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Clinical impact of hypothalamic-pituitary disorders after conformal radiation therapy for pediatric low-grade glioma or ependymoma

Laura van Iersel[1,2] | Hanneke M. van Santen[2] | Brian Potter[3] | Zhenghong Li[4] | Heather M. Conklin[3] | Hui Zhang[5] | Wassim Chemaitilly[1,4] | Thomas E. Merchant[6]

[1] Division of Endocrinology, St. Jude Children's Research Hospital, Memphis, Tennessee

[2] Department of Pediatric Endocrinology, Wilhelmina Children's Hospital, Utrecht, the Netherlands

[3] Department of Psychology, St. Jude Children's Research Hospital, Memphis, Tennessee

[4] Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, Memphis, Tennessee

[5] Department of Biostatistics, St. Jude Children's Research Hospital, Memphis, Tennessee

[6] Department of Radiation Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee

Correspondence
Thomas E. Merchant, St. Jude Children's Research Hospital, 201 Danny Thomas Place, MS 201, Memphis, TN 38105.
Email: thomas.merchant@stjude.org

Abstract

Background: To determine the impact of hypothalamic-pituitary (HP) disorders on health outcomes in children and adolescents who received conformal radiation therapy (RT) for central nervous system tumors.

Procedure: Cohort study including 355 patients (age ≤25 years at diagnosis) treated with high-dose (50.4-59.4 Gy) RT using photons for low-grade glioma or ependymoma. Patients (median age, 6.4 years at RT) received systematic endocrine follow-up (median duration, 10.1 years; range, 0.1-19.6). Associations between HP disorders and adverse health outcomes were determined by multivariable analysis.

Results: Prevalence was 37.2% for growth hormone deficiency (GHD), 17.7% for gonadotropin deficiency (LH/FSHD), 14.9% for thyroid-stimulating hormone deficiency (TSHD), 10.3% for adrenocorticotropic hormone deficiency (ACTHD), and 12.6% for central precocious puberty (CPP). Hypothalamus mean dose ≥ 36 Gy was associated with higher odds of any deficiency. GHD was associated with short stature (OR 2.77; 95% CI 1.34-5.70), low bone mineral density (OR 3.47; 95% CI 1.16-10.40), and TSHD with dyslipidemia (OR 5.54; 95% CI 1.66-18.52). Patients with ACTHD and CPP had lower intelligence quotient scores, and memory scores were impaired in patients with GHD ($P = 0.02$). Treatment of GHD was not associated with increased risk for tumor recurrence, secondary tumors, or mortality.

Conclusions: HP disorders occur frequently in patients receiving high-dose RT and are related to physical and neurocognitive well-being. Future studies are needed to assess whether further optimization of endocrine management yields better health outcomes.

KEYWORDS
central nervous system neoplasms, childhood cancer survivor, hypopituitarism, radiotherapy

Abbreviations: ACTH, adrenocorticotropic hormone; ACTHD, adrenocorticotropic hormone deficiency; BMD, bone mineral density; CNS, central nervous system; CPP, central precocious puberty; FSH, follicle-stimulating Hormone; FSHD, follicle-stimulating Hormone Deficiency; GH, growth hormone; GHD, growth hormone deficiency; HDL, high-density lipoproteins; HP, hypothalamic-pituitary; IQ, intellectual quotient; LDL, low-density lipoproteins; LH, luteinizing hormone; LH/FSHD, gonadotropin deficiency; RT, radiation therapy; TSH, thyroid-stimulating hormone; TSHD, thyroid-stimulating hormone deficiency

1 | INTRODUCTION

Brain tumors are purveyors of hypothalamic-pituitary (HP) disorders in children and adolescents treated for cancer.[1] Radiation therapy (RT) to the HP region is a major risk factor for HP disorders and requires lifelong endocrine surveillance.[2,3]

In the general population, adverse effects of HP disorders, such as poor growth, increased cardiovascular morbidity, metabolic disorders, bone mineral density deficit, and impaired neurocognitive functioning, have been well studied.[4,5] Data on clinical consequences of HP disorders in childhood cancer survivors are limited and mainly focus on growth hormone (GH) deficiency (GHD).[6–9] In addition, whether GH replacement contributes to the risk of tumor recurrence, secondary tumors, and mortality remains controversial.[9]

Herein, we (1) assess the consequences of HP disorders on physical and neurocognitive outcomes in a large population of systematically followed children and adolescent patients diagnosed with ependymoma or low-grade glioma and exposed to RT; and (2) describe associations between GH treatment variables and risk for tumor recurrence, occurrence of secondary tumors, and mortality.

2 | METHODS

2.1 | Patients

Patients diagnosed with ependymoma or low-grade glioma before age 25 years and treated with conformal and intensity-modulated RT using photons at a single institution between 1996 and 2016 were identified ($n = 355$).

