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Original Article

Neuroendocrine Deficits and Weight Development Before and After Proton Therapy in Children With Craniopharyngioma

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Abstract

Aims: Our objective was to analyse tumour- and treatment-related factors influencing endocrine morbidity and obesity pre- and post-proton beam therapy (PBT) in paediatric patients with craniopharyngioma.
Materials and methods: A total of 65 patients at the onset of PBT were included in the analysis within our prospective registry study. The data pertaining to endocrine deficits and BMI prior to PBT were retrieved from the medical records on a retrospective basis. Cumulative incidences (CI) of endocrinopathies, age- and sex-adjusted BMI standard deviation scores (BMI-SDS) were calculated.
Results: Before PBT, 90.8% had ≥1 neuroendocrine deficit. Diabetes insipidus (DI) was attributed to surgery in 96%. Patients with postoperative DI had a higher 3-year CI of adrenocorticotropic hormone and thyroid-stimulating hormone deficiency rates compared to those without DI ($p < .001$). At PBT start, 47.7% had already panhypopituitarism compared to 67.7% at the last follow-up (FU). Median FU post-PBT was 3.2 years (range, 1.0–9.6). Post-PBT, 38.2% remained free of additional hormone deficiencies. A trend towards lower endocrine morbidity scores for patients who received PBT during their primary treatment compared to irradiation at progression did not reach statistical significance ($p = .068$). The BMI-SDS increase from diagnosis to the start of radiotherapy was significantly greater than from the start of PBT to the end of FU (mean BMI-SDS increase: 0.61, ±1.16 vs. 0.13, ±0.84, $p = 0.019$), with a median time of 10.2 and 38.4 months, respectively. In the multivariate analysis, hypothalamic involvement ($p = .042$) and the BMI-SDS level at diagnosis ($p = .006$) were identified as clinical factors indicating severe obesity at FU (BMI-SDS ≥+2).
Conclusions: Panhypopituitarism is frequently observed in paediatric patients with craniopharyngioma prior to PBT. The potential benefits of early PBT on endocrine outcomes require further investigation through longer FU periods. The greatest increase in weight occurred before radiotherapy. Endocrine deficiencies and weight gain are multifactorial and require close monitoring.

Key words: Craniopharyngioma; endocrinopathy; obesity; outcomes; paediatrics; radiotherapy

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Nomenclature

ACTHD	adrenocorticotrophic hormone deficiency
ADH	anti-diuretic hormone
BMI	body mass index
CI	cumulative incidence
CP	craniopharyngioma
CTV	clinical target volume
DI	central diabetes insipidus
ECOG	European Childhood Obesity Group
EEFS	endocrine event-free survival
EMS	endocrine morbidity score
FSH	follicle-stimulating hormone
FU	follow-up
GHD	growth-hormone deficiency
GTR	gross total resection
GTV	gross tumour volume
HI	hypothalamic involvement of the tumour
HPA	hypothalamic-pituitary axis
LH	luteinizing hormone
LH/FSHD	luteinizing hormone-/ follicle-stimulating hormone deficiency
MRI	magnetic resonance imaging
OAR	organ at risk
OR	odds ratio
PBS	pencil beam scanning
PENTEC	Pediatric Normal Tissue Effects in the Clinic
PTV	planning target volume
RBE	relative biologic effectiveness
RT	radiotherapy
SDS	standard deviation score
STR	subtotal resection
TSHD	thyroid-stimulating hormone deficiency

Introduction

Craniopharyngiomas (CPs) are rare, low-grade (WHO grade I) tumours that originate from the embryonic development of the pituitary and hypothalamus. CPs are classified into two distinct tumour types (adamantinomatous CPs and papillary CPs) [1]. Adamantinomatous CPs, predominant in paediatric patients, may display markedly aggressive growth patterns, characterised by cystic formation [2]. This tends to be associated with pre-therapeutic neuroendocrine deficiencies [3]. Current therapeutic regimes typically comprise risk-adapted resection followed by radiotherapy (RT) [4].

Both tumour-related factors and the consequences of therapeutic interventions can result in lifelong discernible impairments [5–7]. In particular, the involvement of the hypothalamus (HI) by the tumour and the subsequent development of hypothalamic lesions following surgical procedures have demonstrated a substantial influence on neuroendocrine sequelae and the risk of future obesity [8–16]. The manifestation of endocrine deficiencies and hypothalamic dysfunction may result in the development of hypothalamic syndrome [17], including metabolic disorders, cognitive impairments, and cardiovascular diseases. Consequently, these conditions can significantly impact health-related quality of life.

Proton beam therapy (PBT) is increasingly employed as a highly conformal irradiation technique in paediatric patients with CP [9]. Promising survival rates and local tumour control have been observed [6,9,18]. We have already demonstrated good tolerability of PBT during therapy and excellent progression-free survival within the first years after irradiation at our institute [18,19]. In this study, we present detailed results on the neuroendocrine status before and outcome after PBT in our cohort of paediatric patients with CP. The first objective of this work was to report the outcomes of hypothalamic-pituitary axis (HPA) dysfunction before and after PBT, analysing contributing host-, tumour- and treatment factors. The second objective was to identify clinical factors associated with severe obesity in childhood-onset patients with CP.

