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Declining free thyroxine levels over time in irradiated childhood brain tumor survivors

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Abstract

Objective: The incidence of cranial radiotherapy (cRT)-induced central hypothyroidism (TSHD) in childhood brain tumor survivors (CBTS) is reported to be low. However, TSHD may be more frequent than currently suspected, as its diagnosis is challenging due to broad reference ranges for free thyroxine (FT4) concentrations. TSHD is more likely to be present when FT4 levels progressively decline over time. Therefore, we determined the incidence and latency time of TSHD and changes of FT4 levels over time in irradiated CBTS.

Design: Nationwide, 10-year retrospective study of irradiated CBTS.

Methods: TSHD was defined as 'diagnosed' when FT4 concentrations were below the reference range with low, normal or mildly elevated thyrotropin levels, and as 'presumed' when FT4 declined $\geq 20\%$ within the reference range. Longitudinal FT4 concentrations over time were determined in growth hormone deficient (GHD) CBTS with and without diagnosed TSHD from cRT to last follow-up (paired *t*-test).

Results: Of 207 included CBTS, the 5-year cumulative incidence of diagnosed TSHD was 20.3%, which occurred in 50% (25/50) of CBTS with GHD by 3.4 years (range, 0.9–9.7) after cRT. Presumed TSHD was present in 20 additional CBTS. The median FT4 decline in GH-deficient CBTS was 41.3% ($P < 0.01$) to diagnosis of TSHD and 12.4% ($P = 0.02$) in GH-deficient CBTS without diagnosed TSHD.

Conclusions: FT4 concentrations in CBTS significantly decline over time after cRT, also in those not diagnosed with TSHD, suggesting that TSHD occurs more frequently and earlier than currently reported. The clinical relevance of cRT-induced FT4 decline over time should be investigated in future studies.

Key Words

- ▶ central nervous system neoplasms
- ▶ growth hormone deficiency
- ▶ hypothyroidism
- ▶ radiotherapy

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Introduction

Childhood brain tumor survivors (CBTS) have an increased risk of developing central hypothyroidism due to damage of the hypothalamic–pituitary (HP) region, especially after exposure to cranial radiotherapy (cRT) (1, 2). The prevalence and latency times of cRT-induced HP dysfunction vary among patients, with growth hormone deficiency (GHD) usually occurring first and at a prevalence ranging from 29.0 to 39.1% (3). In contrast, central hypothyroidism primarily occurs after high-dose cRT, with a prevalence ranging between 2.6 and 14.9% (4).

Detection of central hypothyroidism may be challenging (5). Its diagnosis is generally based on plasma free thyroxine (FT4) concentrations below those of the reference range, in combination with low, normal or mildly elevated thyrotropin (TSH) levels. However, the use of population-based FT4 reference ranges as diagnostic criteria for central hypothyroidism is questionable because the variability of FT4 concentrations within individuals is small, in contrast with large interindividual differences (6, 7). This suggests that an individual reduction in thyroid function within the reference range can be indicative of central hypothyroidism in CBTS who receive cRT. Previous studies have suggested that central hypothyroidism is underdiagnosed in patients with FT4 concentrations in the lower tertile of the reference range (8, 9).

Changes in FT4 concentration over time within one individual may be considered abnormal, even if they are maintained within the reference range (6). For this reason, adults with $\geq 20\%$ reductions in FT4 concentrations may be presumed to have mild central hypothyroidism and may be replaced with levothyroxine therapy (LT4), although high-quality evidence supporting this is lacking (10). According to a recent guideline for surveillance of HP deficiencies (HPDs) in childhood cancer survivors, the diagnosis of central hypothyroidism is more likely when FT4 concentrations are progressively declining over time (4). A decline in FT4 concentrations, even those that remain within the lower tertile of the reference range, may thus be indicative of early damage to TSH-secreting cells due to radiation exposure. However, this has not been systematically assessed, and the clinical consequences of declining FT4 concentrations in these patients remain unclear. To this end, we retrospectively analyzed the incidence and latency time of ‘diagnosed’ central hypothyroidism (i.e., FT4 concentrations below those of the reference range) and ‘presumed’ central hypothyroidism (i.e., decline in FT4 concentration $\geq 20\%$ with levels in the lower tertile of the reference range

during follow-up) in a nationwide cohort of longitudinally assessed CBTS who received cRT. Secondly, we assessed the clinical effects of central hypothyroidism on height and weight outcomes during follow-up.

Subjects and methods

Patients

All patients were younger than 18 years at the time of diagnosis of a primary brain tumor, excluding craniopharyngioma or a pituitary gland tumor, between January 2002 and December 2012 ($n=258$). The patients received cranial or craniospinal irradiation and had survived ≥ 2 years after diagnosis with either stable residual disease or no evidence of disease after completion of therapy at the time of follow-up. The methodology we used for patient selection has been described in detail (11). Because both the pituitary and thyroid gland were exposed to radiotherapy during craniospinal irradiation, we limited the interference of thyroïdal dysfunction on thyroid function parameters by excluding all patients with overt primary or subclinical (primary) hypothyroidism, as defined below ($n=39$). In addition, patients with HPDs before receiving cRT were excluded ($n=12$). Because the data were collected retrospectively, our institutional review board determined that the Act on Medical Research Involving Human Subjects did not apply to our study and provided a waiver for informed consent.

Definitions used for endocrine deficiencies

Central hypothyroidism

Diagnosed central hypothyroidism was defined as FT4 concentrations below those of each institutional age-specific reference range, in combination with low, normal or mildly elevated TSH concentrations (i.e. <7 mIU/L) or by the use of LT4 for documented diagnoses of central hypothyroidism. Presumed central hypothyroidism was defined as $\geq 20\%$ decline in individual FT4 concentration that remained within the lower tertile of the age-specific reference intervals from the time of cRT to last follow-up, in combination with normal TSH concentrations.

Primary hypothyroidism

Overt primary hypothyroidism was defined as elevated plasma TSH concentrations (i.e. ≥ 7 mIU/L) in combination

with low FT4 concentrations, according to those of each institutional age-specific reference range or by LT4 administration for documented diagnoses of primary hypothyroidism. Subclinical primary hypothyroidism was defined as FT4 concentrations within those of each institutional age-specific reference range in combination with raised TSH levels at last follow-up.