2.2 | Data collection

Sociodemographic and treatment data for primary tumor diagnosis, relapse, or secondary tumor for eligible patients were retrospectively abstracted from medical records and protocol databases after institutional review board approval. All patients were treated using photons. The prescribed RT dose to the primary site was 54 Gy for low-grade glioma and 54-59.4 Gy for ependymoma. Two patients with low-grade glioma received less than 54 Gy. Craniospinal irradiation (≥36 Gy) was administered to 12 patients with metastatic disease. The median age for patients treated with craniospinal irradiation was 13.15 years (range, 6.48-19.12 years). Earliest patients were treated on prospective therapeutic protocols that included evaluation of endocrine function, growth, and development. The same evaluations were used in more recent patients as a standard. Patients received ongoing follow-up in a dedicated late-effects clinic and were enrolled in a survivorship study for long-term monitoring and periodic follow-up appointments.[10] Neurocognitive testing was performed before RT treatment (baseline), at six months, and yearly post-RT for a total of five years. Primary outcomes, endocrine and cognitive, were associated with the initial course of RT and time interval prior to tumor progression or last follow-up.

2.3 | HP disorders

GHD was defined as GH peak response < 10 ng/mL after provocative testing in children aged ≤16 years before January 2012 and as < 5 ng/mL thereafter due to assay changes. For patients older than 16 years, a peak GH response < 3 ng/mL was considered abnormal. Luteinizing hormone (LH)/follicle-stimulating hormone (FSH) deficiency (LH/FSHD) was diagnosed based on clinical examination (i.e., Tanner staging) in relation with chronological age, supplemented by laboratory values to prove the central origin of the deficit in sex hormones. Bone age delay was not used as a criterion for the diagnosis of LH/FSHD. In post-pubertal patients, LH/FSHD in males was defined by total testosterone < 8.7 nmol/L (or 250 ng/dL), coinciding with LH < 7 IU/L, and in females by secondary amenorrhea with estradiol < 62 pmol/L (or 17 pg/mL) and FSH < 11.2 IU/L. Thyroid-stimulating hormone (TSH) deficiency (TSHD) was diagnosed if free thyroxine concentrations were < 12 pmol/L (or 0.9 ng/dL) and coincided with TSH < 4 mIU/L. Adrenocorticotropic hormone deficiency (ACTHD) was based on abnormal results after dynamic testing; the low-dose ACTH test was most frequently used; a cortisol peak < 500 nmol/L (or 18.1 μg/dL) 30 min after administering 1 μg ACTH intravenously was considered abnormal.[11] Central precocious puberty (CPP) was defined as onset of puberty based on Tanner 2 pubertal stage before age 8 and 9 years in girls and boys, respectively. Dates of onset of HP disorders and start/stop dates of hormonal replacement therapy, if applicable, were collected. Eligibility for analysis of specific HP disorders is outlined in Figure 1.

2.4 | Physical health outcomes

Last-available measurements were used to characterize physical and neurocognitive health outcomes. Height and weight measurements were converted into age- and gender-adjusted z-scores for patients aged < 20 years. Short stature was defined as a height z-score ≤ 2 at last follow-up. Body mass index was calculated as weight in kilograms/(height in meters)^2 and converted into age- and gender-adjusted z-scores for patients aged < 20 years. Obesity was defined as body mass index z-score > 2 for patients aged < 20 years and absolute body mass index ≥30 kg/m^2 in patients aged ≥20 years. Whole-body fat was calculated as total fat grams divided by total mass grams measured by whole-body dual-energy X-ray absorptiometry scans with a QDR 4500 fan-array scanner (Hologic) and expressed as percentage. Males and females with body fat ≥25% and ≥30%, respectively, were considered as having high fat mass. Bone mineral density (BMD) was assessed by quantitative computed tomography with GE VCT Lightspeed 64-detector (GE Healthcare) and quantitative CT calibration phantoms and software (Mindways). Average volumetric trabecular BMD for lumbar vertebrae L1 and L2 was calculated and reported

