RESEARCH

Growth hormone deficiency in adult survivors of childhood brain tumors treated with radiation

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Abstract

Objective: Growth hormone deficiency (GHD) is the most common endocrine late effect in irradiated survivors of childhood brain tumors. This study aimed to determine the prevalence of GHD in adults treated with proton or photon irradiation for a brain tumor in childhood and to detect undiagnosed GHD.
Design: This study is a cross-sectional study.
Methods: We investigated GHD in 5-year survivors from two health regions in Denmark treated for childhood brain tumors with cranial or craniospinal irradiation in the period 1997–2015. Medical charts were reviewed for endocrinological and other health data. Survivors without a growth hormone (GH) test at final height were invited to a GH stimulation test.
Results: Totally 41 (22 females) survivors with a median age of 21.7 years (range: 15.1–33.8 years) at follow-up and 14.8 years (range: 5.1–23.4 years) since diagnosis were included; 11 were treated with proton and 30 with photon irradiation; 18 of 21 survivors were previously found to have GHD; 16 of 20 survivors with no GH test at final height were tested, 8 (50 %) had GHD. In total, 26 of 41 patients (63%) had GHD. Insulin-like growth factor-1 (IGF-1) is associated poorly with the insulin tolerance test (ITT).
Conclusion: This study identified a high prevalence of undiagnosed GHD in survivors with no GH test at final height. The results stress the importance of screening for GHD at final height in survivors of childhood brain tumors with prior exposure to cranial irradiation, irrespective of radiation modality and IGF-1.
Significance statement: This cross-sectional study reports a prevalence of 63% of GHD in irradiated childhood brain tumor survivors. Furthermore, the study identified a considerable number of long-term survivors without a GH test at final height, of whom, 50% subsequently were shown to have undiagnosed GHD. Additionally, this study confirmed that a normal serum IGF-1 measurement cannot exclude the diagnosis of GHD in irradiated survivors. This illustrates the need for improvements in the diagnostic approach to GHD after reaching final height in childhood brain tumor survivors at risk of GHD. In summary, our study stresses the need for GHD testing in all adult survivors treated with cranial irradiation for a brain tumor in childhood irrespective of radiation modality.

Key Words
- brain tumor
- childhood
- survivor
- growth hormone
- growth hormone deficiency

Endocrine Connections (2023) **12**, **e220365**

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-22-0365

Introduction

Brain tumors are the most common solid neoplasm in children (1) with an annual incidence rate of 42 per million in the Nordic countries (2). Survival rates for children with brain tumors have improved significantly over the last 5 decades (3, 4), due to treatment improvements with targeted cranial radiotherapy (CR) in combination with chemotherapy and improved surgery techniques (5). The overall 5-year survival rate is now approaching 83% in the Nordic countries (6). With more children surviving a brain tumor, it is evident that survivorship comes with a cost.

Childhood brain tumor survivors have an increased risk of long-term and possibly lifelong morbidity affecting multiple organ systems (4). Compared to survivors of other childhood cancers, childhood brain tumor survivors are among those at highest risk of both cognitive and physical sequelae (7, 8, 9, 10, 11, 12, 13, 14). Endocrine complications are, however, some of the most frequent physical chronic late effects (15) with growth hormone deficiency (GHD) being the most common endocrinopathy (16) followed by thyroid-stimulating hormone deficiency (17).

CR is the most significant risk factor for the development of GHD (18). Irradiation-induced GHD is dose-dependent (19), might occur even after low radiation doses (20), and can evolve over time years after treatment has been completed (21).

The consequences of GHD are many: reduced linear growth in children, decreased bone mineral density, an adverse lipid profile, abdominal adiposity, reduced lean muscle mass, and fatigue (22, 23). Lifelong periodic clinical assessment for GHD in brain tumor survivors exposed to CR of more than 18 Gy is recommended (21). In childhood, GHD can be monitored by linear growth. However, assessment of linear growth is of no use when final height has been reached. Furthermore, insulin-like growth factor 1 (IGF-1) has been questioned as a reliable biochemical proxy marker of GHD in CR patients (21, 24). Therefore, children treated with CR are recommended a growth hormone (GH) stimulation test after reaching final height (21, 25). One of the most sensitive and specific tests for GHD in youths is the insulin tolerance test (ITT) (26, 27).