Patients and Methods

Paediatric patients (age at RT $<$18 years) were enrolled in the prospective registry "KiProReg" (DRKS0000536) following the provision of informed consent by their legal guardian(s). From August 2013 to June 2022 84 patients with childhood-onset CP received PBT at West German Proton Therapy Center Essen (WPE). Patients were excluded in case of prior RT, combined photon/proton treatment, incomplete baseline endocrine parameters before RT or unavailable follow-up (FU) data. Eventually, data from 65 patients were analysed. Treatment concepts were performed in accordance with the German KRANIOPHARYNGEOM 2007 trial (n = 52) and KRANIOPHARYNGEOM 2019 Registry (n = 13), respectively.

Tumour-Associated and Prior Treatment Characteristics

HI before surgical resection was evaluated based on neuroradiological findings and graded according to Müller *et al.* [20]. The extent of resection was confirmed by neuroradiological imaging (MRI). Any tumour removal that did not achieve a gross total resection (GTR) was classified as a subtotal resection (STR). Patients' and treatment characteristics are presented in Table 1.

Irradiation Characteristics

The prescribed radiation dose was 5400 cGy relative biologic effectiveness (RBE) at 180 cGy (RBE) per day. The target volumes, comprising the gross tumour volume (GTV), clinical target volume (CTV) and planning target volume (PTV) as well as the organs at risk (OAR) pituitary gland and

Table 1
Patient characteristics

Characteristic	N = 65	%
Age at diagnosis, y, median	8.12 (range, 0.01–17.40)	
Age at PBT, y, median	9.13 (range, 3.38–17.52)	
Age at last FU, y, median	13.27 (range, 4.46–23.29)	
Sex[a], female	38	58.5
Histology		
Adamantinomatous	61	93.8
NOS	4	6.2
Hypothalamic involvement		
Typ 0	5	7.7
Typ 1	24	36.9
Typ 2	36	55.4
Hydrocephalus at diagnosis	22	33.8
CSF-shunting	14	21.5
Cyst-reservoir	19	29.2
Surgery at diagnosis		
GTR	6	9.2
STR	55	84.6
Biopsy/cyst aspiration	4	6.2
Number of surgical interventions[b]		
≤2	44	67.7
>2	21	32.3
Time from 1st diagnosis to PBT, m, median	10.15 (range, 1.3–113.4)	
PBT in sedation	14	21.5
Timing of PBT		
Initial/first event	16	24.6
At relapse/progression	49	75.4
PBT technique		
PBS	54	83.1
US	9	13.8
US+PBS	2	3.1
Initial tumour size, cc, median	17.3 (range, 3.1–300.1)	
GTV, cc, median	3.3 (range, 0.0–64.9)	
CTV, cc, median	26.2 (range, 9.7–197.9)	
PTV, cc, median	52.3 (range, 21.4–328.8)	

[a] The use of the term "sex" in tables and text refers to the biological aspect.
[b] Total number of cranial surgeries before PBT including tumour resections, procedures due to hydrocephalus and/or cyst enlargement, reservoir implantation or shunt replacement.
Abbreviations: CSF, cerebrospinal fluid; CTV, clinical target volume; GTR, gross total resection; GTV, gross tumour volume; NOS, not otherwise specified; PBS, pencil beam scanning; PTV, planning target volume; STR, subtotal resection; US, uniform scanning.

hypothalamus were contoured and the corresponding volume doses D_1, D_2, D_{50}, and D_{mean} were calculated with the planning software RayStation 10B (RaySearch Laboratories AB, SE-104 30 Stockholm, Sweden) (Table 2). Further details regarding the treatment of this cohort can be found elsewhere [18].

Neuroendocrine Assessment

Diagnosis and treatment of the following deficiencies were recorded: somatotropic (growth-hormone deficiency [GHD]), thyrotrophic (thyroid-stimulating hormone deficiency [TSHD]), adrenocorticotropic (adrenocorticotropic hormone deficiency [ACTHD]), and gonadotropic (luteinizing hormone [LH]/follicle-stimulating hormone [FSH]-deficiency [LH/FSHD]). The examination of LH/FSHD was conducted on individuals aged 11 years and above in the female cohort and 13 years and above in the male cohort. Presence of central diabetes insipidus (DI) was employed to identify a deficit in the neurohypophyseal antidiuretic hormone (ADH). The degree of hypopituitarism was assessed using the endocrine morbidity score (EMS) [10] ranging from "0" (no deficit) to "4" (panhypopituitarism) or "5" in patients who were old enough to test the gonadotropic axis. Evaluation and grading of obesity was assessed using the body mass index (BMI; w/h2; w= weight [kilogram], h= height [metre]). Age- and sex-adjusted BMI-standard deviation scores (BMI SDS) were calculated using the LMS method with the formula $SDSLMS = \frac{\left(\frac{BMI}{M(t)} \cdot L(t) - 1\right)}{L(t) \cdot S(t)}$ [21]. Respective reference data were used for patients ≤18 [22] and >18 years of age [23]. Weight was classified in accordance with the guidelines of the European Childhood Obesity Group (ECOG) [24].

