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Long-Term Endocrinologic Follow-Up of Children with Brain Tumors and Comparison of Growth Hormone Therapy Outcomes: A Single-Center Experience

Zehra Yavaş Abalı[1], Ayşe Pınar Öztürk[1], Firdevs Baş[1], Şükran Poyrazoğlu[1], Neşe Akcan[1,2], Rejin Kebudi[3], Ayça İribaş Çelik[4], Rüveyde Bundak[1,5], Feyza Darendeliler[1]

[1]Department of Pediatric Endocrinology and Diabetes, İstanbul University İstanbul Faculty of Medicine, İstanbul, Turkey
[2]Department of Pediatric Endocrinology, Near East University Faculty of Medicine, Nicosia, Turkish Republic of Northern Cyprus
[3]Department of Pediatric Hematology-Oncology, İstanbul University Institute of Oncology, İstanbul, Turkey
[4]Department of Radiation Oncology, İstanbul University İstanbul Faculty of Medicine, İstanbul, Turkey
[5]Department of Pediatric Endocrinology, University of Kyrenia Faculty of Medicine, Kyrenia, Turkish Republic of Northern Cyprus

What is already known on this topic?

- *Brain tumors in childhood carry a high risk for endocrine disorders due to the direct effects of the tumor and/or surgery and radiotherapy.*

What this study adds on this topic?

- *In craniopharyngioma cases, the response to growth hormone (GH) therapy was satisfactory. However, in medulloblastoma patients, there was no improvement in height prognosis with recombinant GH treatment.*

ABSTRACT

Objective: Brain tumors in childhood carry a high risk for endocrine disorders due to the direct effects of the tumor and/or surgery and radiotherapy. Somatotropes are vulnerable to pressure and radiotherapy; therefore, growth hormone deficiency is one of the most frequent abnormalities. This study aimed to evaluate endocrine disorders and recombinant growth hormone treatment outcomes in brain tumor survivors.

Materials and Methods: In this study, 65 (27 female) patients were classified into 3 groups as craniopharyngioma (n = 29), medulloblastoma (n = 17), and others (n = 19). "Others" group included astrocytoma, ependymoma, germinoma, pineoblastoma, and meningioma patients. Anthropometric data and endocrine parameters of patients and their growth outcome with/without recombinant growth hormone therapy were collected from medical records, retrospectively.

Results: Mean age at the first endocrinological evaluation was 8.7 ± 3.6 years (range: 1.0-17.1 years). Height, weight, and body mass index standard deviation score, mean ± standard deviation (median) values were −1.7 ± 1.7 (−1.5), −0.8 ± 1.9 (−0.8), and 0.2 ± 1.5 (0.4), respectively. Hypothyroidism (central 86.9%, primary 13.1%) was detected during follow-up in 81.5% of patients. Primary hypothyroidism in medulloblastoma (29.4%) was significantly higher compared to other groups ($P = .002$). The frequency of hypogonadotropic hypogonadism, central adrenal insufficiency, and diabetes insipidus was significantly high in the craniopharyngioma cases.

Conclusion: In our study, endocrine disorders other than growth hormone deficiency were also frequently observed. In craniopharyngioma cases, the response to recombinant growth hormone therapy was satisfactory. However, there was no improvement in height prognosis during recombinant growth hormone therapy in medulloblastoma patients. A multidisciplinary approach to the care of these patients, referral for endocrine complications, and guidelines on when recombinant growth hormone therapy is required.

Keywords: Brain tumors in childhood, craniopharyngioma, medulloblastoma

Corresponding author:
Zehra Yavaş Abalı
✉ zehra_yavas@yahoo.com
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INTRODUCTION

Brain tumors constitute the most common solid tumors in childhood. Due to advancements in treatment modalities, the survival rate in children with brain tumors is increasing, and

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endocrine disorders may be encountered more frequently. Craniopharyngiomas are by far the commonest suprasellar tumor of childhood, accounting for up to 50%-80% of masses in this region and 1.5%-11.6% of all pediatric brain tumors.[1,2] Despite the benign histology and high overall survival rate of craniopharyngioma, tumor, and/or treatment-related damage results in impaired function of the hypothalamic-pituitary axes, causing severe morbidity.[3] In 70%-80% of the cases, pituitary insufficiency is detected at admission, and in 32%-50% of cases, short stature develops before the tumor diagnosis. Growth hormone (GH) deficiency is the most common endocrine disorder, followed by adrenocorticotropic hormone (ACTH) (20%-70%) and thyroid-stimulating hormone (TSH) (3%-30%) deficiencies.[2]