The primary objectives of this study were to determine the prevalence of GHD in adult long-term survivors after proton or photon CR for a brain tumor in childhood and to unveil undiagnosed GHD. The secondary objective was to evaluate the diagnostic value of IGF-1 regarding GHD in adult childhood brain tumor survivors treated with CR.

Materials and methods

Study design and recruitment

Survivors for this cross-sectional study were recruited from the Central and Northern Region of Denmark and have been treated for a primary brain tumor at Aarhus University Hospital or Aalborg University Hospital in the period from January 1997 to December 2015. Clinical data from the medical charts were extracted from October 2020 to April 2021 and the GHD testing was conducted from May to September 2021 at the Medical Research Laboratory, Aarhus University Hospital.

Study cohort

Inclusion criteria were (i) children diagnosed with a primary brain tumor from January 1 1997, to December 31, 2015, in the Central and Northern Region of Denmark, (ii) age below 15 years at diagnosis, (iii) 5 years since diagnosis, (iv) age above 15 years at inclusion, and (v) children treated with CR. Patients, who met all those criteria, were included in the main study cohort.

A subgroup of survivors from the main cohort was invited to a GH stimulation test. To be invited to a GH stimulation test, the participants had to fulfill one of the following criteria: (i) no GH stimulation test performed at final height or (ii) previously treated with recombinant human growth hormone and no stimulation test performed after end of treatment. Childhood brain tumor survivors currently treated with recombinant human growth hormone due to an abnormal GH stimulation test after having reached final height were included in the main study cohort but were not retested.

Exclusion criteria were (i) a CNS tumor diagnosed after the age of 15 years, (ii) spinal cord tumors, (iii) a GH-producing pituitary adenoma, or (iv) disease progression at time of inclusion.

Using the Danish Childhood Cancer Registry, a total of 241 children were retrospectively identified with a primary brain tumor treated in the Central and Northern Region of Denmark and diagnosed between January 1, 1997, and December 31, 2015 (Fig. 1). Of these 241 children, 74 children died. Of the remaining 167 children, 126 were excluded due to age below 15 at time of inclusion ($n = 37$), intraspinal tumor/spinal cord tumor ($n = 9$), disease progression ($n = 2$), GH-producing pituitary adenoma ($n = 1$), and no CR ($n = 77$). Hence, the main study cohort consisted of 41 survivors who had been treated with CR (Fig. 1).

The medical charts of the 41 survivors were scrutinized. Fifteen survivors had had a GH stimulation

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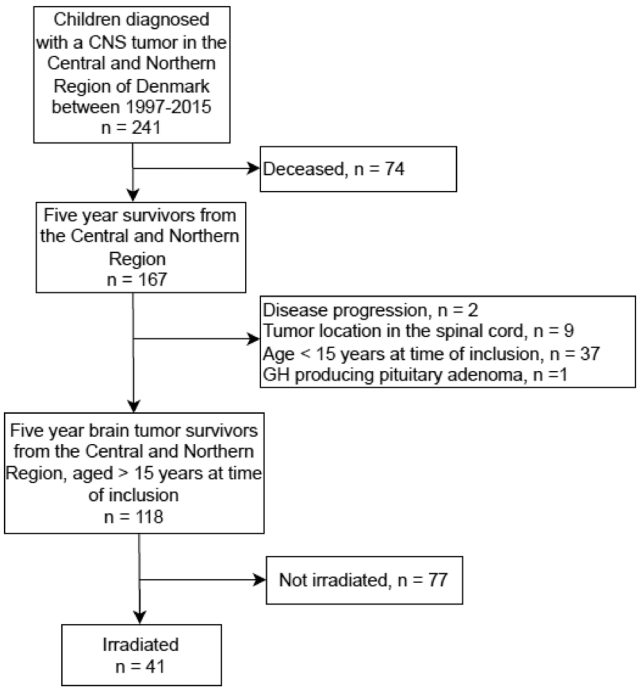