Statistical Analysis

Distribution and relationship of attributes were calculated and compared using cross tables and chi-square test. Differences across categorical variables were tested using the two-tailed Fisher's exact test. Endocrine FU time since diagnosis and since PBT was defined as the time of initial diagnosis or start of PBT to the date of death due to any cause or the date of the last endocrine FU used for censoring. Cumulative incidences (CI) for each hormonal axis, calculated from both the date of diagnosis and the commencement of PBT, were determined using the respective start date and either the date of the event or the last contact for each event of interest. Endocrine event-free survival (EEFS) was defined as the time until the first occurrence of any new hormonal deficit (of all examined axes), that developed after the commencement of PBT. Without an event, the date of death or the last endocrine FU was used for censoring in EEFS. EEFS and cumulative incidences (CI) of hormone deficiencies were estimated using the Kaplan-Meier method. Log-rank tests were performed to determine statistical significance between the binary categories (sex, HI, hydrocephalus at diagnosis, timing of PBT, presence of endocrinopathies, number of surgical procedures) or mean-splits of continuous variables (age, hypothalamic and pituitary dose distribution, target volume size). Bivariate Pearson's correlation was performed for continuous variables. The Kruskal–Wallis test was used to detect significant differences between three or more independent groups. For univariate comparison of BMI-SDS values over time, either the Student's t-test or the non-parametric Wilcoxon signed-rank test for paired data was used. Logistic regression analysis was performed to determine factors influencing the risk of severe obesity (BMI-SDS ≥ +2) at the end of the FU, first without adjustment and subsequently with adjustment based on statistically significant association in the univariable analysis. Two-sided *P*

Table 2
Dose distribution to neuroendocrine structures

	D1[a]	D2[b]	D50[c]	D_{mean}[d]
Pituitary	55.09 (53.2–56.5)	54.99 (52.5–55.5)	54.34 (53.5–55.4)	54.34 (52.5–55.4)
Hypothalamus	54.74 (53.6–56.8)	54.67 (53.5–56.8)	54.02 (49.7–55.2)	53.99 (47.9–55.4)

Dose in Gy (Relative Biological Effectiveness), median, range.
[a] Dose received by 1% of the organ at risk.
[b] Dose received by 2% of the organ at risk.
[c] Dose received by 50% of the organ at risk.
[d] Mean (average) dose received by the organ at risk.

values were considered notable ("statistically significant") in case $p \leq 0.05$ without adjustment for multiple testing. Statistical analysis was performed using IBM®SPSS®Statistics software, version 29 and R version 4.2.3.

Results

The median FU time since diagnosis was 5.3 years (range 1.6–14.7 years) and the median FU time since PBT was 3.2 years (range 1.0–9.6 years). Nine of 65 (13.8%) children had endocrine deficits prior to CP diagnosis at a median of 1 month (range, 0.1–11.9 months) before surgery. CIs of the different hormonal axes since diagnosis and PBT are shown in Figure 1, A and B. The 5-year CI since diagnosis was 90.7% (±4.0), 88.2% (±5.2), 87.5% (±4.8), 82.9% (±4.8) and 48.3% (±9.1) for TSHD, ACTHD, GHD, DI and LH/FSHD, respectively. After PBT, the 3-year CI was 65.0% (±11.8), 57.6% (±19.8), 30.2% (±12.8), 24.0% (±9.5) and 14.3% (±9.4) for GHD, TSHD, ACTHD, LH/FSHD and DI, respectively.

Endocrine Event-Free Survival

The estimated 1-, 3-, and 5-year EEFS rates from the start of PBT were 70.6% (±7.8), 43.4% (±9.0) and 18.1% (±8.4), respectively (Figure 2). None of the variables analysed (age at PBT, sex, timing of PBT, HI, initial tumour size, size of PTV, or doses (D_1, D_2, D_{50}, D_{mean}) for pituitary and hypothalamus) were statistically significant in the univariate log-rank test.