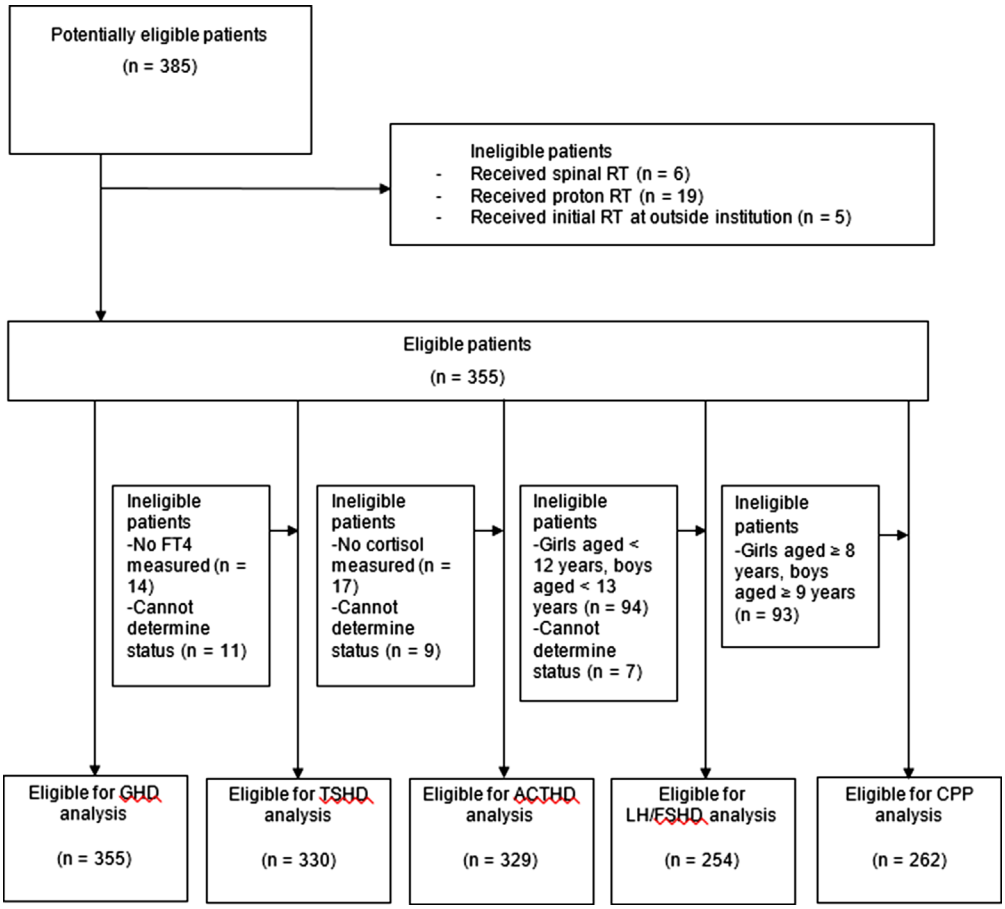

FIGURE 1 Flow diagram of the study cohort.
Abbreviations: ACTHD, adrenocorticotropic hormone deficiency; CPP, central precocious puberty; FT4, free thyroxine; GHD, growth hormone deficiency; LH/FSHD, luteinizing hormone/follicle-stimulating hormone deficiency; RT, radiation therapy; TSHD, thyroid-stimulating hormone deficiency

as age- and gender-adjusted *z*-scores; low BMD was defined as a *z*-score ≤ 2. Glucose disorder was considered present if patients had an elevated fasting insulin level (insulin ≥118 pmol/L or ≥17 mIU/L), impaired glucose tolerance (glucose ≥7.8 mmol/L or 140 mg/dL), overt diabetes mellitus type 2, and/or treatment with glucose-lowering medications. Patients with morning glucose ≥5.6 mmol/L (or 100 mg/dL) but < 7.8 mmol/L were excluded from this analysis, as fasting state during blood withdrawal could not be determined for all patients. Fasting cholesterol, triglycerides, and high- and low-density lipoproteins (HDL and LDL) were measured by an enzymatic spectrophotometric assay (Modular P Chemistry Analyzer, Roche). Dyslipidemia was defined by either total cholesterol ≥5.2 mmol/L (or ≥200 mg/dL), LDL ≥3.4 mmol/L (or ≥130 mg/dL), HDL < 1.0 mmol/L (or < 40 mg/dL), triglycerides ≥1.7 mmol/L (or ≥150 mg/dL), and/or use of lipid-lowering medications.

2.5 | Neurocognitive outcomes

Intellectual ability was estimated by age-appropriate Wechsler scales. Due to high collinearity between estimated intellectual quotient (IQ) scores and full-scale IQ scores, either score could be used to determine IQ.[12] Attention was assessed by Conners' continuous performance test; the omission score was used as a measure of inattentiveness. Memory was assessed by total score from the age-appropriate version of the California Verbal Learning Test. Psychosocial functioning was assessed by parent report on the Child Behavior Checklist or Behavior Assessment System for Children, and internalizing index was used for analysis. Neurocognitive assessments were available for 263 (74.1%), 161 (45.4%), 211 (59.4%), and 206 (58.0%) patients for the intelligence, attention, memory, and psychosocial functioning domains, respectively. The median number of cognitive evaluations was 7 (range, 1-12) for intelligence, 5 (range, 1-17) for attention, 4 (range, 1-10) for memory, and 5 (range, 1-11) for psychosocial functioning.

2.6 | Statistical analyses

Data were expressed as median (range). The point prevalence was defined as the proportion of eligible patients with each HP disorder. Associations between HP disorders and clinical outcomes were first tested in univariable models by chi-squared, exact chi-squared