Figure 1
Flowchart of the study cohort.

test performed after having reached final height, five survivors had more than two hormonal deficiencies in addition to GHD and hence continued their GH treatment into adulthood without further GH testing (21) and one survivor moved out of the region. Twenty survivors had not had a GH stimulation test performed at final height and were invited to an ITT or if contraindication for ITT, a growth hormone-releasing hormone (GHRH)-arginine stimulation test (Fig. 2) (28).

Data extraction

Demographics, tumor-related characteristics, and treatment were retrieved from the medical charts. Further, endocrine data including growth data and hormone replacement therapy were retrieved from the charts. When calculating the cumulative CNS irradiation doses, both whole brain irradiation and boost irradiation were included, and the median cumulative CNS irradiation doses therefore correlate to the irradiation doses received in the boost area.

Growth hormone stimulation tests

Both the ITTs and the GHRH-arginine stimulation tests were carried out in the morning after an overnight fast. For the ITT, a peak GH response < 5 ng/mL was interpreted as being diagnostic of GHD in adulthood (29). A peak GH > 5 ng/mL was interpreted as a normal response.

The cut-off values for the GHRH-arginine stimulation test were adjusted for BMI. A peak GH below 11 ng/mL (BMI < 25), 8 ng/mL (BMI: 25–30), or 4 ng/mL (BMI > 30) was interpreted as diagnostic of GHD (28).

Statistical analyses

Continuous variables are shown as median and range, whereas categorical variables are shown as absolute numbers and percentage. Serum IGF-1 values were converted to S.D. scores using the formula by Bidlingmaier *et al.* (30). Height was converted into an age- and sex-adjusted height S.D. score using national growth charts for participants younger than 20 years (31). For participants aged ≥ 20 years, Z-score data for age 20 years was applied. Target height was calculated as: ((height of father (cm) + height of mother (cm))/2) ± 6.5 cm (male/female). Statistical analyses were carried out using Stata version 17.

Ethics

The study was approved by the Danish Data Protection Agency (#1-16-02-118-19) and by the National Committee on Health Research, Denmark (#1-10-72-65-19). The protocol conforms to the ethical standards of the Helsinki Declaration revised in 2008. All test participants gave written informed consent after full explanation of the purpose and nature of all procedures used.

Results

Patient characteristics of the main cohort

The median age at follow-up was 21.7 years (range: 15.1–33.8 years), and the median time since brain tumor diagnosis was 14.8 years (range: 5.1–23.4 years). The median age at diagnosis was 8.5 years (range: 0.4–14.6 years) with 13 (32%) diagnosed between 0 and 4 years and 16 (39%) diagnosed between 5 and 10 years and 12 (29%) diagnosed between 10 and 14 years. The most common tumor location was in cerebellum/fourth ventricle (44%, $n = 18$) and the most common tumor types were medulloblastoma ($n = 12$) and astrocytoma ($n = 8$) (Table 1).