Endocrine Morbidity Score

Panhypopituitarism was present in 31 patients (47.7%) before PBT and in 44 patients (67.7%) at the last FU (Suppl.Table 1). No patient remained without any neuroendocrine deficit at the last FU. Of the 34 patients without panhypopituitarism before the start of PBT, 38.2% had no additional hormone deficiency after PBT (Suppl.Table 1). The most frequent new deficiency post-PBT was GHD (N = 15). The distribution by hormone axes affected is shown in

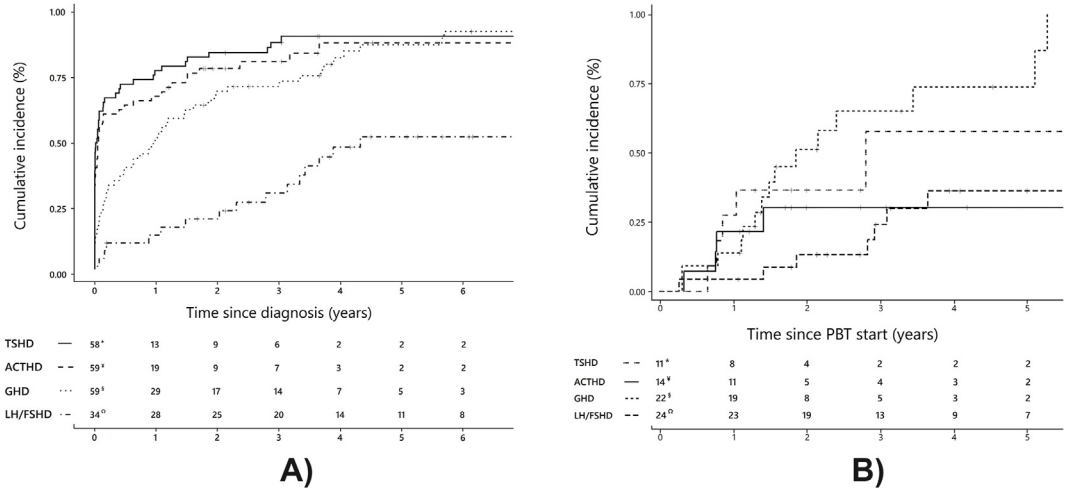

Fig 1. Cumulative incidence (CI) of hormone axis deficits.
(A) CI since diagnosis. The graph illustrates CIs since diagnosis in years. *Abbreviations:* TSHD, Thyroid-Stimulating Hormone Deficiency; ACTHD, Adrenocorticotropic Hormone Deficiency; GHD, Growth Hormone Deficiency; LH/FSHD, Luteinizing Hormone/Follicle-Stimulating Hormone Deficiency. *Patients without TSHD at diagnosis, N = 58. § Patients without ACTHD at diagnosis, N = 59. Ω Patients without GHD at diagnosis, N = 59. ¥ LH/FSHD was examined in ≥11 years old girls and ≥13 years old boys, without LH/FSHD at diagnosis, N = 34.
(B) CI since PBT start. The graph illustrates the CIs since completion of proton beam therapy in years. *Abbreviations:* TSHD, Thyroid-Stimulating Hormone Deficiency; ACTHD, Adrenocorticotropic Hormone Deficiency; GHD, Growth Hormone Deficiency; LH/FSHD, Luteinizing Hormone/Follicle-Stimulating Hormone Deficiency. * Patients without TSHD at PBT start, N = 11. § Patients without ACTHD at PBT start, N = 14. Ω Patients without GHD at PBT start, N = 22. ¥ LH/FSHD was examined in ≥11 years old girls and ≥13 years old boys, without LH/FSHD at PBT start, N = 24.

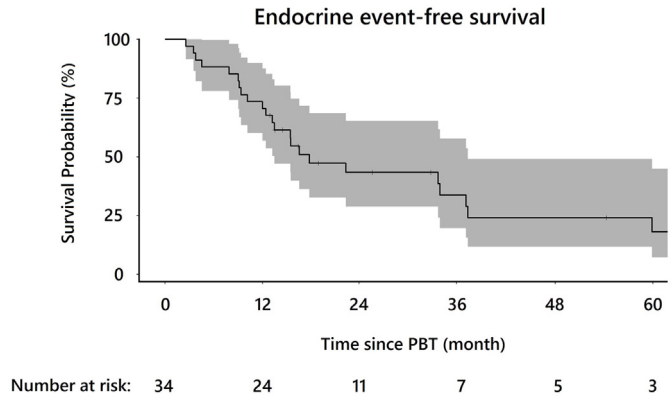

Fig 2. Endocrine event-free survival (EEFS).
The graph illustrates the EEFS since PBT start in months, accompanied by the respective 95% confidence intervals and the number at risk.

(Suppl.Table 2). DI was attributed to surgery in 96% (51/53). The association between the timing of PBT and EMS at the last FU did not reach statistical significance ($p = .068$). An EMS of ≥4 was observed in 89.6% of patients who received PBT at progression, compared to 50.0% of patients who received PBT as part of their primary treatment (Suppl.Table 3). In all investigations, resection status, sex, age at PBT, HI, size of initial tumour, size of the target volumes and number of surgical interventions prior to PBT were not associated with the EMS at the last FU.

Adrenocorticotropic Hormone Deficiency

Six patients had ACTHD before diagnosis. Patients who exhibited postoperative DI had a significantly ($p < .001$) higher 3-year CI of ACTHD 91.5% (±4.1) compared to those who did not exhibit postoperative DI 37.5% (±15.5) Figure 3A.