Optic hypothalamic glioma and other tumors affecting the optic tract are among the rare causes of pediatric brain tumors (4%-6%). However, endocrine disorders are common due to their anatomical proximity to the hypothalamic-pituitary axis.[4]

Radiotherapy (RT) to the head and neck region is also an important cause of endocrine dysfunction in brain tumors. Endocrine disorders in medulloblastoma are associated with treatment protocols, especially RT.[5] The degree of the deficiency is related to the radiation dose. Low doses typically cause GH deficiencies and early puberty, while multiple pituitary hormone deficiencies are observed at high doses.[5,6]

Given the most prevalent and earliest hormone deficiency seen in these patients, diagnosis of GH deficiency (GHD) and early treatment are crucial. It is reported that the earlier onset of recombinant GH (rGH) therapy led to a better growth velocity.[7] Despite the concern about the oncological risk related to GH administration, the role of GH replacement therapy during childhood—aiming to prevent short stature—is currently well-acknowledged.[8]

The aim of this study was to evaluate the endocrine dysfunctions and response to rGH treatment in children with brain tumors.

MATERIALS AND METHODS

In this retrospective observational study, the clinical features of the children with brain tumors followed in the Pediatric Endocrinology Unit of İstanbul University, İstanbul Faculty of Medicine, were evaluated. All patients with a diagnosis of a primary brain tumor before the age of 18 years who visited the outpatient clinic at least once were included. Exclusion criteria were insufficient records, untreated tumors, and pituitary adenomas. Diagnostic features of the patients, endocrine evaluations, hormone replacement treatment, and treatment responses were obtained from the patient records.

Treatment Protocols for the Primary Tumor

The primary treatment protocol for craniopharyngioma cases was neurosurgery. In cases with aggressive behavior, location, involvement of critical structures, and tumor size which may limit the extent of resection additional strategies were included. Surgery was followed by RT in cases with residual tumor or progression.

In medulloblastoma cases, maximal tumor resection was performed in all the patients. Patients with a residual tumor of more than 1.5 cm^2 postoperatively were considered high risk. All patients were scheduled to receive postoperative craniospinal RT followed by chemotherapy. Following radiation and a rest period, patients received adjuvant (maintenance) chemotherapy.[9]

In the study, patients were divided into 3 groups: craniopharyngioma, medulloblastoma, and other brain tumors. Other brain tumors group included patients with astrocytoma, pons glioma, oligodendroglioma, ependymoma, germinoma, pineoblastoma, and meningioma.

Endocrine Evaluation

Height measurements were performed on all patients and their parents with a wall-mounted, calibrated Harpenden stadiometer (Holtain Ltd, Crymych, United Kingdom) (sensitive 0.1 cm). Weight was measured using an electronic scale (SECA GMBH&Co. kg, Hamburg, Germany) (sensitive to 0.1 kg). The body mass index (BMI) of each patient was calculated as weight/height squared ratio (kg/m^2). Standard deviation scores (SDS) of all measurements according to Turkish standards were calculated.[10,11] Target height was determined by the formulas [(father's height – 13)+mother height]/2 for girls and [father height+(mother's height+13)]/2 for boys.[12] Predicted adult height was calculated by using Bayley Pinneau based on bone age (BA) estimation.[13] Adult height was considered as the height reached when the growth velocity was less than 1 cm, and/or the BA was 15 years in girls and 17 years in boys.[14,15] Children were evaluated for puberty according to Tanner classification.

Laboratory Evaluation

Fasting blood samples were collected for glucose, insulin, lipids (in selected cases), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and estradiol. Glucose was measured by the hexokinase method (Roche Diagnostics, Cobas Integra, Germany). Insulin levels were measured by immunoradiometric assay (IRMA) (DIAsource ImmunoAssays S.A. Nivelles). Luteinizing hormone levels were measured by DSL-4600 Active LH coated tube (IRMA, Diagnostic Systems Laboratories, Inc., Texas, USA), and the limit of detection was 0.12 IU/L with an intra- and inter-assay (CV) of 4.8%-8.9% and 6.8%-8.9%, respectively. Follicle-stimulating hormone levels were measured by DSL-4700 Active FSH-coated tube (IRMA, Diagnostic Systems Laboratories, Inc.) with an intra- and inter-assay CV of 1.6%-3.6% and 5.6%-7.7%, respectively, and the limit of detection was 0.11 IU/L. Estradiol levels were measured by electrochemiluminescence immunoassay (ECLIA, Cobas e 601 analyzers, Roche Diagnostics) kits with intra- and inter-assay CV of 1.3%-6.1% and 1.9%-7.0%, respectively, and the functional sensitivity was 44 pmol/L.

