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Early development of endocrine and metabolic consequences after treatment of central nervous system tumors in children

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ABSTRACT

Background and objective: Survival after childhood cancer has dramatically improved during last few decades, implying the need for evaluation and correction of late consequences of the disease and its treatment. The aim of this study was to characterize endocrine and metabolic late effects after treatment of brain tumors in children.

Materials and methods: Late complications were analyzed in 51 children treated for brain tumors at the Hospital of Lithuanian University of Health Sciences during 2000–2011. Data on late endocrine and metabolic effects were collected from medical records. Most frequently patients suffered from low-grade glioma ($n = 17$, 33.3%) and medulloblastoma ($n = 13$, 25.5%). The majority ($n = 42$, 82.4%) of the patients underwent surgery; 29 (56.9%) received radiotherapy (RT); 26 (51.0%), chemotherapy; and 17 (33.4%), combined treatment.

Results: The median follow-up was 21 months (range 0.25–10.6 years). Most common endocrine consequence was low serum insulin-like growth factor (IGF-I) levels (58.3%), found on average in 30.7 months after cancer treatment. Short stature was observed in 34.6% (mean time to development, 47.7 months), and hypothyroidism in 40.7% of patients (mean time to development, 63.6 months). Low bone mineral density was found in 50.0% of the cases after 44.5 months and overweight in 30.0% after 49.9 months of follow-up.

Conclusions: Survivors of brain tumors suffer from numerous endocrine and metabolic consequences, majority of them developing within the first 5 years after brain tumor therapy. An active follow-up aiming for early diagnosis and therapy is essential for improvement of quality of life in these patients.

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1. Introduction

Central nervous system (CNS) tumors are the second most common oncological diseases in children and the most common among solid tumors [1]. Incidence rates vary from 130 per 1,000,000 children in the British Isles to 160 per 1,000,000 children in Scandinavian countries [2]. The Lithuanian Cancer Registry documents 30 cases of brain tumors per 1,000,000 children [3]. Treatment results of all oncological diseases, including CNS tumors, are constantly improving, and the overall 5-year survival in children nowadays reaches over 80% [4,5]. However, the survival rate improvement is mostly achieved at the expenses of serious long-term consequences. Long-term health problems that occur as a result of cancer treatment are known as late effects [6]. 75% of all oncological patients, and up to 95% of patients treated for CNS tumors are diagnosed with at least one late effect [1,5,7]; one-third of them develop two or more complications [7]. By definition, a late complication of treatment is a side effect manifesting during or after treatment and does not disappear after treatment is completed. Treatment of CNS tumors is most frequently associated with the disorders of endocrine system (up to 96% of cases) [8,9], due to the tumors treatment modalities: surgery, chemotherapy or radiotherapy. Among the complications related to the endocrine system, growth hormone deficiency, insufficient levels of thyrotropic and adrenocorticotropic hormones, and sexual maturation disorders prevail. Another rather frequent finding in childhood cancer survivors is the development of osteopenia/osteoporosis related to use of glucocorticoids, chemotherapy, and dysfunction of the endocrine system [9,10]. Evidence exists that adults with history of CNS tumor in childhood often develop overweight/obesity, dyslipidemia and the metabolic syndrome [11–13]. However, data on time to development of late endocrine effects vary among studies, therefore suggestions for investigation and follow-up intensity may also differ. Investigations of endocrine and metabolic consequences are started after 5 years after completion of cancer treatment in mostly studies. The aim of this study was to determine the frequency of endocrine and metabolic disorders and the time of their development after completion of CNS tumor therapy in children in the first 5 years after the end of brain tumor treatment.

2. Materials and methods

2.1. Study subjects

From January 2000 to September 2011, 258 children were treated for CNS tumors in the Hospital of Lithuanian University of Health Sciences (HLUHS). Children treated for craniopharyngioma were not included in this study, since endocrinopathies are often present already at the time of diagnosis due to the tumor localization. Remission was achieved in 133 patients. The final analysis included data of 51 (38.3%) patients (32 boys and 19 girls) who visited the health care institution and were tested regarding endocrinological and metabolic consequences at least once at or later than 3 months after the completion of brain tumor treatment.

Data on endocrine and metabolic consequences were collected from medical records. A late complication was defined as a side effect occurring later than 3 months after the end of the treatment. Data on tumor histology, localization, presence of metastases, age at diagnosis and the treatment applied were selected for analysis. Treatment methods were defined as surgery, chemotherapy, radiotherapy and chemo radiotherapy (chemotherapy and radiotherapy at the same time).