Thyroid-Stimulating Hormone Deficiency

Seven patients were diagnosed with TSHD prior to CP diagnosis. Patients who exhibited postoperative DI had significantly ($p < .001$) higher 3-year CI of TSHD 97.8% (±2.2) compared to those who did not exhibit postoperative DI 51.4% (±14.8) Figure 3B.

Growth Hormone Deficiency

A total of 43 patients (66.2%) were diagnosed with GHD prior to PBT, including six patients with GHD already before CP diagnosis. Female patients had significantly ($p = .037$) lower 3-year CI of GHD 66.5% (±8.1) compared to male patients 79.2% (±8.3).

Gonadotropin Deficiency

LH/FSHD data were available for 37 patients. Thirteen patients were diagnosed with LH/FSHD prior to PBT, including three patients who were diagnosed with LH/FSHD prior to histological tumour confirmation. Age at PBT significantly ($p < .001$) influenced the time to onset of LH/FSHD. 66.7% of patients who were >13 years old at diagnosis (N = 13) had developed LHFSHD three years later and 20% of 10- to 13-year-olds (N = 12).

Diabetes Insipidus

Four patients started desmopressin treatment before CP diagnosis. Fifty-one patients were diagnosed with DI before PBT. 85.7% (12/14) without DI at PBT remained unremarkable at the last FU. The other two patients started desmopressin therapy within the first 13 and 46 weeks after completion of PBT.

Body Mass Index

At diagnosis, 21.1% of patients had a BMI-SDS of ≥ +2, compared to 41.5% at the last FU (Suppl.Table 4). The increase in BMI-SDS was significantly ($p = .019$) greater in the interval from diagnosis to the start of PBT than in the interval from PBT to the end of FU (Table 3A). Patients with postoperative DI before the start of PBT had a significantly

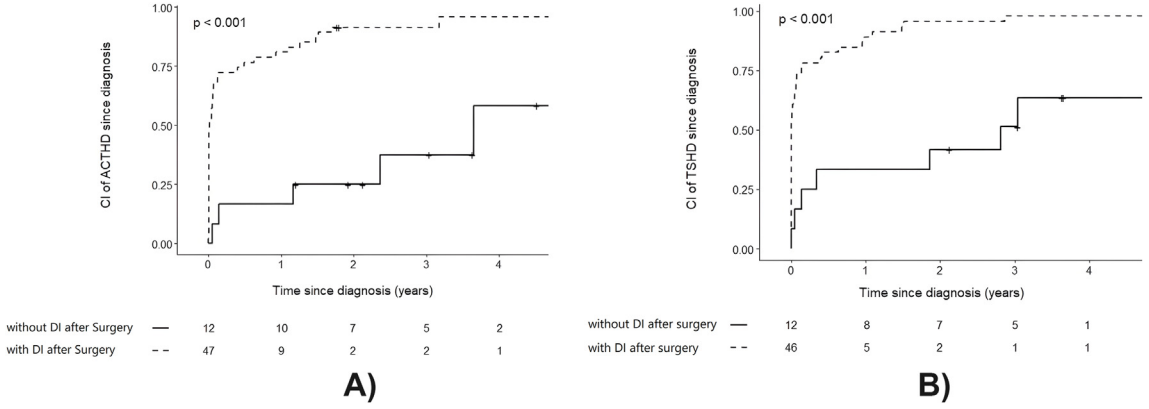

Fig 3. (A, B) Effect of surgery attributed diabetes insipidus (DI) on adrenocorticotropic hormone deficiency (ACTHD) and thyroid-stimulating hormone deficiency (TSHD).
Cumulative incidence (CI) of ACTHD by surgery attributed DI status since diagnosis (3A) and CI of TSHD by surgery attributed DI status since diagnosis (3B). The *p*-value of the log-rank test is *<.001*.

Table 3
Changes in BMI-SDS

	Period	Time (month), median	BMI-SDS increase, mean ± SD		*P* Value[a]
A	baseline until PBT (N=57)	10.2	0.61 ± 1.16		.019
	PBT until last FU (N=65)	38.4	0.13 ± 0.84		
	Variable	BMI-SDS at diagnosis	BMI-SDS at last FU	Difference	*P* value[b]
B	with DI pre PBT, mean ± SD (N=45)	0,94 (±1,37)	1,83 (±1,20)	1,01 (±0,20)	<.001
	without DI pre PBT, mean ± SD (N=12)	0,59 (±1,18)	0,97 (±1,23)	0,47 (±0,30)	.239
C	HI 0/1, mean ± SD (N=27)	0,57 (±1,25)	1,13 (±1,12)	0,52 (±0,22)	.041
	HI 2, mean ± SD (N=30)	1,13 (±1,37)	2,06 (±1,21)	0,95 (±0,28)	.002