Statistical Analysis

All statistical analyses were performed using Statistical Package for the Social Sciences 16.0 program (IBM Inc., Chicago, IL, USA). Complementary statistical methods (mean, standard deviation [SD], median, frequency, ratio, minimum, and maximum) were utilized for data analysis. The suitability of normal distribution of the quantitative data was tested by the Shapiro–Wilk. For the comparison of quantitative data, Student's *t*-test was used in the comparison of 2 variables with

normal distribution, and the Mann–Whitney *U* test was utilized for the comparison of 2 variables without normal distribution. For the analysis of categorical data, chi-square test (Fisher's exact test) was used. For the intra-variable comparison of the variables with normal distribution, the "paired *t*-test" was used, and for the intra-variable comparison of the variables without normal distribution, the Wilcoxon Signed Ranks test was used. A *P* value of <.05 was considered statistically significant.

RESULTS

In this study, 65 patients (27 girls) who were followed up with the diagnosis of brain tumors were included. The mean age at admission to the pediatric endocrinology clinic was 8.7 ± 3.6 years (range: 1.0-17.1). The patients were divided into 3 groups, craniopharyngioma (44.6%; n = 29), medulloblastoma (26.2%; n = 17), and other brain tumors (29.2%; n = 19). The ratio of male and female cases was similar between the 3 groups. Nine patients (13.8%) (craniopharyngioma n = 4, astrocytoma n = 4, germinoma n = 1) were diagnosed with brain tumors after admission to endocrinology. The initial symptoms or diagnoses of these patients at admission were short stature, polyuria, thyroid dysfunction, and precocious puberty. The time of referral in 56 patients diagnosed before endocrinology admission was a median of 0.8 years (interquartile range [IQR] 0.1-2.0). The medulloblastoma patients' time to referral was significantly higher (mean 2.1 ± 1.6 years, median 2.0) (*P* = .002).

All patients had undergone surgical treatment; 56.9% had received RT (cranial n = 18, craniospinal n = 19), and 35.4% had received chemotherapy. The percentage of patients who had both chemotherapy and RT was 35.4% (n = 23). In the study group, 2 patients (craniopharyngioma n = 1, astrocytoma n = 1) had residual tumors after surgery.

Mean (median) height, weight, and BMI SDS of patients at admission were −1.7 ± 1.7 (−1.5), −0.8 ± 1.9 (−0.8), and 0.2 ± 1.5 (0.4), respectively. The clinical characteristics of the patients are shown in Table 1.

In the study, the mean follow-up period of the patients in the endocrinology unit was 6.3 ± 4.0 years.

Growth hormone deficiency was detected in 47 patients (72.3%), and rGH treatment was recommended in 33 of those who had completed the oncologic treatment regimen and who had no contraindications to use rGH. Growth hormone treatment could not be commenced in 8 of these cases. In 25 patients, rGH treatment was initiated, and 20 of these patients used rGH for at least 1 year during the study period.

Growth hormone treatment doses ranged between 0.025 and 0.035 mg/kg/day. This study does not give GH doses as they vary with insulin-like growth factor I (IGF1) and growth responses during treatment." cümlesi "GH doses were adjusted according to insulin-like growth factor I (IGF1) levels and growth responses during treatment.

Responses to rGH therapy during the study are shown in Table 2.

The mean period to use rGH after the tumor diagnosis in craniopharyngioma, medulloblastoma, and other brain tumors group was 3.0 ± 2.0, 5.6 ± 0.1, and 2.9 ± 2.0 years, respectively.

Figure 1 illustrates the height SDS of the patients at admission, initiation of rGH treatment, and last evaluation.

As shown in Table 2 and Figure 1, only patients with craniopharyngioma showed a significant increase in height SDS on rGH treatment.