Growth hormone deficiency

GHD was defined as insufficient peak responses after one or more GH stimulation tests (<20 mU/L) or a peak GH <30 mU/L in combination with an insulin-like growth factor-1 (IGF1) concentration <-2 standard deviation score (SDS). The date of GHD diagnosis was recorded as the date that the last GH stimulation test was performed to establish GHD diagnosis.

Adrenocorticotrophic hormone deficiency

Adrenocorticotrophic hormone deficiency (ACTHD) was defined by the use of hydrocortisone maintenance or substitution for suspected hypocortisolism, as documented by the treating endocrinologist at the last follow-up.

Luteinizing hormone and follicle-stimulating hormone deficiency

Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) deficiency (LH/FSHD) was defined by repeatedly low LH and/or FSH concentrations in the absence of pubertal development (girls aged >12 years, puberty stage B1; boys aged >13 years, testes volumes <4 mL) or by use of estrogens or testosterone treatment for documented LH/FSHD cases at last follow-up.

Data collection

Data were retrospectively collected from patient medical records, which included demographic and tumor-related characteristics, treatment modalities, anthropometrics (i.e., height and weight) and use of antiepileptic drugs until the last follow-up for each patient. The CRT dose comprised the total CRT doses prescribed for tumor treatment. All endocrine laboratory measurements, including basal measurements of IGF1, FT4 and TSH, as well as dynamic testing results for GHD, were collected together with the age-specific reference ranges for FT4 and TSH concentrations of each institution. The lower

limits of the FT4 reference ranges varied between 8 and 12.5 pmol/L, and the upper limits ranged from 18 to 26 pmol/L. The lower tertiles of each institutional-specific reference ranges were defined by dividing the difference between the upper and lower limits by three. The lower limits of the TSH assays were between 0.3 and 0.5 mIU/L, whereas the highest reported upper limit was 5.0 mIU/L.

Statistical analyses

Descriptive analyses were performed for the prevalence and cumulative incidence of HPDs in all CBTS who received CRT. For diagnosed central hypothyroidism, presumed central hypothyroidism, and GHD, the latency time was also examined. Because we assumed that GHD has the shortest latency time after CRT treatment, the presence or absence of GHD during follow-up was used to categorize the cohort into distinct subgroups. The first subgroup consisted of CBTS who experienced GHD during follow-up. Changes in FT4 concentration (absolute and percent changes in FT4 (Δ FT4)) were compared at the following time points with paired analyses: (1) at the time of CRT start, (2) at diagnosis of GHD, (3) after starting GH treatment and (4) at diagnosis of central hypothyroidism or at the last follow-up if central hypothyroidism was not diagnosed. A second subgroup consisted of all CBTS who received CRT but did not receive diagnoses of GHD or other HPDs at follow-up. Changes in FT4 concentration (absolute and Δ FT4) were compared at the time of CRT start and at the last follow-up. Missing values are indicated in the figures and explained in the legends.

Between-group differences were examined by Student *t*-tests for continuous data with normal distributions and χ^2 or Fisher exact tests for categorical data. Non-normally distributed data were analyzed by Mann-Whitney *U* tests. Cumulative incidence was calculated by using the Kaplan-Meier survival method (1 minus Kaplan-Meier probability). Paired *t*-tests were used to evaluate differences in Δ FT4 concentrations within groups, and Wilcoxon signed-rank tests were used for TSH concentrations. Serial FT4 and TSH measurements for each individual were obtained from the same clinical laboratories to allow proper paired analyses. A *P* value less than 0.05 was considered statistically significant. Analyses were performed with SPSS 21.0 for Windows (IBM SPSS System Inc). GraphPad Prism 7.02 was used to generate figures for longitudinal data.

Results

Study cohort

We included a total of 207 CBTS who received cRT in our study (Fig. 1 and Table 1). The median follow-up time after brain tumor diagnosis was 6.9 years (range, 2.0–13.3) and 6.1 years (range, 0.2–12.7) after cRT start. The median cRT dose was 54 Gy (range, 12.5–72.0).

Incidence of anterior pituitary deficiencies

Sixty-eight of 207 (32.9%) CBTS experienced one or more HPDs after exposure to cRT. Thirty-three of these (48.5%) experienced one HPD, and 35 (51.5%) experienced multiple HPDs at last follow-up. The 5-year cumulative incidence was 31.4% (95% confidence interval (CI) 21.8–41.4) for GHD, 20.3% (95% CI 10.7–32.1) for central hypothyroidism, 6.6% (95% CI 0.7–22.6) for ACTHD, and 3.1% (95% CI 0.02–23.9) for LH/FSHD. The latency time of GHD and central hypothyroidism after cRT start was 2.5 years (range, 0.6–7.4) and 2.7 years (range, 0.3–9.7), respectively. The prevalence of HPDs at last-follow-up was 28.5% (59/207) for GHD, 20.3% (42/207) for central hypothyroidism, 6.3% (13/207) for ACTHD and 4.3% (9/207) for LH/FSHD. Figure 2 summarizes the prevalence and overlap of all HPDs. The prevalence of antiepileptic drug use was similar among CBTS with and without diagnosed central hypothyroidism (17.6 vs 11.5%, $P=0.55$).

Nine of the 68 CBTS (13.2%) experienced an HPD other than GHD (i.e., central hypothyroidism, ACTHD, LH/FSHD, or a combination of these). In two of these nine CBTS, GH stimulation tests were performed, ruling out GHD. In two other CBTS, low IGF1 concentrations were found, suggestive of GHD. In the 59 CBTS with GHD, nine (15.3%) had central hypothyroidism before GHD diagnosis. In these CBTS, IGF1 concentrations at diagnosis of central hypothyroidism were low (median IGF1 SDS, -2.57 ; range, -5.11 to -1.79).