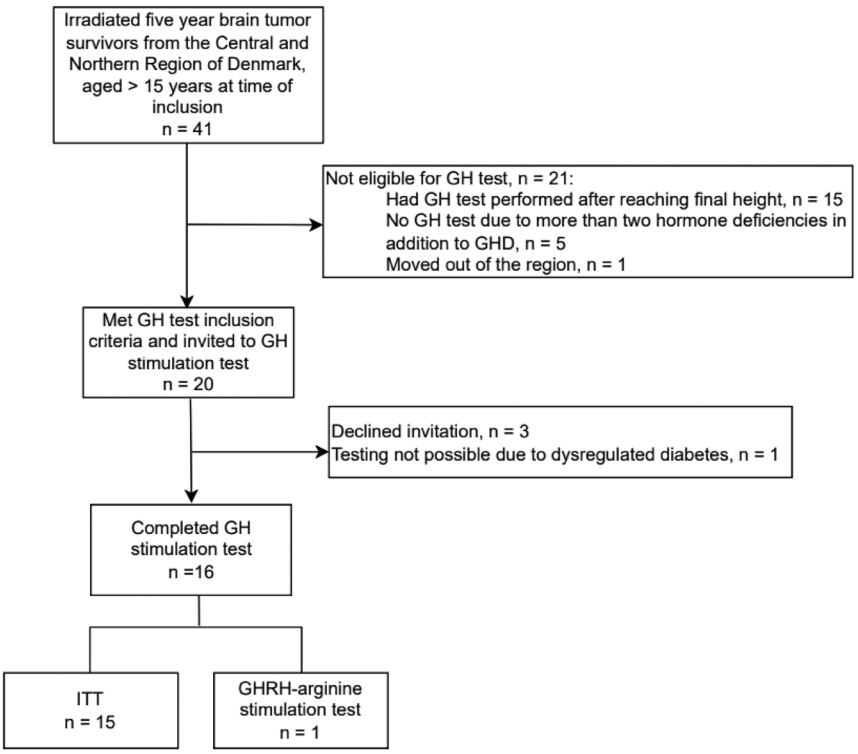

Figure 2
Flowchart for the GH test participants.

Treatment modalities of the main cohort

The median age at the start of irradiation was 8.8 years (range: 1.3–18.8 years); 30 (73%) had received photon radiation and 11 (27%) had received proton radiation. The median cumulative CNS irradiation doses was 54 Gy (range: 12–61 Gy). A total of 28 (68%) had received focal CR, whereas 13 (32%) had received craniospinal irradiation. Furthermore, 23 (56%) had received chemotherapy as part of their treatment, and of these, 5 had received gonadotoxic chemotherapy (cyclophosphamide with median dose of 2400 mg/m^2 (range: 2400–12,587 mg/m^2). In total, 37 (88%) had undergone surgery (Table 2).

Endocrinopathies of the main cohort

A total of 18 of 41 (44%) survivors treated with CR were receiving GH replacement therapy at the time of the study (Table 2). The median age at start of GH treatment was 11 years (range: 2.4–15.2 years).

Additionally, 18 (44%) were currently treated with thyroid hormone, 8 (20%) with hydrocortisone, and 12 (29%) with sex steroids (Table 2). In total, 15% ($n = 6$), 7% ($n = 3$), and 7% ($n = 3$) had two, three, and four hormonal deficiencies, respectively, excluding GHD.

Patient characteristics of the GH test participants

A total of 20 survivors had not had a GH test performed after final height had been reached and were invited to a GH test. The median age at follow-up was 22.9 years (range: 15.9–34.2 years), the median time since brain tumor diagnosis was 14.8 years (range: 5.5–23.7 years), and the median time since CR was 14 years (range: 4.3–23.6 years) (Table 3).

The median height S.D. score was 0.2 S.D. (range: –2.5; 2.5 S.D.). The median BMI was 25.3 (range: 18.4–34). Six of the 16 GH test participants (38%) had received proton irradiation.

The GH tests

Three survivors declined to participate in an ITT and in one case, testing was not possible due to dysregulated diabetes, yielding a participation rate of 80% (16/20). A total of 15 survivors completed the ITT, and 1 completed the GHRH-arginine test, due to epilepsy (Fig. 2).

Two ITT test participants were retested due to insufficient primary test.

Eight (50%) of the 16 GH test participants had GHD; 7 had a peak GH < 5 ng/mL at the ITT and 1 had a peak GH

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https://doi.org/10.1530/EC-22-0365

Table 1 Patient demographics for irradiated childhood brain tumor survivors in the Middle and Northern Region of Denmark (*n* =41) and for the sub-population invited to a growth hormone stimulation test (*n* = 20).