During the follow-up period, in patients who received rGH, two patients with craniopharyngioma had tumor recurrence. Among the 29 patients with craniopharyngioma, the recurrence rate was 14.3% (2/14) in those who received rGH and 40% (6/15) in those who did not (should take into account that some of them did not receive rGH, due to recurrences). There was no significant difference between these 2 subgroups (*P* = .290). No recurrence was observed in tumors other than craniopharyngioma that received rGH treatment.

Tumor recurrence was observed in 13 patients (craniopharyngioma n = 6, medulloblastoma n = 3, astrocytoma n = 1, glioma n = 1, ependymoma n = 1, and germinoma n = 1) in the whole group who did not receive rGH treatment.

In addition to GHD, endocrinological disorders detected during the follow-up were diabetes insipidus, hypothyroidism, ACTH deficiency, and hypogonadism. Hormonal deficiencies besides GHD are shown in Table 3.

Table 1. Clinical Features of Children With Brain Tumors

	Craniopharyngioma (n = 29)	Medulloblastoma (n = 17)	Other Tumors (n = 19)
Girls n (%)	11 (37.9)	7 (41.2)	9 (47.4)
Age at tumor diagnosis (years)*	8.7 ± 4.6 (0.7-16.9)*	5.6 ± 2.4 (1.6-11.1)*	7.9 ± 3.9 (2.2-14.4)*
Age at admission to pediatric endocrinology (years)	9.1 ± 4.3 (1.0-17.1)	7.8 ± 2.0 (3.9-12.5)	8.9 ± 3.6 (2.3-14.4)
Height SDS at admission	−1.9 ± 1.1	−1.7 ± 1.4	−1.4 ± 1.4
Sitting height/height SDS at admission	−0.3 ± 1.4	0.3 ± 1.3	−0.6 ± 1.7
Target height SDS	−0.9 ± 0.7	−1.6 ± 0.8	−1.5 ± 0.5
BMI SDS at admission	0.7 ± 1.5	−0.2 ± 1.3	−0.1 ± 1.5
Follow-up period (years) (range)	7.6 ± 3.8 (2.2-13.4)	7.5 ± 1.9 (5.3-8.6)	7.1 ± 1.6 (4.9-8.8)

*$P = .047$.
SDS, standard deviation score.
Mean ± standard deviation are given with range in parenthesis
"Other tumors" group includes the patients with astrocytoma, pons glioma, oligodendroglioma, ependymoma, germinoma, pineoblastoma, and meningioma

Table 2. Evaluation of Growth Response on rGH Therapy in Patients With Brain Tumors

rGH Treatment	Mean ± SD	Craniopharyngioma	Medulloblastoma	Other Tumors	All Patients
At initiation of treatment	Age	12.0 ± 3.5	10.7 ± 2.0	11.8 ± 1.3	11.6 ± 2.9
	Height SDS	−2.9 ± 1.4	−3.3 ± 1.3	−1.8 ± 1.4	−2.8 ± 1.4
	BMI SDS	0.5 ± 1.4	−0.3 ± 1.0	−0.3 ± 1.4	0.2 ± 1.3
First year of treatment	Age	13.5 ± 3.4	12.0 ± 2.2	12.7 ± 1.3	13.0 ± 2.9
	Height SDS*	−2.2 ± 1.4*	−3.9 ± 0.8*	−1.4 ± 1.1	−2.4 ± 1.5
	BMI SDS	1.1 ± 3.2	−0.8 ± 2.0	0.0 ± 1.6	0.5 ± 2.8
Second year of treatment	Age	14.1 ± 3.3	13.2 ± 2.5	14.0 ± 1.3	13.9 ± 2.8
	Height SDS*	−1.6 ± 1.5**	−4.0 ± 0.7**	−1.3 ± 1.4	−2.0 ± 1.7
	BMI SDS	1.1 ± 3.9	−0.3 ± 1.0	0.8 ± 0.9	0.7 ± 3.1
Last evaluation	Age	18.3 ± 5.1	16.5 ± 1.6	16.6 ± 2.5	17.5 ± 3.9
	Height SDS	−1.2 ± 1.5	−3.9 ± 1.4	−1.4 ± 1.3	−1.9 ± 1.8
	BMI SDS	3.0 ± 6.2	−0.3 ± 1.0	0.0 ± 1.6	1.5 ± 4.7
Adult height SDS		−1.5 ± 1.5	−4.0 ± 1.9	−2.0 ± 0.4	−2.2 ± 1.8
Adult height SDS—Target height SDS (median)		−1.1	−2.0	−0.5	**−1.2**

BMI, body mass index; rGH, recombinant growth hormone; SDS, standard deviation score.
*$P < .05$; **$P < .05$.