Longitudinal effect of cranial radiotherapy on free thyroxine concentrations

CBTS with GHD

We performed paired analyses of the longitudinal FT4 concentrations in 50 CBTS who did not have central hypothyroidism before GHD. Their median FT4 concentrations declined by 9.0% (-1.4 pmol/L) from cRT start to GHD diagnosis ($P<0.01$) after a median follow-up period of 1.7 years (Fig. 3). In the 45 CBTS who subsequently received GH treatment, a 14.9% (-2.0 pmol/L) decline in FT4 occurred after a median period of 0.6 years ($P<0.01$). The total median decline of FT4 was 26.1% (-3.5 pmol/L) between start cRT and after GH treatment ($P<0.01$). TSH concentrations did not significantly change over time (median TSH at GHD diagnosis, 2.7 mIU/L vs median TSH at GH treatment start, 2.8 mIU/L; $P=0.44$).

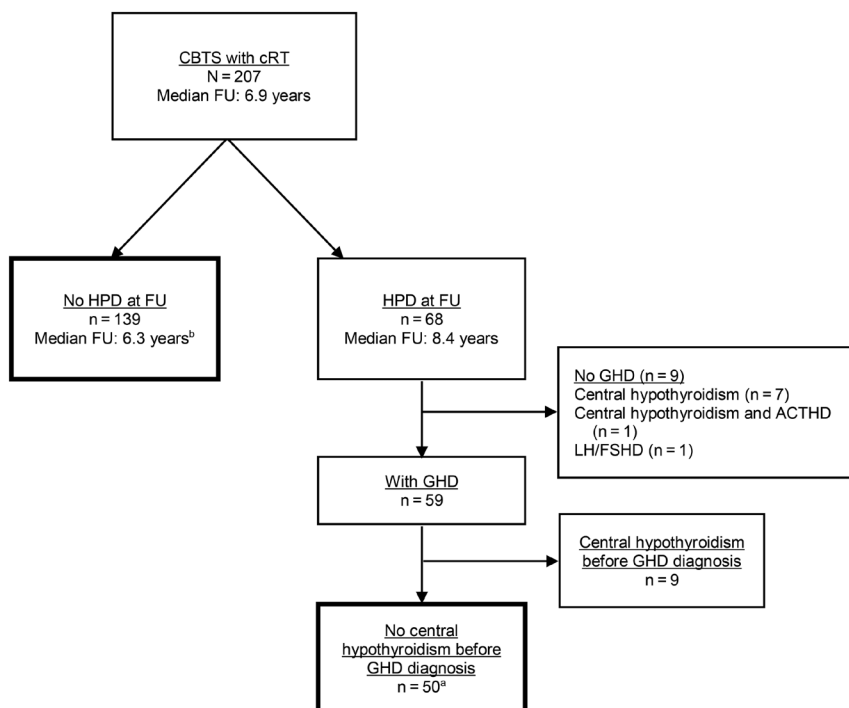


Figure 1 Flow chart of retrospective study cohort. ACTHD, adrenocorticotrophic hormone deficiency; CBTS, childhood brain tumor survivors; cRT, cranial radiotherapy; FT4, free thyroxine; FU, follow-up time after diagnosis; GHD, growth hormone deficiency; HPD, hypothalamic–pituitary deficiency; LH/FSHD, luteinizing hormone–follicle-stimulating hormone deficiency. ^aFT4 concentrations were longitudinally analyzed in this cohort at cRT start, at GHD diagnosis, after GH treatment, at central hypothyroidism diagnosis, or at last follow-up without central hypothyroidism diagnosis. ^bFT4 concentrations were longitudinally analyzed at cRT start and at last-follow-up in this cohort.

Table 1 Demographic and treatment characteristics of the study cohort ($n=207$).

Characteristic	No.	%
Sex		
Male	125	60.4
Female	82	39.6
Age at diagnosis brain tumor (years)		
Median (range)	8.9 (0.1–17.7)	
Age at follow-up (years)		
Median (range)	16.2 (4.7–27.4)	
Follow-up time after brain tumor diagnosis (years)		
Median (range)	6.9 (2.0–13.3)	
Follow-up time after cRT (years)		
Median (range)	6.1 (0.2–12.7)	
Histology		
Medulloblastoma	63	30.4
Low-grade glioma	45	21.7
High-grade glioma	13	6.3
sPNET	7	3.4
Ependymoma	43	20.8
Choroid plexus tumor	1	0.5
Germ-cell tumor	15	7.2
ATRT	5	2.4
Other ^a	8	3.9
Without histology	7	3.4
Location of primary tumor		
Infratentorial region	107	51.7
Supratentorial region	80	38.6
Suprasellar region	20	9.7
Hydrocephalus at diagnosis ^b		
Yes	142	68.6
No	65	31.4
Single and combined treatment modalities applied at any time		
cRT only	5	2.4
Neurosurgery + cRT	84	40.6
cRT + CT	2	1.0
Neurosurgery + cRT + CT	116	56.0
cRT localization		
Cranial	132	63.8
Craniospinal	75	36.2
Age at primary cRT (years)		
Median (range)	9.7 (1.5–22.9)	
<5	41	19.8
5–10	67	32.4
>10	99	47.8
Total cRT dose (Gy)		
Median (range)	54.0 (12.5–72.0)	
Recurrence/progression requiring treatment		
Yes	63	30.4
No	144	69.6

^aIncludes meningioma ($n=4$), schwannoma ($n=3$), and desmoplastic small-round-cell tumor ($n=1$). ^bHydrocephalus was defined as the presence of increased ventricle width during magnetic resonance imaging.

ATRT, atypical teratoid rhabdoid tumor; CT, chemotherapy; cRT, cranial radiotherapy; sPNET, supratentorial primitive neuro-ectodermal tumor.

In 25 of the 50 CBTS with GHD, central hypothyroidism was diagnosed 3.4 years (range, 0.9–9.7) after cRT start and 0.7 years (range, 0.1–5.9) after GHD diagnosis. The median FT4 decline in these CBTS was 41.3% (–6.1 pmol/L) from cRT start to central hypothyroidism diagnosis (Fig. 4A) ($P<0.01$). In these CBTS, central hypothyroidism may have been already presumed 2.4 years after cRT start.