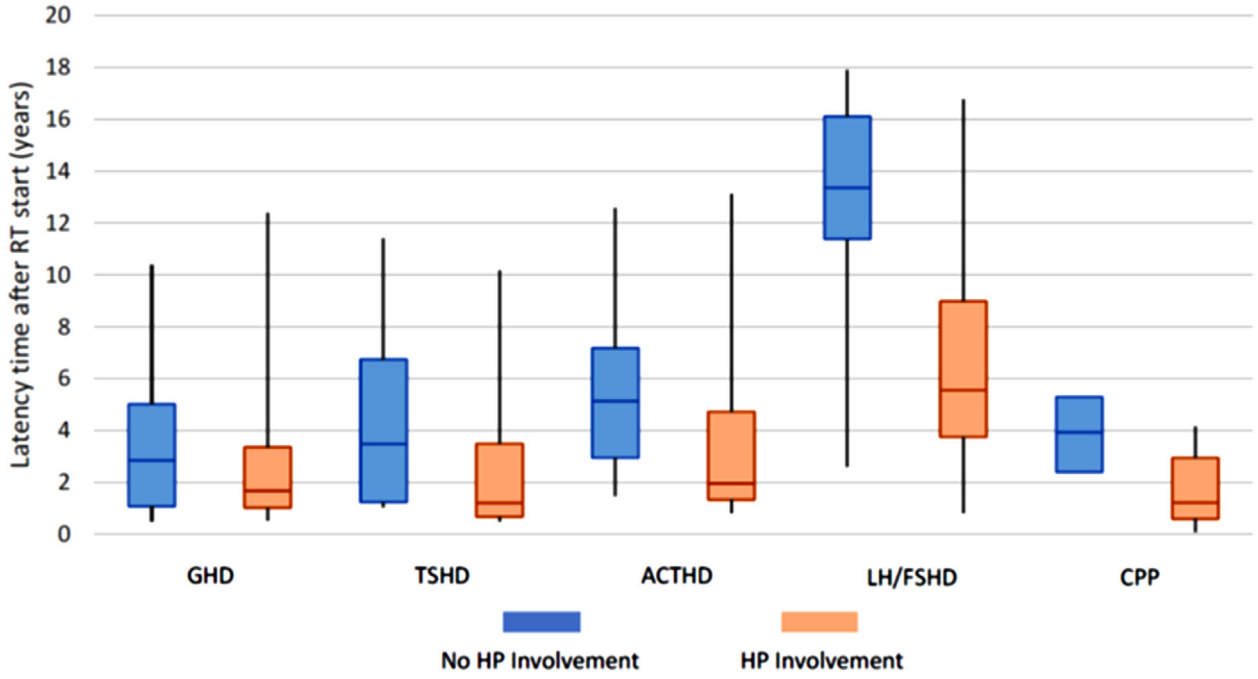

FIGURE 2 Latency times (median, interquartile range) after RT start for each hypothalamic-pituitary (HP) disorder, divided by either HP tumor involvement or no HP involvement.
Abbreviations: ACTHD, adrenocorticotropic hormone deficiency; CPP, central precocious puberty; GHD, growth hormone deficiency; HP, hypothalamic-pituitary; LH/FSHD, luteinizing hormone/follicle-stimulating hormone deficiency; RT, radiation therapy; TSHD, thyroid-stimulating hormone deficiency

tests, and *t* tests or nonparametric tests. Variables with $P \leq 0.1$ from univariable analyses were included in multivariable logistic regression models to determine independent associations. As those eligible for outcomes LH/FSHD and CPP were limited, multivariable analysis for physical outcomes was adjusted only for either or all GHD, TSHD, and ACTHD, depending on their *P* values in univariable analysis. As a subset of GH-deficient patients never received GH replacement therapy, a subanalysis for the physical outcomes was performed only including GH-deficient individuals who received GH therapy during follow-up. Neurocognitive outcomes were adjusted for HP disorders and patient and treatment characteristics possibly influencing neurocognitive functioning. Unadjusted logistic regression models were used for univariable analysis to assess associations between GH treatment variables and tumor recurrence, secondary tumors, and mortality. Patients ($n = 6$) developing secondary tumors after a second RT course were excluded from this analysis. SAS version 9.4 (SAS Institute) was used for all analyses.

3 | RESULTS

3.1 | Study characteristics

The study included 355 eligible patients (median age, 17.8 years at last follow-up), with a median follow-up of 10.1 years (range, 0.1-19.6) from RT (Figure 1). The median age at RT exposure was 6.4 years (range, 0.9-24.9) and initial median RT dose was 54.0 Gy (range, 50.4-59.4). The cohort was composed of 193 (54.4%) ependymoma and 162 (45.6%) low-grade glioma patients. Table 1 lists baseline characteristics.

In total, 37.2% (95% CI 32.1-42.4) had GHD, 17.7% (95% CI 13.2-23.0) had LH/FSHD, 14.9% (95% CI 11.2-19.2) had TSHD, 10.3% (95% CI 7.3-14.1) had ACTHD, and 12.6% (95% CI 8.8-17.2) had CPP. Figure 2 illustrates the time to occurrence for all HP disorders.

3.2 | Radiation dose and HP disorders

Patients were grouped according to mean hypothalamus dose calculated from treatment planning data: 1-23.4 Gy, 23.4-36 Gy, and ≥36 Gy. By univariate analysis, mean dose ≥ 36 Gy was associated OR (95% CI) *P* value with GHD (OR 2.87; 95% CI 1.71-4.82), TSHD (OR 4.37; 95% CI 1.83-10.45), ACTHD (OR 6.95; 95% CI 2.02-23.86), and LH/FSHD (OR 7.65; 95% CI 2.88-20.33). Multivariate analysis was performed including gender, race, age, hypothalamus mean dose, follow-up time, hydrocephalus and/or shunt, surgery, and alkylating agent in the model whose $P < 0.1$ from univariate analysis. Mean dose ≥ 36 Gy to the hypothalamus was associated (OR; 95% CI) with a higher risk of GHD (OR 3.07; 95% CI 1.60-5.89), TSHD (OR 3.30; 95% CI 1.19-9.10), ACTHD (OR 6.74; 95% CI 1.89-24.02), and LH/FSHD (OR 6.34; 95% CI 2.05-19.55). Mean dose to the hypothalamus 23.4-< 36 Gy was associated with a higher risk of ACTHD (OR 5.59; 95% CI 1.13-27.82).