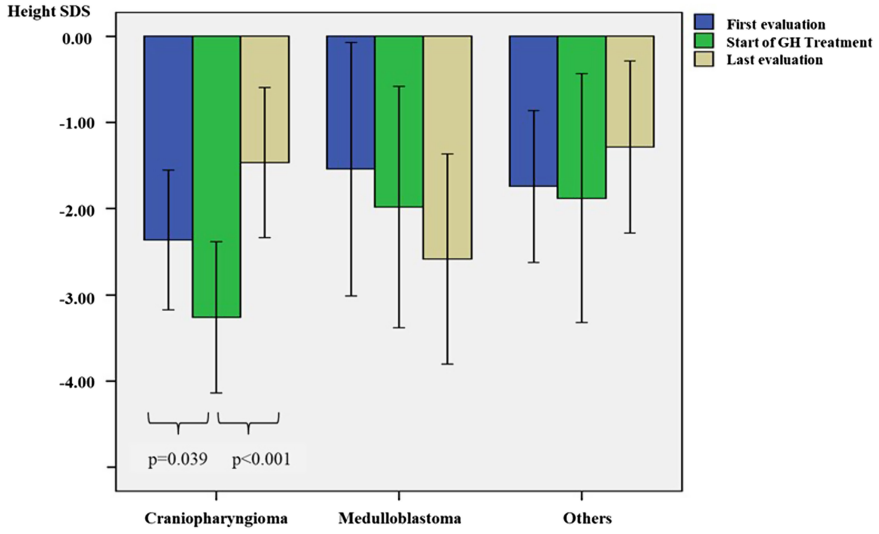

Figure 1. Median height SDS of the patients before and after rGH treatment. SDS, standard deviation score.

Table 3. Endocrinological Disorders Besides GH Deficiency in the Patients With Brain Tumors

		Craniopharyngioma (n = 29)	Medulloblastoma (n = 17)	Other Tumors (n = 19)
Thyroid functions	Normal	1	5	6
	Central hypothyroidism	28	7	11
	Primary hypothyroidism	–	5	2
Puberty	Prepubertal patients	10	6	5
	Precocious puberty	–	1	4
	Normal puberty	4	6	6
	Hypogonadotropic hypogonadism	15	2	3
	Hypergonadotropic hypogonadism	–	2	1
Central adrenal insufficiency		27	2	8
Diabetes insipidus		26	–	4

GH, growth hormone.
"Other tumors" group includes the patients diagnosed with astrocytoma, pons glioma, oligodendroglioma, ependymoma, germinoma, pineoblastoma, and meningioma.

Hypothyroidism was detected in 81.5% of the patients, 86.9% of those were central, and 13.1% were primary. The rate of primary hypothyroidism in the medulloblastoma group (29.4%) was significantly higher than in the craniopharyngioma group ($P = .002$). All of the cases with primary hypothyroidism had received RT (craniospinal RT n = 5, cranial RT n = 2). Of the 46 patients with central hypothyroidism, 24 had no history of RT, 8 received craniospinal, and 14 received cranial RT.

The frequency of hypogonadotropic hypogonadism, central adrenal insufficiency, and diabetes insipidus was significantly high in the craniopharyngioma cases.

DISCUSSION

Herein, we present the endocrine outcomes of a cohort of childhood brain tumor survivors who were closely followed after completing their oncological therapies.

In this study, the most common tumor was craniopharyngioma, constituting nearly half of the patients. The reason for this is the more frequent occurrence of pituitary deficiencies observed before diagnosis or after treatment due to the localization of the tumor. However, in brain tumors, which do not affect the pituitary region and do not cause hypopituitarism, referral to endocrinology may not be considered by some physicians. Chemotherapy, cranial, and craniospinal RT have also negative effects on the growth and pubertal development of brain tumor survivors; hence, endocrinological follow-up must also be performed.[2,7]

Delays in diagnosis and treatment of endocrine dysfunctions can adversely impact growth, puberty, and general health.[2,7] The mean referral time of brain tumor patients to our clinic was 1.2 ± 1.5 years after diagnosis, and this was significantly higher in patients with medulloblastoma. This can be explained by the fact that patients are often referred after their primary oncologic treatment has been completed and they are stable, and the more severe course of medulloblastoma may prolong this period in some cases.