In the 25 CBTS with GHD who did not have diagnosed central hypothyroidism, the median decline in FT4 concentration was 12.4% (–2.1 pmol/L) from cRT start to last follow-up ($P=0.02$). In five of these 25 CBTS, presumed central hypothyroidism was present. CBTS with diagnosed central hypothyroidism were most often medulloblastoma survivors and were older at diagnosis,

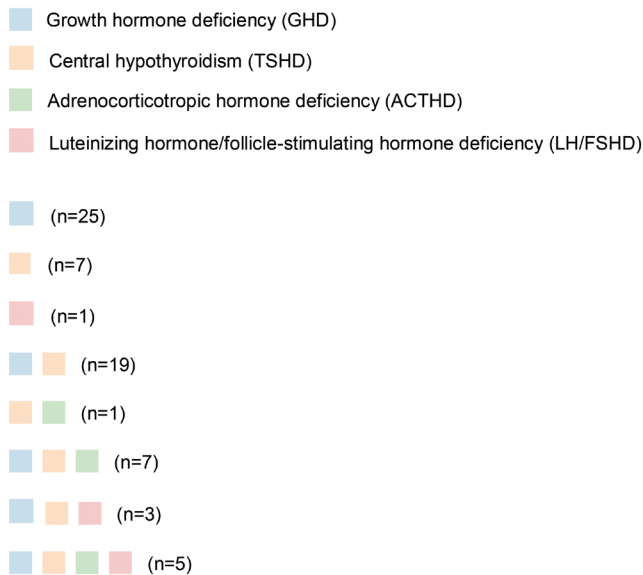
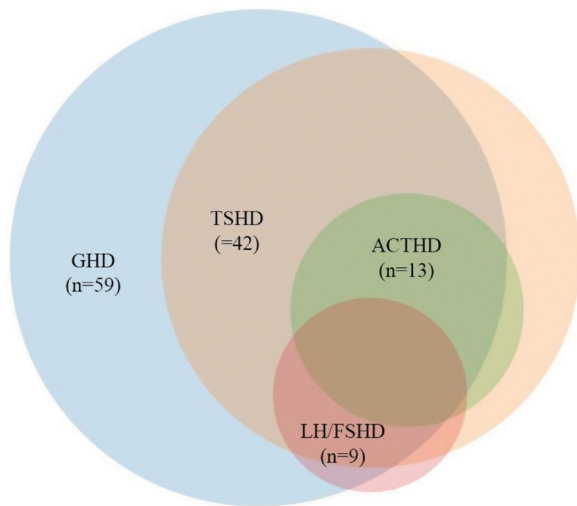


Figure 2
Prevalence and overlap of hypothalamic-pituitary deficiencies in childhood brain tumor survivors who received cranial irradiation.

cRT start and follow-up than were CBTS without central hypothyroidism. The characteristics of the 50 CBTS with GHD and with or without diagnosed central hypothyroidism are listed in Table 2.

CBTS without growth hormone or other hypothalamic-pituitary deficiencies

Of the CBTS who received cRT but did not have HPDs during follow-up (n=139), the median ΔFT4 was -4.4% (-0.7pmol/L) from cRT start to last follow-up (P=0.02) after a median time of 4.2 years (range, 0.2–11.3). Presumed central hypothyroidism was present in 15 of these CBTS (Fig. 4B).

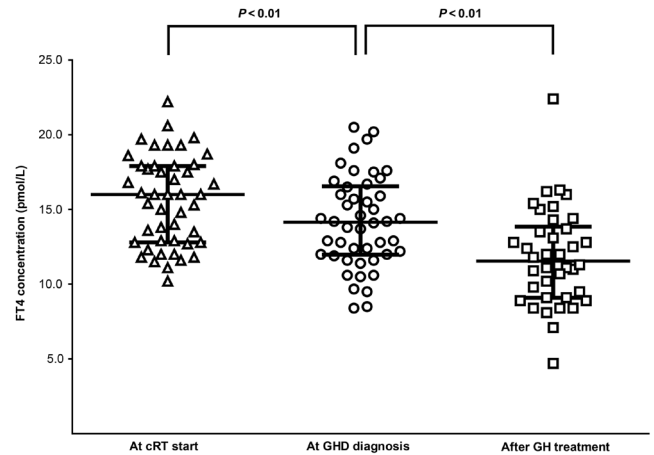


Figure 3
Scatter dot plot (median with interquartile range) of absolute FT4 concentrations at cRT start, before GHD diagnosis, and after GH treatment start. Available FT4 concentrations for 50 CBTS with GHD were compared. FT4 concentrations before cRT start could be retrieved for 24 CBTS. In the remaining 26 CBTS, the first measured FT4 concentration after cRT start was deemed the baseline value for cRT start. FT4 concentrations could be compared at cRT start and at GHD diagnosis for 46 CBTS. FT4 concentrations could be compared at GHD diagnosis and after GH treatment for 38 CBTS. Median FT4 concentrations declined from cRT start to GHD diagnosis (P<0.01; 95% CI 0.82–2.14; paired t-test, n=46) and after GH treatment (P<0.01; 95% CI 1.06–3.33; paired t-test, n=38). CBTS, childhood brain tumor survivors; cRT, cranial radiotherapy; FT4, free thyroxine; GH, growth hormone; GHD, growth hormone deficiency.

Clinical effects on height and weight

All CBTS who received cRT but did not have GHD were included for analysis of height and weight (n=148). Neither height or BMI SDSs of patients with presumed and diagnosed central hypothyroidism were significantly different from those of patients without central hypothyroidism.

Discussion

We performed a large-cohort study of CBTS who received cRT and found a high incidence of diagnosed central hypothyroidism. More importantly, our longitudinal analyses revealed marked declines in FT4 concentrations over time, with a decline of even >40% from initial FT4 values before the diagnosis of central hypothyroidism was made. In addition, a decline in FT4 concentration ≥20% (i.e. presumed central hypothyroidism) was present in 20 additional CBTS.

