients (B), standard errors (SE) and 95% confidence interval (CI) for predictors of BMI change at 3 months. The model included ΔT2 SI (left hemisphere), cystic tumor composition (>50%), and post-operative Müller grading, adjusted for age at diagnosis and BMI z-score at diagnosis. Variance inflation factor (VIF) values

ranged from 1.07 to 1.59, indicating no multicollinearity. Abbreviations: BMI, body mass index; MBH, mediobasal hypothalamus; PUT, putamen; Δ, delta. p*<0.05, p**<0.01

Figures

Figure 1: Placement of ROIs for T2 signal intensity (SI) measurements and T2 SI before and after surgery.

T2 SI: T2 signal intensity,

1A: Coronal FLAIR MRI showing ROIs in the mediobasal hypothalamus (MBH), and putamen (PUT).

1B: MBH/PUT T2 SI ratios for left (n=61) and right (n=62) hemispheres pre- and post-operation.

Figure 2: (A–D) MBH/PUT T2 signal intensity ratio pre- and post-operative in relation to Müller score, tumor composition, and dexamethasone treatment. MBH: mediobasal hypothalamus; PUT: putamen; T2 SI: T2 signal intensity, *p < 0.05

Legend:

(A) Boxplot of pre-operative MBH/PUT T2 SI ratio by pre-operative Müller grading (F=0.05, p=0.3, n=71)

(B) Boxplot of post-operative MBH/PUT T2 SI ratio by post-operative Müller grading (F=4.7, p=0.01, n=84).

(C) Boxplot of post-operative MBH/PUT T2 SI ratio by tumor cystic composition >50% (t=2.9, p=0.006, n=79).

(D) Boxplot of post-operative MBH/PUT T2 SI ratio by perioperative dexamethasone treatment (treated n=11, untreated n=73; t=0.22, p=0.81).

Figure 3: Hypothalamic signal intensity change and BMI change after 3 months(n=39).

Scatterplot showing the correlation between the mediobasal hypothalamus (MBH) to putamen (PUT) T2 signal intensity (SI) ratio change (pre-operative to post-operative) and BMI z-score change during the first 3 post-operative months. A positive correlation was observed between the bilateral sum ΔT2

SI ratio and ΔBMI z-score at three months post-operatively (r = 0.56, CI: 0.29–0.74, p=0.0002). The left MBH/PUT ratio (r=0.5, CI: 0.22-0.70, p=0.001) showed a stronger correlation with BMI increase compared to the right MBH/PUT ratio (r=0.42, CI: 0.12-0.65, p=0.007).

Abbreviations: MBH, mediobasal hypothalamus; PUT, putamen; ΔT2SI, change in T2 signal intensity; ΔBMI, change in Body-mass index z-score.