Comparison of the changes in BMI-SDS.
A) Between the two time periods "diagnosis until the start of proton beam therapy (PBT)" and from "PBT start to the end of follow-up (FU)". Although there is a notably longer period between the start of PBT and the last FU, the increase in BMI-SDS between diagnosis and the start of PBT is significantly greater.
B) Between patients with and without diabetes insipidus (DI) before PBT start. Patients with postoperative DI prior to the start of PBT experienced notably higher increases in BMI-SDS compared to those without DI.
C) Between patients with hypothalamic involvement (HI) grad 0/1 and grad 2. Patients with grade 0/1 and grade 2 HI both exhibited significant weight gain.
[a] Student's t-test for paired data.
[b] Wilcoxon's test for paired data.

higher increase in BMI-SDS than patients without DI ($p < .001$ vs. $p = .239$, Table 3B). Patients with both grade 0/1 and grade 2 HI showed significant weight gain since diagnosis ($p = .041$, $p = .002$; Table 3C). Normal-weight patients (<85th percentile) had lower EMS (excluding gonadotropic axis) compared to patients with overweight or severe obesity at last FU ($p = .018$). Analysis of clinical variables associated with BMI-SDS $\geq +2$ at FU is shown in Table 4. After adjustment, relevant odds ratios (ORs) with a statistically significant association with a BMI-SDS $\geq +2$ at the end of FU were observed for the variables HI ($p = .042$) and BMI-SDS at diagnosis ($p = .006$).

Discussion

A high prevalence of endocrinopathies in patients with CP is well documented [4,5,8,9,25–28]. Many patients with CP have panhypopituitarism prior to RT due to tumour expansion and surgical procedures [5,8,9,25–27,29,30]. Our 5-year CI rates of individual HPA deficits and the number of patients with DI are comparable to published paediatric cohorts with 90.7% TSHD (83.8–92%), 87.5% GHD (90.5–95.3%), 88.2% ACTHD (68.8–89.1%) and 48.3% LHFSHD (32–91%) [5,25,27,31]. Our observed increase in new deficits after RT could be explained by the extensive inclusion of the hypothalamus and pituitary gland in the irradiation volume. Consequently, the doses we administered, around 54 Gy to the neuroendocrine OAR, are significantly higher than published tolerance levels [32–34]. According to the Pediatric Normal Tissue Effects in the Clinic (PENTEC) consortium, there is a 20% risk of TSH, ACTH, and GH deficiency in children receiving a mean dose of 22 Gy, 34 Gy, and 21 Gy in 2Gy fractions to the HPA, respectively [34].

Tan *et al.* [27] retrospectively analysed 185 paediatric patients with CP. They attributed the higher number of patients with panhypopituitarism in their historical cohort (1973–2000) to a higher proportion of radical surgeries compared to the more recent group (1998–2011). In the latter, a more frequent use of the STR+RT approach (60% vs. 25%) was observed, resulting in 43% panhypopituitarism. The vast majority (85%) of our patients received STR+RT, with 68% experiencing panhypopituitarism after multimodal treatment. Miao and colleagues [8], who analysed 200 children with CP who underwent GTR, primarily via craniotomy, also observed a lower proportion of patients with at least 3 affected HPA (EMS $\geq$3) at the end of FU compared to our cohort (74.7% vs. 86.2%). However, our patients had a longer FU compared to both mentioned studies, which according to the results of Vatner *et al.* [32] is associated with the number of defective hormone axes.

In our previous analysis of adverse events after PBT in children with CP, our results showed a significant association between the timing of PBT and the incidence of vision disorders ($p = .021$) [18]. Patients who received early irradiation (within the primary treatment concept) had fewer deficits compared to those who received PBT at the time of progressive or recurrent disease. Due to the close anatomical relationship between the neuroendocrine structures and the chiasma, we hypothesised that earlier use of PBT might also mitigate the effects of a recurrent tumour on the HPA by improving local tumour control. Additional endocrine disruption caused by tumour progression or multiple surgeries could be prevented, leading to better EMS outcomes. Our observed trend suggesting endocrine benefits of earlier irradiation in children with CP needs to be validated with longer FU and a larger cohort of patients irradiated directly in the adjuvant setting to determine whether the benefits are due to the earlier use of PBT itself or simply due to the 10-month shorter FU period in patients irradiated as part of their primary treatment concept.