Central hypothyroidism in CBTS has been reported to be infrequent or absent after low-dose cRT (12, 13, 14, 15, 16, 17). The relatively high (20.3%) 5-year cumulative

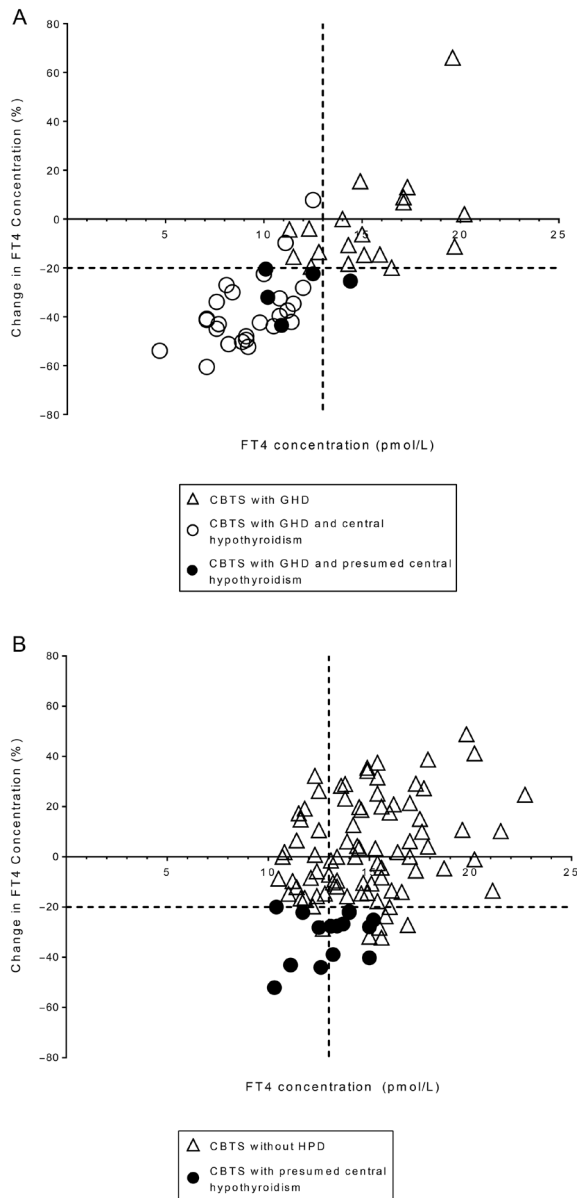


Figure 4

Scatter dot plot of the percent change in FT4 concentration (Δ FT4), in relation to absolute FT4 concentrations of all CBTS with GHD and without GHD or other HPDs who received cRT. (A) CBTS with GHD ($n=50$); Δ FT4 was calculated by comparing FT4 concentrations at cRT start to central hypothyroidism diagnosis or to last follow-up if central hypothyroidism was not diagnosed. Central hypothyroidism was presumed when FT4 levels declined $\geq 20\%$ and were in the lower tertile of the reference range ($n=5$). (B) CBTS without GHD or other HPDs ($n=139$); Δ FT4 was calculated by comparing FT4 concentrations at cRT start to last follow-up. FT4 concentrations before cRT start could be retrieved for 64 CBTS. The first measured FT4 concentration after the cRT start was deemed the baseline FT4 value at cRT start for the remaining 75 CBTS. FT4 concentrations could be compared between baseline and last follow-up for 98 CBTS. Central hypothyroidism was presumed when FT4 declined $\geq 20\%$ and was in the lower tertile of the reference range ($n=15$). Dashed lines indicate Δ FT4 of -20% . CBTS, childhood brain tumor survivors; cRT, cranial radiotherapy; FT4, free thyroxine; GHD, growth hormone deficiency; HPD, hypothalamic-pituitary deficiency.

incidence of central hypothyroidism in our cohort may be due to the high-dose cRT that these patients received, as the vulnerability of the HP–thyroid axis is highly dose dependent (18, 19). Our observations are concordant with the 4-year cumulative incidence (23%) reported in a large cohort study including CBTS who received cRT doses ≥ 40 Gy (20).

We demonstrated a clear decline in FT4 concentrations over time that occurred simultaneously with or preceded GHD diagnosis. In previous studies, a decline in total T4 concentrations after cRT by 1.5% per year has been reported (13). However, in one study, only children who received low-dose cRT were included (15–24 Gy), and only single FT4 concentrations from different CBTS were correlated with follow-up time. In another study, the same cross-sectional analysis was applied to a cohort of CBTS receiving high-dose cRT (53.6 Gy), and an inverse association between serum FT4 concentrations and follow-up times was reported (21).

The usefulness of the population-based FT4 reference ranges used to establish central hypothyroidism diagnoses is debatable (22). Diagnostic tests, such as dynamic TRH testing or the use of the nocturnal TSH rise have been suggested as alternative markers of central hypothyroidism (8). However, dynamic testing of the HP–thyroid axis requires hospital admission, limiting its use as a screening tool. In addition, possible abnormalities of TSH dynamics upon dynamic testing may represent subtle variations and may not be indicative for central hypothyroidism (23). Because intraindividual differences in FT4 concentrations in healthy subjects are small (24), some guidelines recommend treatment with LT4 when $\geq 20\%$ declines in FT4 concentrations are observed (10). Following these guidelines, our findings suggest that treatment could have been provided 1 year earlier in CBTS with diagnosed central hypothyroidism and might have been started in an additional 20 CBTS with presumed central hypothyroidism.

Several factors may affect FT4 concentrations. In general, FT4 concentrations decrease with age, especially when entering puberty (25). This may partially explain why the CBTS in our study with diagnosed central hypothyroidism were older than those without diagnosed central hypothyroidism. However, the follow-up time of our cohort (6.9 years) was too short to support a large interference of age with the observed declining FT4 concentrations. Moreover, the follow-up times of CBTS with GHD and with and without diagnosed central hypothyroidism were similar, suggesting that age and not follow-up time unmasked the presence of central

Table 2 Demographic and treatment characteristics of growth hormone deficient CBTS, with and without subsequent central hypothyroidism.