TABLE 1 Demographic and treatment characteristics of the study cohort

Variable	Patients ($N = 355$)	
	n	%
Gender		
Male	183	51.55
Female	172	48.45
Race		
White	275	77.46
Black	50	14.08
Other	30	8.45
Current status		
No evidence of disease	129	36.34
Stable disease	133	37.46
Progression of disease	13	3.66
Deceased	80	22.54
Age at tumor diagnosis (years)	Median	Range
	4.59	0.20-24.63
Age at follow-up (years)	Median	Range
	17.76	2.02-40.47
Follow-up duration from RT (years)	Median	Range
	10.09	0.12-19.59
Primary tumor diagnosis		
Ependymoma	193	54.37
Low-grade glioma	162	45.63
Primary location of tumor		
Supratentorial	45	12.68
Suprasellar	96	27.04
Infratentorial	213	60.00
Spinal cord	1	0.28
Hypothalamic-pituitary involvement		
Yes	103	29.01
No	252	70.99
Neurofibromatosis		
Yes	19	5.35
Neurofibromatosis, type 1	18	94.74
Neurofibromatosis, type 2	1	5.26
No	336	94.65
Hydrocephalus with or without shunt		
Yes	202	56.90
No	147	41.41
Unknown	6	1.69
Neurosurgery		
Yes	276	77.75
No	79	22.25
Chemotherapy		
Yes	125	35.21
No	229	64.51
Unknown	1	0.28
Alkylating agent		
Yes	58	16.34
No	292	82.25
Unknown	5	1.41
Age at start of RT (years)	Median	Range
	6.40	0.89-24.91
Primary RT location		
Cranial RT	343	96.61
Craniospinal RT	12	3.39
Primary RT dose (Gy)[a]	Median	Range
	54.00	50.40-59.4
Hypothalamus mean dose (Gy)		
1-23.4 Gy	151	42.53
23.4-36 Gy	36	10.14
≥36 Gy	168	47.32
Tumor recurrence post-RT[b]		
Yes	119	33.52
No	236	66.48
Second tumor		
Yes	28	7.89
No	327	92.11

[a]Gy, Gray; [b]RT, radiation therapy.

Black race (OR 0.35; 95% CI 0.13-0.93) and older age at the start of radiotherapy (OR 0.89; 95% CI 0.84-0.95) were associated with a lower risk of GHD. Time after radiotherapy was significantly associated with risk for all deficiencies. When the 12 patients treated with craniospinal irradiation were removed from the analysis, the association between GHD and Black race was no longer significant (Table 2). Scatterplots of the expected incidence of each endocrinopathy by dose to the hypothalamus is presented in Supporting Information Figure S1.

3.3 | Physical outcomes and HP disorders

Of 132 patients with GHD, 84 (63.6%) currently or previously received GH replacement therapy. Five patients received GH

TABLE 2 Multivariate risk-factor analysis of hypothalamic-pituitary disorders

	GHD, *N* = 327		TSHD, *N* = 317		ACTHD, *N* = 323		LH/FSHD, *N* = 252	
Variable	**Yes *N* (row %)**	**OR (95% CI)**	**Yes *N* (row %)**	**OR (95% CI)**	**Yes *N* (row %)**	**OR (95% CI)**	**Yes *N* (row %)**	**OR (95% CI)**
Gender								
Male	55 (32.35)	–	19 (11.73)	–	19 (11.45)	1.00	23 (19.01)	–
Female	49 (31.21)	–	17 (10.97)	–	9 (5.73)	0.51 (0.21-1.24)	20 (15.27)	–
Race/ethnicity								
White	87 (34.39)	1.00	27 (11.02)	–	21 (8.30)	–	32 (16.08)	–
Black	8 (17.78)	0.35 (0.13-0.93)*	5 (11.11)	–	3 (6.67)	–	7 (20.00)	–
Other	9 (31.03)	0.54 (0.21-1.40)	4 (14.81)	–	4 (16.00)	–	4 (22.22)	–
Age at start radiotherapy	Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)	
Continuous	6.01 (4.12)	0.89 (0.84-0.95)*	7.83 (5.62)	–	7.61 (5.88)	–	8.56 (4.33)	–
Hypothalamus Dose (Gy)								
1-23.4	30 (20.98)	1.00	7 (5.00)	1.00	3 (2.26)	1.00	5 (5.10)	1.00
23.4-36	10 (27.78)	1.65 (0.62-4.45)	3 (7.89)	1.40 (0.30-6.49)	4 (10.53)	5.59 (1.13-27.82)*	1 (3.70)	0.73 (0.08-7.07)
≥36	64 (43.24)	3.07 (1.60-5.89)*	26 (18.71)	3.30 (1.19-9.10)*	21 (13.82)	6.74 (1.89-24.02)*	37 (29.13)	6.34 (2.05-19.55)*
Follow-up time	Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)	
Continuous	6.29 (5.06)	0.73 (0.67-0.80)*	8.94 (5.49)	0.71 (0.62-0.81)*	9.27 (5.35)	0.79 (0.71-0.88)*	9.90 (5.90)	0.89 (0.82-0.96)*
Hydrocephalus and/or shunt								
No	36 (26.87)	1.00	10 (7.94)	–	11 (8.46)	–	14 (12.07)	1.00
Yes	67 (35.83)	1.04 (0.56-1.93)	25 (13.51)	–	17 (9.09)	–	28 (21.21)	1.98 (0.91-4.28)
Neurosurgery								
No	26 (37.14)	–	15 (22.73)	1.00	9 (12.68)	–	16 (27.12)	1.00
Yes	78 (30.35)	–	21 (8.37)	0.51 (0.20-1.29)	19 (7.54)	–	27 (13.99)	0.71 (0.32-1.61)
Alkylating agent								
No	86 (31.97)	–	31 (11.97)	–	24 (9.02)	–	38 (16.74)	–
Yes	17 (32.08)	–	5 (9.26)	–	4 (7.69)	–	5 (20.00)	–
Relapse and/or second tumor								
No	66 (33.00)	–	16 (8.08)	1.00	17 (8.54)	–	24 (13.95)	1.00
Yes	38 (29.92)	–	20 (16.81)	1.27 (0.55-2.92)	11 (8.87)	–	19 (23.75)	1.22 (0.56-2.66)