	Main study group *n* = 41	%	Invited to GH stimulation test *n* =20	%
Sex				
Female	22	54	10	50
Male	19	46	10	50
Treatment center				
Aarhus	26	63	14	70
Aalborg	15	37	6	30
Age at brain tumor diagnosis, years				
Median (range)	8.5	(0.4–14.6)	9.4	(2.1–14.6)
0–4	13	32	6	30
5–9	16	39	5	25
10–15	12	29	9	45
Age at follow-up, years				
Median (range)	21.7	(15.1–33.8)	23.9	(15.4–33.8)
15–19	13	32	5	25
20–25	12	29	6	30
>25	16	39	9	45
Time since diagnosis, years				
Median (range)	14.8	(5.1–23.4)	15.6	(5.1–23.4)
Tumor location				
Cerebellum/fourth ventricle	18	44	7	35
Cerebral hemisphere	5	12	2	10
Chiasma/optical nerve	5	12	1	5
Brainstem	3	7	3	15
Hypothalamus	3	10	2	10
Pituitary gland	2	2	0	0
Supratentorial central	1	2	1	5
Pineal gland	4	10	4	20
Histology				
Medulloblastoma	12	29	2	10
Astrocytoma	8	20	6	30
Germ cell tumor	5	12	5	25
Ependymoma	3	7	3	15
DNET	1	2	0	0
Craniopharyngioma	2	5	0	0
Choroid plexus tumors	1	2	1	5
Brainstem glioma	2	5	2	10
Chiasma	1	2	1	5
Opticus glioma	2	5	0	0
Pituitary adenoma	1	2	0	0
Schwannoma	1	2	0	0
PNET	2	5	0	0

DNET, dysembryoplastic neuroepithelial tumor; PNET, primitive neuro-ectodermal tumors.

<11.5 ng/mL (BMI < 25) at the GHRH-arginine test (Table 3). The three patients, who did not accept a GH stimulation test and the one patient, where a GH stimulation test was contraindicated, had received a median cumulative CNS irradiation dose of 50 Gy (range: 40–55 Gy).

Peak GH and IGF-1

The median IGF-1 S.D. for the 16 irradiated GH test participants were 0.3 S.D. (range: –1.3 to 2.5 S.D.). For the irradiated participants with GHD (peak GH < 5 ng/mL), the median IGF-1 was –0.2 S.D. (range: –1.3 to 2.5 S.D.), and for the irradiated test participants with a normal test result (peak GH > 5 ng/mL), the median IGF-1 were 0.5 S.D. (range: –0.1 to 1.8 S.D.) (Table 3 and Fig. 3).

Prevalence of growth hormone deficiency in the cohort

In the main cohort of 41 survivors, 18 survivors had GHD and were on GH treatment. Combined with the 8 GH test participants found to have GHD as described above,

Table 2 Treatment characteristics for irradiated childhood brain tumor survivors in the Middle and Northern Region of Denmark (n = 41) and for the sub-population invited to a growth hormone stimulation test (n = 20).

	Irradiated n = 41	%	Invited to GH stimulation test n =20	%
Received chemotherapy				
Yes	23	56	10	50
No	18	44	10	50
Received gonadotoxic chemotherapy (cyclophosphamide)	n = 23		n = 10	
Yes	5	22	0	0
No	18	78	10	100
Cumulative cyclophosphamide dose, mg/m^2				
Median (range)	2400	(2400–12,587)		
Undergone surgery				
Yes	36	88	17	85
No	5	12	3	15
Current GH treatment				
Yes	18	44	0	0
No	23	56	20	100
Previously treated with GH before reaching final height and no stimulation test after end of treatment				
Yes	4	10	4	20
No	37	90	16	80
Age at start of GH treatment, years				
Median (range)	11	(2.4–15.2)	12.7	(12.5–12.9)
Current hormone replacement therapy other that GH				
Sex hormones[a]	12	29	1	5
Desmopressin	3	7	0	0
Thyroid hormone	18	44	1	5
Hydrocortisone	8	20	0	0
Age at radiotherapy, years				
Median (range)	8.8	(1.3–18.8)	9.5	(2.3–18.8)
0–4	8	20	2	10
5–9	21	51	9	45
>10	12	29	9	45
Type of irradiation				
Photon	30	73	14	70
Proton	11	27	6	30
Irradiation technique				
Focal cranial irradiation	28	68	16	80
Craniospinal irradiation	13	32	4	20
Cumulative CNS irradiation dose, Gy Median (range)	54	(12–61)	54	(40–56)
Time from irradiation to GH treatment, years Median (range)	2.6	(0.5–7.9)	5.6	(1.2–7.9)