Characteristic	No diagnosed central hypothyroidism after GHD (n = 25)		Diagnosed central hypothyroidism after GHD (n = 25)		P
	No.	%	No.	%	
Sex					0.76
Male	17/25	68.0	18/25	72.0	
Female	8/25	32.0	7/25	28.0	
Age at diagnosis brain tumor (years)					<0.01 ^b
Median (range)	4.4 (0.6–12.3)		9.3 (2.4–13.1)		
Age at follow-up (years)					<0.01 ^b
Median (range)	12.6 (5.1–23.1)		16.9 (9.8–25.0)		
Follow-up time after brain tumor diagnosis (years)					0.19
Median (range)	8.2 (2.5–13.3)		8.9 (3.3–12.4)		
Histology					<0.01 ^b
Medulloblastoma	15/25	60.0	20/25	80.0	
Low-grade glioma	1/25	4.0	5/25	20.0	
sPNET	1/25	4.0	–	–	
Ependymoma	5/25	20.0	–	–	
ATRT	1/25	4.0	–	–	
Meningioma	1/25	4.0	–	–	
Without histology	1/25	4.0	–	–	
Location of primary tumor					1.00
Infratentorial region	21/25	84.0	21/25	84.0	
Supratentorial region	1/25	4.0	–	–	
Suprasellar region	3/25	12.0	4/25	16.0	
Hydrocephalus at diagnosis ^a					0.51
Yes	20/25	80.0	18/25	72.0	
No	5/25	20.0	7/25	28.0	
Single and combined treatment modalities applied at any time					0.67
Neurosurgery + cRT	3/25	12.0	2/25	8.0	
cRT + CT	1/25	4.0	–	–	
Neurosurgery + cRT + CT	21/25	84.0	23/25	92.0	
cRT localization					0.05
Cranial	9/25	36.0	3/25	12.0	
Craniospinal	16/25	64.0	22/25	88.0	
Age at primary cRT (years)					<0.01 ^b
Median (range)	5.1 (1.8–12.4)		9.9 (3.0–15.6)		
<5	11/25	44.0	2/25	8.0	
5–10	9/25	36.0	11/25	44.0	
>10	5/25	20.0	12/25	48.0	
Total cRT dose (Gy)					0.72
Median (range)	54.0 (15.0–68.0)		54.0 (45.0–72.0)		
Recurrence/progression requiring treatment					0.33
Yes	8/25	32.0	5/25	20.0	
No	17/25	68.0	20/25	80.0	

^aHydrocephalus was defined as the presence of increased ventricle width during magnetic resonance imaging. ^bSignificant P values.

ATRT, atypical teratoid rhabdoid tumor; CT, chemotherapy; CBTS, childhood brain tumor survivors; cRT, cranial radiotherapy; sPNET, supratentorial primitive neuro-ectodermal tumor.

hypothyroidism in our cohort. Nutritional status, BMI and antiepileptic drug use are also factors that may affect thyroid function parameters. In our cohort, we did not observe significant changes in BMI over time and the prevalence of antiepileptic drug use was similar among CBTS with and without diagnosed central hypothyroidism. However, start and stop dates of antiepileptic drug use had not been retrieved from medical charts. In addition, information

regarding other drugs that potentially influenced thyroid function parameters was not collected. This limits our ability to draw strong conclusions about potential interference of (antiepileptic) drug use and thyroid function parameters. Finally, initiation of GH treatment may induce changes in FT4 and TSH concentrations, possibly by increased T4 to T3 conversion and inhibition of TSH secretion (26). Although these changes are often

transient in non-GH-deficient individuals, in patients with organic GH deficiency or multiple pituitary hormone deficiencies, alterations in thyroid function parameters seem more pronounced and result in the unmasking of central hypothyroidism (27).

The clinical significance of mild (i.e., presumed) central hypothyroidism is an issue of debate. Growth acceleration in children who receive GH therapy occurs only after LT4 treatment in cases of concomitant central hypothyroidism (28). Another study reported that reduced patient heights were found at start of GH treatment in children with multiple pituitary hormone deficiencies, as compared to the heights of children with true isolated GHD (29). These findings suggest that when unrecognized central hypothyroidism is present in children with GHD, it may have already affected linear growth. We did not find any adverse effects on height or BMI from declining FT4 concentrations in our cohort. However, these clinical parameters were not systematically assessed, and a large proportion of CBTS had not yet reached adult height. Therefore, definite conclusions regarding the clinical consequences of declining FT4 concentrations cannot be drawn and should be assessed in future studies.

Patients who experience central hypothyroidism after GH therapy start have a lower quality of life than do patients who remain euthyroid. This difference in quality of life is reversible, as it was shown to resolve after LT4 treatment in adults with hypothyroidism (9). Central hypothyroidism may decrease left ventricular ejection fraction in patients with pituitary disease, even when FT4 concentrations remain within the lower range of the reference interval (30). CBTS may have an altered metabolic state, increasing their risk for dyslipidemia and heart disease because of previous exposures to chemotherapy (e.g., alkylating agents), impaired neurologic function, reduced physical activity, and comorbid endocrine deficiencies. Suboptimal thyroid hormone concentrations may further negatively influence the metabolic state. These arguments may be used to advocate timely and adequate supplementation of LT4 in CBTS with a history of cRT aiming to restore FT4 concentrations to the highest third of the reference range to encourage linear growth potential and improve quality of life, metabolic state and cardiac health. The potential benefits of treatment, however, should be considered in the context of the possible negative aspects of overdiagnosis, overtreatment, daily medication administration and frequent blood tests. Prospective studies with systematic screening for central hypothyroidism are required to define the exact prevalence, most optimal diagnostic criteria, and subsequent clinical relevance of mild central hypothyroidism in CBTS.