Note: Excludes disorders that occurred before radiotherapy; bold values indicate significance. * indicates significance at the $p \leq 0.05$ level.

therapy before starting RT; the remaining patients started GH therapy at a median of 3.28 years (range, 0.94-12.28) after RT. Of 33 patients with CPP, 30 (90.9%) received gonadotropin-releasing hormone analogues. LH/FSHD was treated with estrogen or testosterone in 35/45 (77.8%) patients. All patients with TSHD and ACTHD were on replacement therapy. Multivariable analysis revealed independent associations between GHD and short stature (OR 2.77; 95% CI 1.34-5.70) and low BMD (OR 3.47; 95% CI 1.16-10.40; Table 3). After excluding patients with untreated GHD from analysis, GHD was still associated with short stature (OR 2.44; 95% CI 1.01-5.90) but not with low BMD (OR 2.98; 95% CI 0.84-10.57). The presence of TSHD was associated with higher odds of dyslipidemia (OR 5.54; 95% CI 1.66-18.52).

3.4 | Neurocognitive outcomes and HP disorders

Our cohort had a high proportion of individuals with below-average performance (difference of 1 SD) for all outcomes in comparison with the normative population (16%), except for psychosocial functioning. IQ scores were significantly lower in patients with ACTHD (68.05 vs 94.56, $P = 0.001$) and CPP (77.04 vs 94.60, $P = 0.002$) than those without these HP disorders (Table 3). GHD was significantly associated with worse memory scores (34.90 vs 41.46, $P = 0.02$). No significant associations were found between attention and psychosocial functioning and HP disorders.

3.5 | Safety of growth hormone

Disease relapsed or progressed post-RT in 119 (33.5%). In total, 28 patients (7.9%) developed a secondary tumor, including meningioma ($n = 6$, 21.4%), glioma ($n = 5$, 17.9%), thyroid carcinoma ($n = 4$, 14.3%), glioblastoma ($n = 3$, 10.7%), malignant peripheral nerve sheath tumor ($n = 3$, 10.7%), astrocytoma ($n = 2$, 7.1%), Ewing sarcoma ($n = 1$, 3.6%), renal cell carcinoma ($n = 1$, 3.6%), basal cell carcinoma of the skull ($n = 1$, 3.6%), desmoid tumor ($n = 1$, 3.6%), and nonmelanoma skin cancer ($n = 1$, 3.6%). Of these patients, nine patients previously received GH replacement, whereas 19 did not. Patients who received GH replacement were less likely to experience relapse (OR 0.37; 95% CI 0.19-0.70) or death (OR 0.37; 95% CI 0.18-0.75; Table 4). Duration of GH replacement was not associated with tumor relapse, secondary tumors, or mortality. Occurrence of secondary tumors was similar in patients who received or did not receive GH replacement (OR 1.62; 95% CI 0.70-3.72).

4 | DISCUSSION

This comprehensive and systematic study of a pediatric cohort with central nervous system (CNS) tumors treated with RT is unique for its assessment of associations between HP disorders and several adverse health outcomes. Novel findings include significant associations of HP disorders with impaired physical and neurocognitive health, despite early and frequent endocrine assessments. We also extend previous knowledge about the impact of radiation dose and HP disorders and safety of GH treatment and risk for tumor recurrence, secondary tumors, and mortality.

A high proportion of patients experienced HP disorders, comparable to previous cohorts, although variations may exist by differences in follow-up time, screening protocols, and tumor or treatment characteristics.[1,3,12,13] Especially in patients with HP involvement, HP disorders occurred relatively early; thus, tumor location remains an important risk factor. High upper limits of latency times demonstrate that HP disorders may still occur after longer follow-up, supporting previously reported time- and dose-dependent associations between HP disorders and RT.[14,15] Despite the general trend of early occurrence of HP disorders post-RT, at-risk individuals require extended endocrine screening.[3] Focal irradiation remains a primary treatment modality for children and adolescents with low-grade glioma and ependymoma. Although those with low-grade glioma are more likely to have involvement of the HP unit and have RT deferred and those with ependymoma are more likely to have involvement of a posterior fossa subsite and have RT immediately after surgery regardless of age, the two groups of patients share similar radiation parameters of target volume margins (0.5-1.0 cm) and dose (≥54 Gy).