[a]Includes estrogen and testosterone.
GH, growth hormone; ITT, insulin tolerance test.

the true prevalence of adult GHD in the whole cohort was 26 of 41 survivors (63 %) (Table 2 and 3). Of the 41 irradiated survivors in the cohort, 18 of 30 (60 %) of the photon irradiated survivors had GHD, while 8 of 11 (73 %) of the survivors treated with proton irradiation had GHD.

Of the eight, GH test participants found to have undiagnosed GHD, two (25 %) have decided to start on recombinant human growth hormone treatment until now.

Discussion

In this cross-sectional study, we report a GHD prevalence of 63% in irradiated childhood brain tumor survivors. A considerable number of adult long-term survivors without a GH test performed at final height was identified, and 50% of those subsequently had undiagnosed GHD. Furthermore, GHD was observed in survivors treated with photon as well as proton irradiation. Finally, IGF-1 was not found to be a reliable marker of GHD.

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Table 3 Patient demographics, treatment characteristics, and test results of the growth hormone stimulation test for the GH test participants (n = 16), for the GH test participants found to have GHD (n = 8), and for the GH test participants without GHD (n = 8).

	Test participants *n* =16	(%)	**Test participants with GHD *n* =8**	(%)	**Test participants without GHD *n* =8**	(%)
Test type						
ITT	15	94	7	87	8	100
GHRH-arginine test	1	6	1	13	0	0
Sex						
Female	9	56	4	50	5	63
Male	7	44	4	50	3	37
Age at GH-test, years						
Median (range)	22.9	(15.9–34.2)	20.8	(17.6–28.6)	28.3	(15.9–34.2)
15–19	6	38	4	50	2	25
20–25	4	25	2	25	2	25
>25	6	38	2	25	4	50
Time since diagnosis, years						
Median (range)	14.8	(5.5–23.7)	13.8	(7.6–20)	19.1	(5.5–23.7)
BMI						
Median (range)	25.3	(18.4–34)	27.5	(20.7–34)	22.3	(18.4–34)
<18.5	1	6	0	0	1	13
18.5–24.9	6	38	2	25	4	50
≥25	9	56	6	75	3	37
HSDS						
Median (range)	0.2	(−2; 2.5)	−0.3	(−1.8; 2)	0.2	(−2;2,5)
Reached target height[a]						
Yes	10	63	4	50	6	75
No	6	37	4	50	2	25
Have had children						
Yes	3	19	0	0	3	37
No	13	81	8	100	5	63
Spontaneous menarche	n = 9		n = 4		n = 5	
Yes	9	100	4	100	5	100
No	0	0	0	0	0	0
Regular period	n = 9		n = 4		n = 5	
Yes	8	89	4	100	4	80
No	1	11	0	0	1	20
Type of irradiation						
Photon	10	63	5	62	5	63
Proton	6	38	3	38	3	37
Cumulative CNS irradiation dose, Gy						
Median (range)	54	(45–56)	54	(45–54)	54	(54–56)
Irradiation technique						
Focal cranial irradiation	13	81	7	88	6	75
Craniospinal irradiation	3	19	1	12	2	25
Age at radiotherapy, years						
Median (range)	9.5	(2.3–16.5)	10.2	(2.3–16.5)	9.5	(5.8–14.8)
0–4	2	13	2	25	0	0
5–9	7	44	2	25	5	63
>10	7	44	4	50	3	37
Time since irradiation, years						
Median (range)	14	(4.3–23.6)	12.5	(4.3–19.8)	16.9	(5.3–23.6)

(*Continued*)

Table 3 (Continued).