Anthropometric measurements were evaluated according to national Lithuanian growth references [14]. Short stature was defined as height below the 3rd percentile for age and gender. BMI was calculated as weight in kilograms divided by height in squared meters (kg/m^2). Overweight was defined as BMI between the 85th and 95th percentile and obesity – as BMI above the 95th percentile for age and gender according to World Health Organization standards [15].

The status of endocrine system was evaluated by measuring serum insulin-like growth factor I (IGF-I), thyroid stimulating hormone (TSH), free thyroxin (FT4), and a.m. cortisol levels. Primary hypothyroidism was defined as increased level of TSH and a decreased or normal level of FT4, central hypothyroidism – as low or normal level of TSH and a low level of FT4. The deficiency of adrenocorticotropic hormone (ACTH) was diagnosed when morning (before 10 a.m.) serum cortisol concentration was $<$138 nmol/L [16,17].

Blood samples for hormones determination were centrifuged immediately and stored at $-20\,^{\circ}$C until plasma hormones concentrations were determined. Hormones levels were evaluated by immunoradiometric assay (IRMA) and radioimmunoassay (RIA) using Izotop (Hungary) and DiaSource (Belgium) commercially available reagent kits at the Laboratory of the Institute of Endocrinology, Lithuanian University of Health Sciences.

Bone mineral density (BMD) was measured using Dual-X-Ray (DEXA) method (Hologic Discovery) and expressed in Z-score. Osteopenia was defined as BMD Z-score <-1 standard deviation (SD), osteoporosis – as Z-score <-2 SD.

2.2. Statistical analysis

Statistical analyses were performed using the SPSS version 17.0 program. The time to the development of complications was analyzed using the Kaplan–Meyer method; the relationship between variables was tested using the Chi-square criterion.

3. Results

3.1. Patients' characteristics

The mean age at CNS tumor diagnosis was 7.9 years (range, 0.25–17.2). The median time of the follow-up after completion of cancer treatment was 21 months (range, 0.25–10.6 years). Of the 51 analyzed cases, 48 patients (94.1%) did not have metastases. Data on tumor histology, localization, and applied treatment are presented in Table 1.

Most prevalent CNS tumors were low-grade glioma, medulloblastoma/primitive neuroectodermal tumor (PNET)

Table 1 – Patients characteristics according to patient's sex, age at CNS tumor diagnosis, tumor histology, location and treatment modality.

Characteristics	N (%)	
Sex	Male	32 (62.7)
	Female	19 (37.3)
Age at diagnosis	<10 years	34 (66.7)
	≥10 years	17 (33.3)
Histology	WHO grade I–II glioma	17 (33.3)
	WHO grade III–IV glioma	2 (3.9)
	Medulloblastoma/PNET	13 (25.5)
	WHO grade I–II ependymoma	2 (3.9)
	WHO grade III–IV ependymoma	7 (13.7)
	Intracranial germ cell tumor	1 (2.0)
	Unidentified	9 (17.6)
Localization	Supratentorial	12 (23.5)
	Midbrain/optic nerve	16 (31.4)
	Subtentorial	18 (35.3)
	Brainstem	3 (5.9)
	Disseminated tumor (≥2 localizations)	2 (3.9)
Surgical procedure	Total excision	13 (25.5)
	Partial/subtotal resection	19 (37.3)
	Biopsy	10 (19.6)
	Not applied	9 (17.6)
Radiotherapy	Cranial	13 (25.5)
Mean cumulative dose, Gy	Craniospinal	16 (31.4)
54.2 (45.0–60.0)	Not applied	22 (43.1)
Chemotherapy		26 (51)
Chemo radiotherapy		14 (27.5)

and anaplastic ependymoma. Biopsy was not performed and histology was not determined in 17.6% (9/51) of patients, in 55.6% (5/9) of them the tumor was localized in the midbrain/optic nerve, and the diagnosis was confirmed by imaging examinations. Most frequent localizations of the tumor was subtentorial and midbrain/optic nerve.

Surgical treatment was applied in the 32 patients (62.7%): total resection in 13, partial resection in 19. Chemotherapy was given to 26 (51.0%) patients. The most frequent chemotherapy regimens were carboplatin/vincristine or carboplatin/etoposide/vincristine for the treatment of low-grade gliomas and lomustine/cisplatin/vincristine and/or methotrexate/carboplatin/etoposide for the treatment of medulloblastoma/PNET. Chemotherapy alone was administered to 3 (5.9%). Radiotherapy was applied in 29 patients (56.9%). Of them, 16 patients (55.2%) underwent craniospinal radiotherapy and 13 (44.8%) cranial radiotherapy. The median cumulative dose was 54.2 Gy (range, 45.0–60.0 Gy). Chemotherapy and radiotherapy were given to 14 (27.5%) children simultaneously (chemoradiotherapy). 9 patients (7.8%) received no treatment. The majority of the patients were given glucocorticoids in the preoperative or the postoperative period and/or during radiotherapy. Relapses of the disease were observed in 11 patients (21.6%): 4 cases of medulloblastoma/PNET, 3 cases of ependymoma, and 2 cases of low-grade glioma and ependymoma each. The median time to relapse was 14 months (range, 0.4–8.2 years).