Children treated for CNS tumors have impaired physical health. How HP disorders affect adverse health outcomes is largely unknown. Timely replacement therapy for GHD may increase final height in childhood cancer survivors, although target heights cannot always be achieved.[16] In our patients, GHD was associated with short stature, even after excluding non-GH-treated patients. Delayed GH treatment and interruptions, craniospinal irradiation, or complete cessation of replacement after relapse or secondary tumor may be responsible. Children developing GHD and LH/FSHD post-RT have lower BMD scores.[17] In our cohort, GHD was associated with impaired BMD, although the association became nonsignificant when only GH-treated patients were included in analyses. This suggests that GH treatment may improve bone health in GH-deficient patients.[17] LH/FSHD was not associated with low BMD in univariable analysis. However, relatively young age at follow-up may have resulted in the low incidence of LH/FSHD in our cohort. Adverse effects may be seen in untreated patients with longer follow-up.[3] Finally, childhood cancer survivors can have adverse metabolic outcomes, although this has been mainly studied in survivors of acute lymphoblastic leukemia.[18,19] Increased occurrence of dyslipidemia in patients with TSHD in our study supports that TSHD contributes to adverse metabolic profiles in survivors. GH treatment may improve outcomes as shown in cohorts of adult survivors treated for childhood cancers.[7,20] Although the presence of HP disorders increased the risk for obesity, glucose disorder, and dyslipidemia in univariable analyses, many associations became nonsignificant after adjusting for HP tumor involvement or obesity, possibly overriding effect of direct hypothalamic injury.[21]

Greatest risk for neurocognitive impairment among patients with CNS tumors relates to mass effect and extent, treatment, or complications.[22] Besides direct effects of tumor and treatment, other

TABLE 3 Multivariable analysis of physical and neurocognitive health outcomes associated with hypothalamic-pituitary disorders in the study cohort

Physical outcomes[a]	GHD				TSHD[b]				ACTHD[c]			
	Yes *N* (%)	No *N* (%)	OR (95% CI)	*P* value	Yes *N* (%)	No *N* (%)	OR (95% CI)	*P* value	Yes *N* (%)	No *N* (%)	OR (95% CI)	*P* value
Short stature	25 (20.16)	15 (7.81)	2.77 (1.34–5.70)	0.01	10 (20.41)	30 (11.24)	1.33 (0.57-3.09)	0.51	Not included in model			
Obesity	36 (29.03)	40 (20.83)	1.08 (0.60-1.93)	0.80	20 (40.82)	56 (20.97)	1.41 (0.61-3.27)	0.43	16 (47.06)	60 (21.28)	2.17 (0.88-5.37)	0.09
High fat mass	Not included in model	20 (95.24)	60 (75.00)	3.81 (0.45-32.36)	0.22	Not included in model						
Low BMD	21 (29.17)	5 (8.20)	3.47 (1.16-10.40)	0.03	10 (41.67)	16 (14.68)	1.72 (0.48-6.17)	0.40	8 (47.06)	18 (15.52)	2.53 (0.64-10.06)	0.19
Glucose disorder	Not included in model	15 (39.47)	56 (24.45)	1.18 (0.41-3.42)	0.77	10 (38.46)	61 (25.31)	0.98 (0.27-3.53)	0.98			
Dyslipidemia	44 (57.14)	33 (36.26)	1.56 (0.74-3.27)	0.24	24 (77.42)	53 (38.69)	5.54 (1.66-18.52)	0.01	16 (69.57)	61 (42.07)	0.53 (0.13-2.15)	0.37

Neurocognitive outcomes[b]	GHD			TSHD			ACTHD[c]			LH/FSHD			CPP		
	Yes, adjust mean (SE)	No, adjust mean (SE)	*P* value	Yes, adjust mean (SE)	No, adjust mean (SE)	*P* value	Yes, adjust mean (SE)	No, adjust mean (SE)	*P* value	Yes, adjust mean (SE)	No, adjust mean (SE)	*P* value	Yes, adjust mean (SE)	No, adjust mean (SE)	*P* value
Intelligence	91.40 (2.40)	90.95 (2.59)	0.90	101.84 (5.92)	88.75 (2.21)	0.07	68.05 (6.92)	94.56 (1.94)	0.001	87.11 (7.26)	92.00 (2.07)	0.56	77.04 (4.83)	94.60 (2.03)	0.002
Attention	83.62 (3.19)	74.82 (3.97)	0.08	86.66 (9.28)	77.91 (3.29)	0.43	82.41 (10.35)	79.13 (2.98)	0.78	83.65 (11.94)	78.74 (3.18)	0.72	86.85 (8.87)	77.79 (3.01)	0.37
Memory	34.90 (1.97)	41.46 (1.72)	0.02	Not included in model			36.74 (4.62)	39.04 (1.33)	0.64	34.99 (4.28)	39.36 (1.38)	0.36	Not included in model		
Psychosocial functioning[c]	NA														

[a] Physical outcomes: All outcomes were adjusted for either GHD, TSHD, and/or ACTHD, if *P* value was ≤0.1 in univariable analysis. In addition, obesity and high fat mass were adjusted for hypothalamic-pituitary involvement. Glucose disorder and dyslipidemia were adjusted for obesity and age at last follow-up.