Gan *et al.* [35] examined a cohort of 166 paediatric patients with optic pathway, hypothalamic, and other suprasellar gliomas. The authors demonstrated that tumour

Table 4
Final BMI-SDS ≥ +2

Variables N = 65	Crude OR	95% CI		*P* value[a]	Adjusted OR[b]	95% CI		*P* value[a]
		Lower Bound	Upper Bound			Lower Bound	Upper Bound	
Sex, Ref.: female	1.058	0.388	2.881	.912	0.667	0.187	2.831	.532
Age at PBT	0.966	0.842	1.107	.616	1.041	0.880	1.232	.640
initial tumour volume	1.001	0.991	1.012	.831	0.986	0.972	1.000	.048
HC at diagnosis, Ref.: No	2.992	1.034	8.659	.043	2.768	0.700	10.955	.146[e]
Yes								
Timing of PBT, Ref.: initial	2.654	0.750	9.384	.130	1.201	0.275	5.238	.807
recurrence/progress								
PTV	1.002	0.993	1.011	.609	0.991	0.977	1.005	.211
HI, Ref.: grade 0/1 grade 2	5.367	1.757	16.388	.003	4.011	1.054	15.261	.042[f]
Surgical interventions before PBT, Ref.: 1								
2	1.048	0.257	4.268	.948	0.374	0.06	2.320	.291
>2	2.667	0.608	11.703	.194	1.155	0.166	8.048	.884
EMS4[c] at FU, Ref.: No	2.283	0.747	6.971	.147	2.428	0.580	10.170	.225
Yes								
GHD, Ref.: No	0.941	0.193	4.595	.940	1.163	0.153	8.860	.884
Yes								
TSHD, Ref.: No	3.939	0.433	35.828	.224	5.756	0.435	76.234	.184
Yes								
ACTHD, Ref.: No	3.333	0.648	17.147	.150	6.338	0.790	50.859	.082
Yes								
LH/FSHD[d], Ref.: No	0.441	0.105	1.854	.264	0.319	0.037	2.737	.297
Yes								
DI pre PBT, Ref.: No	3.259	0.812	13.085	.096	3.750	0.636	22.091	.144
Yes								
FU since diagnosis	1.046	0.879	1.246	.613	1.064	0.837	1.351	.614
BMI-SDS at diagnosis	2.163	1.301	3.597	.003	2.391	1.295	4.415	.006[g]

Univariate and multivariate analyses of factors associated with a final BMI-SDS ≥ +2 at follow-up.
Missing data were handled by multiple imputation.
Abbreviations: BMI-SDS, body mass index standard deviation score; OR, odds ratio; 95% CI, 95% confidence interval; ref., reference; PBT, proton beam therapy; HC, hydrocephalus at diagnosis; PTV, planning target volume; HI, hypothalamic involvement; EMS, endocrine morbidity score; GHD, growth hormone deficiency; TSHD, thyroid-stimulating hormone deficiency; ACTHD, adrenocorticotropic hormone deficiency; LH/FSHD, luteinizing hormone [LH]/follicle-stimulating hormone [FSH]-deficiency; DI, diabetes insipidus; FU, follow-up.
[a] Logistic regression.
[b] Adjusted on hydrocephalus (HC) at diagnosis, hypothalamic involvement (HI), BMI-SDS at diagnosis.
[c] Panhypopituitarism = EMS4, without gonadotropic axes.
[d] Deficiency of gonadotropic axes in N = 37 patients, ≥11 year old girls and ≥13 year old boys at follow-up.
[e] Adjusted only for HI and BMI-SDS at diagnosis.
[f] Adjusted only for HC and BMI-SDS at diagnosis.
[g] Adjusted only for HI and HC at diagnosis.

location is a predictor of the rate of onset of HPA deficiency developed. With regard to the incidence of endocrinopathies over a five-year period, the observed rates were substantially lower than those of our cohort. According to their analysis, the authors suggested that HI has a greater impact on the early occurrence of endocrinopathies than RT. In our cohort, 92.3% exhibited HI (grade 1 or 2), which may contribute to the pronounced discrepancies between the low-grade gliomas and our CP cohort.

We can confirm that both the location of the tumour and the treatment factors impact the development of metabolic disorders. A number of dosimetric comparisons have identified specific OAR where integral dose reduction can be achieved by employing highly conformal techniques, such as PBT [36–38]. It is evident that substantial dose reductions to the neuroendocrine risk structures in the sellar region are not feasible. However, it appears that surgically induced DI may influence the frequency and timing of additional endocrine disorders, particularly TSHD and ACTHD. The markedly elevated CI of ACTHD and TSHD in patients with postoperative DI indicates that these patients experience more severe or extensive damage to the hypothalamic-pituitary system.

Another objective of this study was to determine clinical factors associated with severe obesity. The proportion of patients with a BMI-SDS value of ≥ +2 in our cohort increased from 21.1% at the time of diagnosis to 41.5% at the last FU assessment. Our findings indicate that damage to the

hypothalamus, whether caused by tumour or treatment factors, is a significant contributor to substantial weight gain. This finding is consistent with those of previous studies [15,39]. In particular, a grade 2 HI manifestation is associated with severe obesity (BMI-SDS of $\geq +2$), as evidenced by the results of our multivariate analysis. In a recent retrospective study on 709 children with CP, Beckhaus *et al.* [15] found that posterior HI and post-surgical hypothalamic lesions are not only linked to obesity but also correlate with decreased functional capacity and a negative body image self-assessment. Our analysis revealed that patients diagnosed with hydrocephalus were more likely to develop a BMI-SDS of $\geq +2$. Although this result was not significant in the multivariate analysis, it provides insights into potential tumour-related factors that may contribute to the development of severe obesity. In keeping with earlier studies, the BMI-SDS value at the diagnosis of CP is correlated with the value at FU [39]. It is striking that comparatively high ORs are observed for hormone deficiencies in the regression analysis. However, these values do not reach statistical significance, which may be attributed to the limited sample size and the broad confidence intervals. It seems plausible that, in addition to HI and hydrocephalus at diagnosis, the initial tumour size may also play a potential role in the long-term weight outcomes in these patients.