3.2. *Prevalence of endocrine and metabolic outcomes and relation to tumor type and treatment*

The most frequent and earliest appearing disorder of the endocrine system was low IGF-I concentration, found in 58.3% of patients determined after the mean of 30.7 months of the follow-up (95% CI; 19.9–41.4 months). A low serum IGF-I concentration was more frequently determined in boys than girls (90.9% vs. 30.8%, $P = 0.003$), and in those who underwent radiotherapy (RT) compared with patients without RT (75.0% vs. 25.0%, $P = 0.019$). Combined treatment was significantly associated with low IGF-I compared with chemotherapy treatment alone (90% vs. 10%, $P = 0.015$). Low IGF-I concentration was found in 57.1% of the patients who received craniospinal RT, compared to only 28.6% in those after cranial RT ($P = 0.028$). Chemotherapy was associated with earlier decrease in IGF-I levels: after the mean of 20.2 months (95% CI; 11.4–28.9 months), compared to 44.4 months (95% CI; 25.7–63.1 months) in those who did not underwent such treatment ($P = 0.035$). Short stature was found in 34.6% of patients. All of them had a low IGF-I concentration ($P = 0.049$). No significant difference in prevalence of short stature and low IGF-I were found according to the patients age at tumor diagnosis.

Thyroid function deficiency was diagnosed in 40.7% (11/27) of children. There was no difference in prevalence of hypothyroidism according to gender, age at tumor diagnosis and tumor location. Central hypothyroidism was diagnosed in 63.6% after a mean time of 61.1 months (95% CI; 44.7–77.4 months) of follow-up, and primary hypothyroidism in 36.4%, mean time to diagnosis, 66.2 months (95% CI; 50.4–81.9 months). One case of papillary thyroid carcinoma was diagnosed. Prevalence of hypothyroidism was significantly higher in patients who were treated with radiotherapy than in those who were not (41.2% vs. 0.0% for central hypothyroidism; and 17.6% vs.11.1% for primary hypothyroidism; $P = 0.045$).

Cortisol deficiency was found only in one patient (4.2%) after a mean time 83.4 months (95% CI; 71.1–95.5). DEXA scan was performed in 12 patients and low bone mineral density (BMD) was diagnosed in 6 of them: 3 cases of osteopenia and osteoporosis each. The mean time to the development of low BMD was 44.5 months (95% CI, 29.6–59.5 months). All of patients with low BMD had low IGF-I concentration, and 8 of them had hypothyroidism.

30.0% of children were overweight, but no cases of obesity were identified. Mean time to the occurrence of overweight was 49.9 months (95% CI, 32.9–66.9 months). Tumor location in the midbrain/optic nerve was related to earlier weight gain compared with other tumor sites (29.6 vs. 63.7 months, $P = 0.023$). No significant difference in the prevalence of low BMD and overweight were found according to patients' age at diagnosis and treatment regimens.

The prevalence endocrine and metabolic consequences and the mean time to their development are presented in Table 2.

Table 2 – Late consequences of childhood CNS tumors treatment.

Complication	%	Mean time to first occurrence of complication, months (95% CI)
Low IGF-I	58.3	30.7 (19.9–41.4)
Short stature	34.6	47.7 (35.8–59.6)
Central hypothyroidism	25.9	61.1 (44.7–77.4)
Primary hypothyroidism	14.8	66.2 (50.4–81.9)
Low cortisol	4.2	83.4 (71.7–95.5)
Low bone mineral density	50.0	44.5 (29.6–59.4)
Overweight	30.0	49.9 (32.9–66.9)

3.3. *Cumulative incidences of endocrine and metabolic complications*

The cumulative incidence (CI) of the endocrine and metabolic complications was calculated over the first 5-year follow-up: at 12, 24, 36, 48, and 60 months. A cumulative incidence of low IGF-I concentration was 52.1% and 84.0% at 24 and 48 months after the end of treatment, respectively. As expected, growth retardation appeared in most children later. The cumulative incidence of short stature at 60 months was 56.1% (Table 3).