[b] Neurocognitive outcomes: All four neurocognitive outcomes were adjusted for age at start of radiation therapy, neurofibromatosis, hydrocephalus with or without shunt, neurosurgery, and for specific HP disorders, if *P* value was ≤0.1 in univariable analysis. For psychosocial functioning, none of the *P* values of HP disorders were ≤0.1 in univariable analysis.

[c] Intellectual ability was estimated by age-appropriate Wechsler scales (standard scores with mean of 100 and SD of 15). Attention was assessed by Conners' Continuous Performance Test; the omission score was used as a measure of inattentiveness (percentiles with mean of 50 and SD of 34). Memory was assessed by total score from the age-appropriate version of the California Verbal Learning Test (*T*-scores with a mean of 50 and SD of 10). Psychosocial functioning was assessed by the Parent Rating Scale, and internalizing index was used for analysis (*T*-scores with a mean of 50 and SD of 10). A higher score indicates better performance on measures of intellectual ability and memory, but greater attention problems and parental concerns for measures of psychosocial functioning.

ACTHD, adrenocorticotropic hormone deficiency; BMD, bone mineral density; CI, confidence interval; CPP, central precocious puberty; GHD, growth hormone deficiency; LH/FSHD, luteinizing hormone/follicle-stimulating hormone deficiency; N.A., not applicable; OR, odds ratio (calculated for GHD vs no GHD, TSHD vs no TSHD, and ACTHD vs no ACTHD); SE, standard error; TSHD, thyroid-stimulating hormone deficiency.

TABLE 4 Unadjusted odds ratios for secondary tumor, tumor recurrence, and mortality

	Tumor recurrence		Secondary tumor[a]		Mortality	
GH treatment	Yes *N* (%)	OR (95% CI)	Yes *N* (%)	OR (95% CI)	Yes *N* (%)	OR (95% CI)
No	106 (89.08)	1.00	19 (7.09)	1.00	70 (26.12)	1.00
Yes	13 (10.92)	0.37 (0.19-0.70)*	9 (10.98)	1.62 (0.70-3.72)	10 (11.49)	0.37 (0.18-0.75)*
Duration GH treatment (years)[b]	Mean (SD)		Mean (SD)		Mean (SD)	
Continuous	9.36 (4.58)	0.93 (0.79-1.10)	8.79 (4.72)	1.13 (0.94-1.37)	8.58 (4.70)	0.86 (0.72-1.02)

[a] Patients with neurofibromatosis who developed benign peripheral nerve sheath tumors, were not considered as having a secondary tumor.
[b] Patients with intermittent use of GH treatment were excluded from this analysis.
CI, confidence interval; GH, growth hormone; OR, odds ratio; SD, standard deviation
* indicates significance at the $p \leq 0.05$ level

comorbidities (e.g., endocrine disorders) may contribute to neurocognitive impairment.[23] In our study, lower performance on measures of intelligence and memory was associated with HP disorders. We cannot draw conclusions about the causality of HP disorders on neurocognitive impairment. In the general population, GHD may impair neurocognitive functioning, especially memory, although benefits of GH treatment remain uncertain due to lack of follow-up in large interventional studies.[24,25] For other HP disorders, studies on neurocognitive performance are scarce and mainly focus on deficiencies due to primary endocrine organ dysfunction.[26,27] Associations between HP disorders and neurocognitive outcomes in our cohort are concerning and should be investigated in large, well-designed studies.

In our patients, GH treatment was not associated with higher risk of secondary tumors consistent with most but not all reports.[28] A recent meta-analysis found no difference in the risk of secondary neoplasms in childhood cancer survivors treated with or without GH, although confirmatory studies are warranted.[9] Associations between GH treatment and reduced risk of tumor recurrence or mortality suggest that patients with a better prognosis were offered GH treatment. Indication and timing of GH treatment should be carefully determined after careful discussion.[2]

The current study has limitations. Presence of low BMD was defined by *z*-scores of the lumbar vertebrae, the most frequently assessed site in our cohort. Evaluations of other sites may be more accurate, especially in patients who received craniospinal RT. The study of the effects of GHD on health outcomes included individuals who were on active GH therapy when the outcomes were assessed, as well as those previously or never treated with GH. This may have resulted in a heterogeneous cohort. We performed a subanalysis for GH-deficient patients who received GH replacement. Neurocognitive assessments were mainly performed on patients participating in specific RT protocols. This may have resulted in data being available only from specific subgroups. Finally, we included adolescents up to the age of 25 years at diagnosis. Although only a minority of patients ($n = 30$) were > 15 years at RT, their older age and post-pubertal status may have limited the impact of GHD and influenced the decision to initiate replacement, and associations with health outcomes.

In conclusion, we demonstrate that HP disorders occur frequently after a short follow-up in CNS tumor patients treated with high-dose RT and are associated with impaired health outcomes. Timing and initiation of replacement therapies should be carefully determined by a multidisciplinary team. GH treatment should only be initiated after considering benefits and risk. Impaired neurocognitive functioning in patients with HP disorders requires validation in future studies.

DATA AVAILABILITY STATEMENT

Author elects not to share data.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

ORCID

Heather M. Conklin https://orcid.org/0000-0001-8931-4134
Thomas E. Merchant https://orcid.org/0000-0002-0412-6255

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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