Tables

Table 1

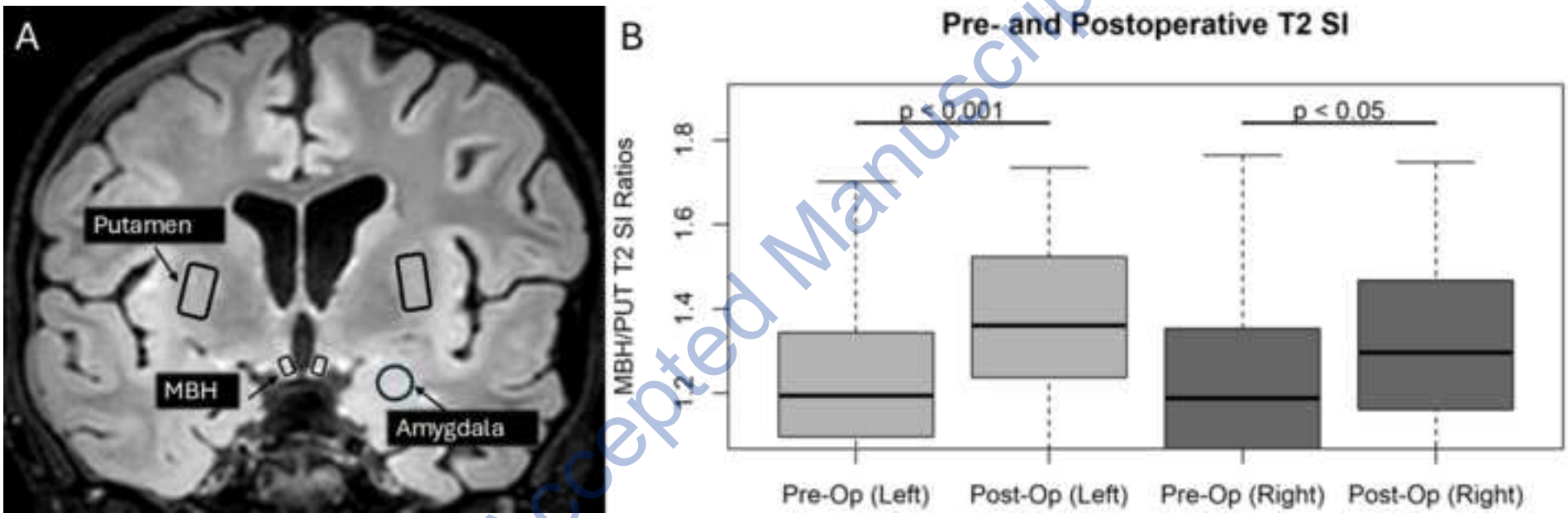
Variables	n	Total number
Nationality (Dutch vs German)		107
Dutch	40 (37.4%)	
Sex (Female)	42 (39.3%)	107
Age at diagnosis, Median (IQR)	8.00 (6.24)	107
Perioperative dexamethasone administration		107
Given	15 (14.0%)	
Extent of resection		103
Complete resection	15 (14.6%)	
Radiotherapy (yes)	23 (21.5%)	107
BMI z-score at diagnosis		85
Mean (SD)	0.784 (1.56)	
BMI z-score at post-op 3 months		70
Mean (SD)	1.82 (1.50)	
BMI z-score at post-op 1 year		67
Mean (SD)	1.49 (1.54)	
Hypothalamic syndrome (6 months)		51
Present	21 (41.2%)	
Hypothalamic syndrome (1 year)		47
Present	20 (42.6%)	

Table 2

Variables	B(SE)	%95 CI	P value	n
Pre-op signal intensity	0.27 (0.09)	0.08–0.46	0.005 **	61
Pre-op Müller Score 1	0.27(0.2)	-0.12–0.67	0.17	84
Pre-op Müller Score 2	0.37(0.19)	-0.01–0.75	0.05	84
Post-op Müller Score 1	0.28(0.12)	0.04–0.53	0.02 *	84
Post-op Müller Score 2	0.38(0.12)	0.12–0.62	0.003 **	84
Cystic tumor part >50%	-0.20(0.09)	-0.04– -0.01	0.03 *	79
Eagle sign groups B and D combined	0.17 (0.07)	0.02–0.31	0.02*	84
Ischemic sign on DWI	0.17(0.09)	-0.01–0.36	0.07	76
Dexamethasone	-0.02(0.10)	-0.24– 0.19	0.81	84
Tumor volume (cm^3)	-0.002 (0.0009)	-0.003–0.00006	0.05	79
Complete resection	-0.07(0.11)	-29–0.15	0.52	83
Age at diagnosis	0.02(0.008)	0.0006–0.03	0.042 *	84
Male sex	0.06(0.07)	-0.08–0.21	0.41	84

Table 3

Variables	B(SE)	95% CI	P value
Δ MBH/PUT T2 signal intensity (Left)	1.4 (0.68)	0.09–2.8	0.04*
Age at diagnosis	-0.09 (0.03)	-0.15– -0.03	0.002**
Cystic tumor part >50%	-0.70 (0.36)	-1.45–0.04	0.06
BMI z-score at diagnosis	-0.16 (0.10)	-0.37–0.04	0.12
Post-op Müller Score 2	0.04 (0.26)	-0.49–0.58	0.85



Figure