The cumulative incidence of central hypothyroidism was 33.7% at 24 months, and remained unchanged 5 years (60 months) after the end of treatment. The cumulative incidence of low BMD and overweight at 48 months of follow-up was 64.6 and 55.2%, respectively.

4. Discussion

The treatment of brain tumors, as other oncological diseases is complex and it has been shown that each of the treatment methods, combined or isolated, has its own side effects. The side effect of radiotherapy depends on the cumulative dose, treatment duration, patient's age at the time of radiotherapy, and the target organ. The greater the dose is administered, the earlier the complications develop. Unfortunately, we did not find the significant effect of patients' age at the time of tumor diagnosis to the prevalence of analyzed complications.

The hypothalamus–pituitary axis is extremely sensitive to radiotherapy. Its damage depends on the radiation dose and progresses with time. Certain tumors (craniopharyngiomas and optic tract gliomas), or their surgery, often cause hormonal disorders due to their localization in the hypothalamus/pituitary region. In the recent years, consequences of treatment of cancer, their development time and risk factors have been under extensive investigation. In the vast majority of studies, investigations of endocrine and metabolic complications start 5 years after the end of treatment or later and suggestions for investigation and follow-up intensity vary among studies. Data on these complications in the first years after completion of treatment are scarce. However, in our study we found most endocrine and metabolic complications appearing already during the first 60 months (5 years) following treatment. According to our data, IGF-I deficiency indicating growth hormone deficiency should already be suspected after 24 months of monitoring; metabolic disorders, after 48 months; and thyroid dysfunction, after 60 months after treatment completion.

4.1. *Low IGF-I and short stature*

According to the data in the literature, growth hormone deficiency is caused by a direct damage to the hypothalamus due to a tumor localization, surgery or radiotherapy. Approximately 40% of adults treated for the CNS tumor in childhood are short (height <10th percentile) [18]. Diagnosis of growth hormone deficiency (GHD) is related to certain difficulties as there is no gold standard for the diagnosis. Short stature is a late result of GHD, and growth retardation should be noticed much earlier as a deviation from the child's growth trajectory before the manifestation of short stature. Because of highly probable GHD, careful follow-up of growth is essential in children who were treated with ionizing radiation to the brain. In case of growth retardation, IGF-I concentration and growth hormone stimulation tests are used [9,19,20].

In our study, short stature was found in 34% of the patients, and the mean time to its appearance was 47.7 months (4 years). Most frequent and the earliest disorder of endocrine system was low IGF-I level, observed after 2.5 years of follow-up in our study cohort. Nearly a half (45.5%) of these patients were in the underweight status, also 36.4% were within normal weight (not significant difference). Half of the normal height patients had low serum IGF-I levels too, possibly secondary to malnutrition or GHD, which will probably manifest later with growth retardation, as cumulative incidence of short stature of more than 50% in our study

Table 3 – Cumulative incidence of complications over the first 5 years after treatment.

Late effect	Cumulative incidence over the period after the end of treatment				
	12 months	24 months	36 months	48 months	60 months
Low IGF-I	32.4 ± 10.1	52.1 ± 12.0	60.1 ± 12.4	84.0 ± 10.1	84.0 ± 10.1
Short stature	12.5 ± 6.8	26.8 ± 9.5	26.8 ± 9.5	41.4 ± 15.1	56.1 ± 17
Central hypothyroidism	4.8 ± 4.6	33.7 ± 11.4	33.7 ± 11.4	33.7 ± 11.4	33.7 ± 11.4
Primary hypothyroidism	8.5 ± 5.8	16.8 ± 9.5	27.2 ± 12.8	27.2 ± 12.8	27.2 ± 12.8
Low cortisol	0	9.1 ± 8.7	9.1 ± 8.7	9.1 ± 8.7	9.1 ± 8.7
Low BMD	9.1 ± 8.7	19.2 ± 12.2	19.2 ± 12.2	64.6 ± 16.1	64.6 ± 1.1
Overweight	16.9 ± 8.5	14.8 ± 7.9	32.8 ± 16.5	55.2 ± 21.3	55.2 ± 21.3

Values are percentage ± standard error.