Our findings suggest the presence of pre-existing hormonal imbalances or hypothalamic damage prior to PBT. This is supported by findings pertaining to the weight development of patients with and without postoperative DI. A significant increase in weight was observed in patients who developed postsurgical DI. Furthermore, a significant increase in BMI-SDS was only observed in the comparatively short period preceding irradiation. RT appears to have no additional impact on the development of morbid obesity beyond that associated with the existing hypothalamic lesion. However, in their analysis of 142 patients with CP Hussein *et al.* [28] found higher BMI in those treated with surgery plus RT compared to surgery alone. The use of advanced hypothalamus-sparing surgical techniques may prove an effective method of mitigating the progression of morbid BMI [11,16], but managing hypothalamic obesity remains a major concern.

It is important to acknowledge some limitations of our study. Although the data were recorded as part of a prospective registry since 2013, additional data were collected retrospectively for the purpose of this analysis. The prospective investigation period for newly occurring deficits post-PBT may be insufficiently long to allow for the adequate determination of the extent of endocrinopathies, with the potential for underestimation of values, particularly with regard to the gonadotrophic axis. The existence of different national and international referring institutions resulted in heterogeneous examination standards and intervals within the FU, which in turn led to a relatively high rate of missing parameters and subsequent exclusions from the analysis. Additionally, not all patients underwent a baseline provocation test prior to RT. The values were determined based on standard hormone blood levels and the need for replacement therapy. However, regarding this rare disease, our analysis represents a large cohort of patients treated with particles (protons) by a single institution. Furthermore, the predominant modern active pencil-beam scanning technique was used.

Conclusion

Neuroendocrine deficits are a common occurrence in paediatric patients with CP, both prior to and following multidisciplinary therapy. These deficits often manifest at an early stage and frequently precede radiotherapy. Due to the sellar location of the target volume, doses exceeding known tolerance levels for neuroendocrine structures are unavoidable. Trends suggesting the possible benefits of early radiotherapy on endocrine outcomes need to be investigated through longer FU. It appears that surgical interventions, particularly those resulting in DI, may influence the frequency and timing of additional endocrine disorders such as ACTHD and TSHD. The greatest increase in weight occurs in the period preceding PBT. No significant weight gain was observed following PBT. Factors existing prior to radiotherapy (such as the initial tumour volume, HI, and the BMI-SDS at diagnosis) exert the strongest influence on severe obesity (BMI-SDS $\geq +2$). Our findings emphasise the crucial role of hypothalamus-sparing surgical techniques. Overall, endocrine deficiencies and BMI development are multifactorial and require close monitoring.

Ethics

The study was conducted in accordance with the ethical standards set forth in the Declaration of Helsinki. Ethical approval was obtained from the local Ethics Committee (21-10088-BO).

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Author contribution

M.B. was the principal researcher and responsible for all aspects of the manuscript including conceptualisation, methodology, data analysis, interpretation and writing of the original manuscript, and the review and editing of the manuscript.

1.Guarantor of integrity of the entire study M.B.

2.Study concepts and design; Statistical analysis: M.B., J.B., S.F.

3.Literature research: M.B., J.B., F.S.

4.Clinical studies: C.K., C.F., B.B., H.L.M., B.T.

5.Experimental studies: N/A.

6.Manuscript preparation; Manuscript editing: All authors.

Conflict of interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Brigitte Bison reports a relationship with German Childhood Cancer Foundation (Deutsche Kinderkrebsstiftung) that includes: consulting or advisory and non-financial support. Brigitte Bison reports a relationship with Merck Healthcare Germany GmbH that includes: speaking and lecture fees. Hermann Mueller reports a relationship with Ferring that includes: paid expert testimony. Hermann Mueller reports a relationship with Pfizer that includes: paid expert testimony and speaking and lecture fees. Hermann Mueller reports a relationship with Sandoz Pharmaceuticals AG that includes: paid expert testimony. Hermann Mueller reports a relationship with Novo Nordisk that includes: paid expert testimony. Hermann Mueller reports a relationship with Ipsen that includes: paid expert testimony and travel reimbursement. Hermann Mueller reports a relationship with Merck Serono that includes: paid expert testimony. Hermann Mueller reports a relationship with Rhythm Pharmaceuticals Inc that includes: speaking and lecture fees and travel reimbursement. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Research data are stored in an institutional repository and will be shared upon request.

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Appendix A. Supplementary data

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