The comprehensive nature and the intraindividual analyses of FT4 concentrations over time exemplify the strengths of our study. In addition, we evaluated thyroid function parameters only after completion of therapy, excluding FT4 declines from nonthyroidal illnesses or the effects of supportive care drugs such as dexamethasone on thyroid function determinants (31). Nevertheless, the retrospective design, lack of screening guidelines for HPDs in CBTS, and nonsystematic reporting of HP-thyroid function parameters, resulting in missing values for a proportion of CBTS, are limitations of our study. In addition, the lack of systematic and repetitive screening may have underestimated the true prevalence of HPDs in our cohort, given the time dependent character of cRT-induced HPDs. Especially the occurrence of ACTHD might have been under-represented in our cohort, as dynamic testing was only performed in a minority of all CBTS. Moreover, we defined baseline FT4 concentrations for individual CBTS as FT4 concentrations at cRT start. However, this may underestimate actual FT4 baseline concentrations, as illnesses before cRT were not considered. This may account for our observation of increased FT4 concentrations during follow-ups in a substantial number of CBTS. However, this also suggests that the actual FT4 declines in CBTS with presumed central hypothyroidism may have been even larger. A possible coexistence of thyroid-initiated hypothyroidism (leading to combined or mixed hypothyroidism) after craniospinal radiotherapy should be considered because both the HP and thyroid glands are included in the radiation field. We were not able to ascertain detailed cRT dose information for the pituitary or thyroid gland. Therefore, no conclusion can be drawn upon the risk for central hypothyroidism in relation to radiation dose. Also, the HP region of the GH-deficient and nonGH-deficient groups may have been exposed to different cRT doses, which may have biased the comparison results between both groups. In addition, other tumor and treatment characteristics, such as tumor involvement in the HP region, should be considered as cause for the occurrence of central hypothyroidism at follow-up. Secondly, in patients exposed to craniospinal irradiation, it can be difficult to make a clear distinction between primary and central hypothyroidism, and combined forms of hypothyroidism may be present. Declines in FT4 concentration may have been exacerbated by radiation damage to the thyroid gland. For this reason we have used stringent diagnostic criteria for central hypothyroidism. In addition, the large proportion of CBTS with known GHD included in our analysis suggests that these patients may have already experienced cRT-induced HP damage.

In conclusion, FT4 concentrations of irradiated CBTS significantly decline over time, suggesting that high-dose CRT causes more frequent and earlier damage to TSH- or T4-secreting cells than is currently reported. Future prospective studies are required to confirm our findings and the clinical relevance of CRT-induced FT4 decline in CBTS.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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References

- 1 Tonorezos ES, Hudson MM, Edgar AB, Kremer LC, Sklar CA, Wallace WH & Oeffinger KC. Screening and management of adverse endocrine outcomes in adult survivors of childhood and adolescent cancer. *Lancet Diabetes and Endocrinology* 2015 **3** 545–555. ([https://doi.org/10.1016/S2213-8587\(15\)00038-8](https://doi.org/10.1016/S2213-8587(15)00038-8))
- 2 Crowne E, Gleeson H, Benghiat H, Sanghera P & Toogood A. Effect of cancer treatment on hypothalamic-pituitary function. *Lancet Diabetes and Endocrinology* 2015 **3** 568–576. ([https://doi.org/10.1016/S2213-8587\(15\)00008-X](https://doi.org/10.1016/S2213-8587(15)00008-X))
- 3 Mulder RL, Kremer LC, van Santen HM, Ket JL, van Trotsenburg AS, Koning CC, Schouten-van Meeteren AY, Caron HN, Neggers SJ & van Dalen EC. Prevalence and risk factors of radiation-induced growth hormone deficiency in childhood cancer survivors: a systematic review. *Cancer Treatment Reviews* 2009 **35** 616–632. (<https://doi.org/10.1016/j.ctrv.2009.06.004>)
- 4 Sklar CA, Antal Z, Chemaïtily W, Cohen LE, Follin C, Meacham LR & Murad MH. Hypothalamic-pituitary and growth disorders in survivors of childhood cancer: an Endocrine Society Clinical Practice Guideline. *Journal of Clinical Endocrinology and Metabolism* 2018 **103** 2761–2784. (<https://doi.org/10.1210/jc.2018-01175>)
- 5 Beck-Peccoz P, Rodari G, Giavoli C & Lania A. Central hypothyroidism - a neglected thyroid disorder. *Nature Reviews Endocrinology* 2017 **13** 588–598. (<https://doi.org/10.1038/nrendo.2017.47>)
- 6 Alexopoulou O, Beguin C, De Nayer P & Maiter D. Clinical and hormonal characteristics of central hypothyroidism at diagnosis and during follow-up in adult patients. *European Journal of Endocrinology* 2004 **150** 1–8. (<https://doi.org/10.1530/eje.0.1500001>)
- 7 Westgard QC. Desirable specifications for total error, imprecision, and bias, derived from intra- and inter-individual biologic variation. Accessed 22 February 2018. Madison, WI, USA: Westgard QC. (available at: <https://www.westgard.com/biodatabase1.htm>).
- 8 Rose SR, Lustig RH, Pitukcheewanont P, Broome DC, Burghen GA, Li H, Hudson MM, Kun LE & Heideman RL. Diagnosis of hidden central hypothyroidism in survivors of childhood cancer. *Journal of Clinical Endocrinology and Metabolism* 1999 **84** 4472–4479. (<https://doi.org/10.1210/jcem.84.12.6097>)
- 9 Agha A, Walker D, Perry L, Drake WM, Chew SL, Jenkins PJ, Grossman AB & Monson JP. Unmasking of central hypothyroidism following growth hormone replacement in adult hypopituitary patients. *Clinical Endocrinology* 2007 **66** 72–77. (<https://doi.org/10.1111/j.1365-2265.2006.02688.x>)
- 10 Fleseriu M, Hashim IA, Karavitaki N, Melmed S, Murad MH, Salvatori R & Samuels MH. Hormonal replacement in hypopituitarism in adults: an Endocrine Society Clinical Practice Guideline. *Journal of Clinical Endocrinology and Metabolism* 2016 **101** 3888–3921. (<https://doi.org/10.1210/jc.2016-2118>)
- 11 Clement SC, Schouten-van Meeteren AY, Boot AM, Claahsen-van der Grinten HL, Granzen B, Sen Han K, Janssens GO, Michiels EM, van Trotsenburg AS, Vandertop WP, et al. Prevalence and risk factors of early endocrine disorders in childhood brain tumor survivors: a Nationwide, Multicenter Study. *Journal of Clinical Oncology* 2016 **34** 4362–4370. (<https://doi.org/10.1200/JCO.2016.67.5025>)
- 12 Follin C, Link K, Wiebe T, Moell C, Bjork J & Erfurth EM. Prolactin insufficiency but normal thyroid hormone levels after cranial radiotherapy in long-term survivors of childhood leukaemia. *Clinical Endocrinology* 2013 **79** 71–78. (<https://doi.org/10.1111/cen.12111>)
- 13 Lando A, Holm K, Nysom K, Rasmussen AK, Feldt-Rasmussen U, Petersen JH & Muller J. Thyroid function in survivors of childhood acute lymphoblastic leukaemia: the significance of prophylactic cranial irradiation. *Clinical Endocrinology* 2001 **55** 21–25. (<https://doi.org/10.1046/j.1365-2265.2001.01292.x>)
- 14 Livesey EA, Hindmarsh PC, Brook CG, Whitton AC, Bloom HJ, Tobias JS, Godlee JN & Britton J. Endocrine disorders following treatment of childhood brain tumours. *British Journal of Cancer* 1990 **61** 622–625. (<https://doi.org/10.1038/bjc.1990.138>)
- 15 Schmiegelow M, Feldt-Rasmussen U, Rasmussen AK, Poulsen HS & Muller J. A population-based study of thyroid function after radiotherapy and chemotherapy for a childhood brain tumor. *Journal of Clinical Endocrinology and Metabolism* 2003 **88** 136–140. (<https://doi.org/10.1210/jc.2002-020380>)
- 16 Oberfield SE, Allen JC, Pollack J, New MI & Levine LS. Long-term endocrine sequelae after treatment of medulloblastoma: prospective study of growth and thyroid function. *Journal of Pediatrics* 1986 **108** 219–223. ([https://doi.org/10.1016/S0022-3476\(86\)80986-6](https://doi.org/10.1016/S0022-3476(86)80986-6))
- 17 Livesey EA & Brook CG. Thyroid dysfunction after radiotherapy and chemotherapy of brain tumours. *Archives of Disease in Childhood* 1989 **64** 593–595. (<https://doi.org/10.1136/adc.64.4.593>)
- 18 Robinson IC, Fairhall KM, Hendry JH & Shalet SM. Differential radiosensitivity of hypothalamo-pituitary function in the young adult rat. *Journal of Endocrinology* 2001 **169** 519–526. (<https://doi.org/10.1677/joe.0.1690519>)
- 19 Little MD, Shalet SM, Beardwell CG, Robinson EL & Sutton ML. Radiation-induced hypopituitarism is dose-dependent. *Clinical Endocrinology* 1989 **31** 363–373. (<https://doi.org/10.1111/j.1365-2265.1989.tb01260.x>)
- 20 Loughton SJ, Merchant TE, Sklar CA, Kun LE, Fouladi M, Broniscer A, Morris EB, Sanders RP, Krasin MJ, Shelso J, et al. Endocrine outcomes for children with embryonal brain tumors after risk-adapted craniospinal and conformal primary-site irradiation and high-dose chemotherapy with stem-cell rescue on the SJMB-96 trial. *Journal of Clinical Oncology* 2008 **26** 1112–1118. (<https://doi.org/10.1200/JCO.2008.13.5293>)
- 21 Constine LS, Woolf PD, Cann D, Mick G, McCormick K, Raubertas RF & Rubin P. Hypothalamic-pituitary dysfunction after radiation for brain tumors. *New England Journal of Medicine* 1993 **328** 87–94. (<https://doi.org/10.1056/NEJM199301143280203>)
- 22 Persani L. Clinical review: central hypothyroidism: pathogenic, diagnostic, and therapeutic challenges. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** 3068–3078. (<https://doi.org/10.1210/jc.2012-1616>)
- 23 Darzy KH & Shalet SM. Circadian and stimulated thyrotropin secretion in cranially irradiated adult cancer survivors. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 6490–6497. (<https://doi.org/10.1210/jc.2005-1593>)
- 24 Andersen S, Pedersen KM, Bruun NH & Laurberg P. Narrow individual variations in serum T(4) and T(3) in normal subjects: a clue to the understanding of subclinical thyroid disease. *Journal of Clinical Endocrinology and Metabolism* 2002 **87** 1068–1072. (<https://doi.org/10.1210/jcem.87.3.8165>)