	Test participants *n* =16	(%)	Test participants with GHD *n* =8	(%)	Test participants without GHD *n* =8	(%)
Test peak GH						
GHD	8	50	8	100	0	0
No GHD	8	50	0	0	8	100
IGF-1 S.D.						
Median (range)	0.3	(−1.3; 2.5)	−0.2	(−1.3; 2.5)	0.5	(−0.1; 1.8)
Median (range) IFG-1 S.D. if GHD	-0.2	(−1.3; 2.5)	−0.2	(−1.3; 2.5)		
Median (range) IFG-1 S.D. if no GHD	0.5	(−0.1; 1.8)	.			

[a]Target height calculated as ((height of father (cm) + height of mother (cm))/2) ± 6.5 cm (male/female). GHD defined as peak GH < 5 ng/mL at the ITT and a peak GH <11.5 ng/mL (BMI < 25) at the GHRH-arginine test.
GH, growth hormone; GHD, growth hormone deficiency; GHRH, growth hormone-releasing hormone; HSDS, height standard deviation score; IGF-1, insulin-like growth factor-1; ITT, insulin tolerance test.

The prevalence of GHD in irradiated survivors is in line with previous studies (32, 33). However, both higher (34, 35) and lower (20, 36, 37) frequencies of GHD in irradiated childhood brain tumor survivors have been reported. Differences in irradiation modality, irradiation dose, histology, tumor localization, age at diagnosis, age at irradiation, time from irradiation to GH evaluation, and different GH test modalities could explain this discrepancy in previously reported GHD prevalence studies in childhood brain tumor survivors treated with CR. Moreover, the use of different GHD assays and cut-off values for GHD in adults from 3 to 7 ng/mL (21, 28, 29, 38) might also influence the prevalence. We followed an endocrine society guideline (29) and used a cut-off value of 5 ng/mL, whereas other studies applied a higher cut-off, which would lead to a lower prevalence and the risk of missing the diagnosis.

This study reveals a considerable number of undiagnosed GHD with 50% of the participants having GHD. One reason for this high percentage of undiagnosed GHD in the cohort of survivors invited to GH stimulation tests could be that some of them had reached their target height before developing GHD. Another reason may be that IGF-1 is still used in the screening of GHD in childhood brain tumor survivors treated with radiation, and therefore, survivors with a normal IGF-1 might not be referred to GH stimulation test. We confirm previous research that IGF-1 is not a reliable indicator of GHD in cranial irradiated survivors (24, 38, 39). The use of IGF-1 as a screening tool for GHD is not recommended in irradiated patients (21, 29). All survivors previously treated with CR with less than two hormonal deficiencies in addition to GHD should have a growth hormone stimulation test conducted (21, 29).