It is reported that 70%-80% of craniopharyngioma cases have endocrine deficiencies at presentation.[2] In our study, besides GHD the most common pituitary hormone deficiencies were hypothyroidism and ACTH deficiency in craniopharyngioma cases. This is followed by diabetes insipidus and hypogonadism.

Depending on the localization of the tumor, central hypothyroidism rather than primary may occur more frequently in brain tumors. In a previous study, central hypothyroidism was present in approximately 80% of the patients with suprasellar tumors appearing shortly after diagnosis. Hypothyroidism was diagnosed in patients with non-suprasellar tumors in 33.9% of the cases (41% primary hypothyroidism, 58.9% central hypothyroidism).[16] In our study, hypothyroidism, mostly central, was detected in 4/5 of the patients. The ratio of primary hypothyroidism in the medulloblastoma group was significantly higher than that in the craniopharyngioma group, and this was related to the RT to the neck and consequently to the thyroid gland. All of our cases with primary hypothyroidism had received RT. Therefore, patients receiving RT to the head and neck region should be referred to the endocrine clinics earlier, even if the tumor treatment has not been completed. The frequency of hypogonadotropic hypogonadism, central adrenal insufficiency, and diabetes insipidus was significantly high in the craniopharyngioma cases.

In the study of Lawson et al.[17] the possibility of detecting pituitary deficiency in cases with brain tumors was reported most frequently in the first 6 years after diagnosis and treatment. In our study, the follow-up period of the patients in the endocrinology clinic was 6.3 ± 4.0 years, and pituitary deficiencies detected during this period were evaluated. Therefore, even cases without pituitary hormone deficiency at the first admission to endocrinology should be followed up in terms of endocrinological disorders that may develop in the future.

Individuals surviving brain tumors may experience GHD as a result of tumor growth, surgical resection, and/or RT involving the hypothalamic-pituitary region. The diagnosis and treatment of individuals at risk are important to minimize associated morbidities that can be ameliorated by treatment with rGH. However, due to the pro-mitogenic and anti-apoptotic properties of GH and IGF I, there has been concern over the use of GH therapy in patients with tumors.[18,19] In our study, no secondary neoplasia related to rGH treatment was observed. However, long-term data from survivors of childhood brain tumors treated with rGH are still emerging, and underlying factors for an increased malignancy like cranial RT should also be taken into account; thus, the risk versus benefit profile of rGH replacement of this population still needs to be monitored at the long term.[20]

During the follow-up period of this study, there was no significant difference in tumor recurrence between the craniopharyngioma cases in those who received rGH and those who did not ($P = .29$). However, while interpreting this situation, it should be kept in mind that some of the cases did not receive rGH treatment due to recurrence. The risk of tumor recurrence also raises concerns among clinicians dealing with these patients and in families, in terms of initiating and continuing GH treatment and causes them to avoid using rGH. However, large-scale studies have shown that there is no tumor recurrence on GH treatment in childhood brain tumor survivors.[21]

Patients with GHD may not adequately respond to rGH, particularly those exposed to craniospinal irradiation, given the direct effects of radiation on the spine, resulting in inadequate longitudinal growth and skeletal disproportions.[20,22] Although the number of patients in our study was not large, it was observed that the GH response was significantly lower in patients with medulloblastoma who had a history of spinal RT. In craniopharyngioma cases, the response to rGH therapy was satisfactory.

CONCLUSION

In our study, endocrine disorders were frequently seen in patients with brain tumors. In craniopharyngioma, response to rGH therapy was more favorable compared to medulloblastoma. We conclude that to improve the outcomes of these childhood brain tumor survivors, it is extremely important to establish a routine endocrinologic and systematic follow-up.

Ethics Committee Approval: The study was approved by the ethical committee of İstanbul Faculty of Medicine (16.04.2021-172422).

Informed Consent: The study was retrospective and did not involve interventions; thus, informed consent from the parents and patients was not obtained. A consent waiver for this study was obtained from the ethics committee.

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