- 25 Lem AJ, de Rijke YB, van Toor H, de Ridder MA, Visser TJ & Hokken-Koelega AC. Serum thyroid hormone levels in healthy children from birth to adulthood and in short children born small for gestational age. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** 3170–3178. (<https://doi.org/10.1210/jc.2012-1759>)
- 26 Behan LA, Monson JP & Agha A. The interaction between growth hormone and the thyroid axis in hypopituitary patients. *Clinical Endocrinology* 2011 **74** 281–288. (<https://doi.org/10.1111/j.1365-2265.2010.03815.x>)
- 27 van Iersel L, van Santen HM, Zandwijken GRJ, Zwaveling-Soonawala N, Hokken-Koelega ACS & van Trotsenburg ASP. Low FT4 concentrations around the start of recombinant human growth hormone treatment: predictor of congenital structural hypothalamic-pituitary abnormalities? *Hormone Research in Paediatrics* 2018 **89** 98–107. (<https://doi.org/10.1159/000486033>)
- 28 Sato T, Suzukui Y, Taketani T, Ishiguro K & Masuyama T. Enhanced peripheral conversion of thyroxine to triiodothyronine during hGH therapy in GH deficient children. *Journal of Clinical Endocrinology and Metabolism* 1977 **45** 324–329. (<https://doi.org/10.1210/jcem-45-2-324>)
- 29 Child CJ, Blum WF, Deal C, Zimmermann AG, Quigley CA, Drop SL, Cutler GB Jr & Rosenfeld RG. Development of additional pituitary hormone deficiencies in pediatric patients originally diagnosed with isolated growth hormone deficiency due to organic causes. *European Journal of Endocrinology* 2016 **174** 669–679. (<https://doi.org/10.1530/EJE-15-1203>)
- 30 Doin FC, Rosa-Borges M, Martins MR, Moises VA & Abucham J. Diagnosis of subclinical central hypothyroidism in patients with hypothalamic-pituitary disease by Doppler echocardiography. *European Journal of Endocrinology* 2012 **166** 631–640. (<https://doi.org/10.1530/EJE-11-0907>)
- 31 van Santen HM, Thonissen NM, de Kraker J & Vulsma T. Changes in thyroid hormone state in children receiving chemotherapy. *Clinical Endocrinology* 2005 **62** 250–257. (<https://doi.org/10.1111/j.1365-2265.2005.02210.x>)

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