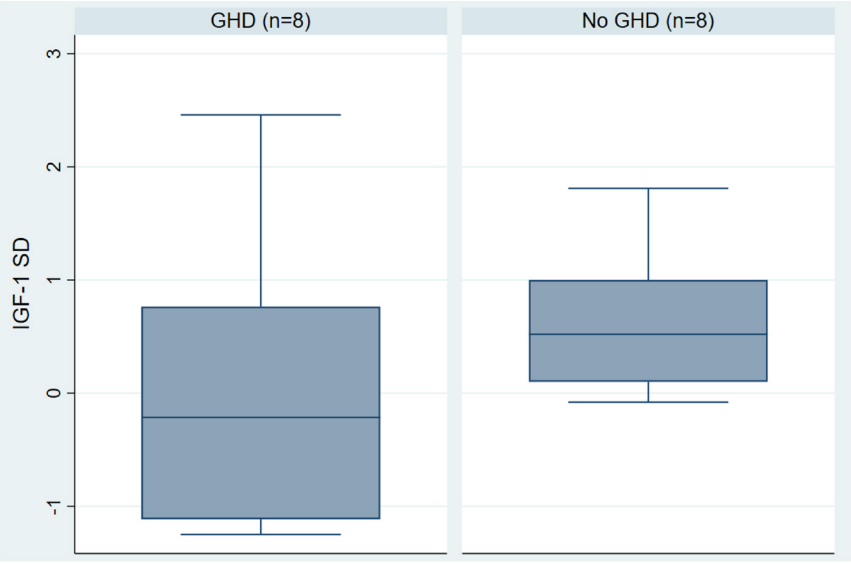

Figure 3
Box plot of IGF-1 S.D. measured at the GH stimulation tests, grouped by the categories; GHD (peak GH < 5 ng/mL) and no GHD (peak GH > 5 ng/mL).

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https://doi.org/10.1530/EC-22-0365

As IGF-1 is an unreliable marker of GHD in children treated with radiation so is the fact that the survivor has reached their target height. The median height in the eight GH test participants found to have undiagnosed GHD were –0.3 S.D., and 50% had reached their target height. This could indicate that some of the participants had developed GHD after reaching their final height, which might explain why GHD was not suspected. The fact that a survivor has reached their genetic target height should therefore not be used to rule out GHD, and a normal IGF-1 is an unreliable proxy marker for GHD in brain-radiated patients.

The frequency of GHD after final height showed no trends between survivors treated with photons vs protons. However, due to the relatively small sample size, we lack the possibility to conclude on differences in prevalence of GHD in survivors treated with protons vs photons. Survivors treated with protons report fewer late effects regarding, for example, neurocognition (40), but importantly, endocrinological late effects are also observed in survivors of childhood brain tumor treated with protons in our study as well as in others (32, 33).

Strengths

Major strengths of this study are first that we recruited the participants through a national register with full coverage. Secondly, the fact that we used dynamic testing such as ITT, which is the golden standard in the diagnostic process of GHD in adults. Thirdly, the follow-up time from diagnosis was very long and often more than the 5 years required. GHD can develop several years after the end of cancer treatment with irradiation, and a long follow-up time is crucial to detect GHD (16, 36, 41). However, it is likely that with a longer follow-up time, the prevalence of undiagnosed GHD would have been even higher, since radiation-induced GHD can develop years after the end of treatment.

Limitations

However, there were also limitations in the study. The relatively small study cohort was identified, but despite this, we found a high prevalence of survivors without a GH stimulation test at final height. Another limitation was that one patient was tested with another test than ITT due to contraindication (29). Finally, three survivors treated with a CR dose of more than 40 Gy did not want to have a GH stimulation test performed. Due to the high radiation dose, one or more of them might have GHD, and the prevalence of GHD in the main study group would have been even higher than 63%.

Conclusion

To conclude, this study reports a high prevalence of GHD in irradiated adult long-term survivors after treatment for a brain tumor in childhood, in line with previous studies. Furthermore, a high prevalence of undiagnosed GHD in adult survivors treated with CR was identified. We observed similar prevalence of GHD in survivors treated with proton and photon irradiation; and the study confirmed that a normal serum IGF-1 measurement cannot exclude the diagnosis of GHD in irradiated survivors. In summary, our study illustrates that there is room for improvements regarding the diagnostic process of GHD and stresses the need for GH testing in adult radiated brain tumor survivors with less than two hormonal deficiencies in addition to GHD, irrespective of IGF-1 and radiation modality.

Declaration of interest
We declare that no author has any conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding
This work was supported by the Aarhus University (grant number AUFF-F-2019-FLS-1-3) and Dagmar Marshalls Fond (grant number 500020).

Acknowledgements
The authors would like to thank all survivors who participated in this study. The authors would also like to thank Steen Rosthøj, MD, Department of Pediatrics, Aalborg University Hospital, Denmark, for his valuable help and knowledge and Pia Buchtrup Hornbek, medical laboratory technician, Medical Research Laboratory, Aarhus University Hospital, Denmark for her experience and guidance in GH testing.

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Received in final form 28 November 2022
Accepted 12 December 2022
Accepted Manuscript published online 12 December 2022