appeared 4 years later than that of low IGF-I concentration. However, GH stimulation tests were unfortunately not performed in these patients, therefore GHD may only be suspected from reduced growth velocity and history of radio-/chemotherapy. Low IGF-I concentration was more common after radiotherapy, and especially after craniospinal RT in our study. Cranial radiotherapy, especially to the area of the hypothalamus/pituitary, and irradiation to the spinal area are well-known risk factors of growth restriction and short stature [18]. A cumulative dose of 16.1 Gy to the hypothalamus would be considered the mean radiation dose to achieve a 50% risk of GHD at 5 years [21]. All patients who were treated by radiotherapy received a high dose of radiotherapy (mean 54 Gy) in our cohort. In our study cumulative incidence of low IGF-I was 84% at 5 years. These patients are appropriate to perform stimulation tests to confirm GHD. It is a further objective of our perspective study. The effects of chemotherapy on IGF-I axis are not well established as those of radiotherapy [20]; however, chemotherapy was associated with earlier decrease in IGF-I concentration in our study. Although in previous studies younger age (<10 years) at diagnosis was generally associated with later short stature, in our study it was not confirmed.

4.2. *Thyroid function deficiency*

Thyroid disorders are rather common after the treatment of oncological diseases in children. Hypothyroidism is diagnosed in 20% of cases after treatment of childhood cancer [9] and up to 65% after combined treatment for the embryonic brain tumors [19]. The prevalence of primary hypothyroidism is determined by the total dose of radiation to thyroid and by duration of follow-up. TSH deficiency (central hypothyroidism) occurs in 23% of patient at 4 years after cranial radiotherapy [20]. In the present study, hypothyroidism was diagnosed in as much as 40% of patients, and the mean time to its development was 5 years. Cumulative incidence at 60 months was 33.7% for central hypothyroidism and 27.2% for primary hypothyroidism, which is significantly higher than previously reported [22]. In our cohort, there were no significant difference in the prevalence of thyroid dysfunction according to tumor localization, in contrast to other studies reporting the incidence of central hypothyroidism hazard ratio 4.0 with the tumor present in the diencephalon [22]. All patients in our study in whom central hypothyroidism were diagnosed underwent radiotherapy. As expected, primary hypothyroidism was also more frequently diagnosed in those who were treated with radiotherapy than in those who were not, since cranial and/or spinal radiotherapy is known to be a risk factor for primary hypothyroidism [23].

4.3. *Metabolic complications*

The prevalence of metabolic complications depends on the existence of hormonal deficits (growth, sexual and thyroid), eating disorders, physical inactivity and familial predisposition, as well as treatment methods of a pre-existing oncological disease. Furthermore, certain cytostatic drugs may directly damage the vascular endothelium, reduce wall elasticity and, promote atherogenesis resulting in increased morbidity and mortality from cardiovascular diseases at older age. Other studies reported approximately 25% of childhood brain tumor survivors had dyslipidemia and up to 10% hyperinsulinism, diabetes and metabolic syndrome [11]. Osteopenia/osteoporosis develops in 30–40% of patients during the follow-up period of median 6–8 years after the treatment of brain tumor due to frequent use of glucocorticoids, chemotherapy with methotrexate, and dysfunction of the endocrine system [9,10]. In our study, bone mineralization disorders were found in as much as 50% of the cases after a mean time of 44.4 months (3.7 years) of follow-up. Mostly of patients were pubertal (83.3%). Low bone mineral density was more frequently identified in patients with IGF-I deficiency and hypothyroidism, pointing to the need of early institution of hormone replacement therapy in these patients. Steroids were included in the treatment in most patients (in the perioperative period, during radiotherapy or for nausea treatment), but there was no prolonged treatment with high doses of steroids.

Previously reported obesity prevalence more than 2 years after CNS tumor treatment varies from 8% to18% [8,11,22]. In our cohort, there were 30% of overweight but no obese patients. The frequency of overweight was similar in both genders, contrasting with other studies reporting higher obesity prevalence among girls and in patients treated for an oncological disease at younger age [18]. We have found the prevalence of early occurring overweight to be higher in patients treated for the midbrain tumors. Radiotherapy to the brain, damage of the hypothalamus/pituitary area and growth hormone deficiency increase the risk for obesity [11], however, no significant difference in the frequency of overweight was found according to treatments groups in our study. None of the overweight patients was of short stature, however, 40% of them had a low IGF-I levels, therefore growth hormone deficiency might be suspected in these patients.

5. Conclusions

Treatment of childhood brain tumors results in endocrine and metabolic complications, most frequent being low IGF-I concentration, short stature, hypothyroidism, low bone mineral density and overweight. All mentioned endocrine and metabolic complications were diagnosed already in the first 5 years of follow-up. Low IGF-I concentration was found already in the first 24 months after tumor treatment in more than half of patients, suggesting growth hormone insufficiency.

Because of dramatically improved survival rate of CNS tumors treatment in childhood, an early and regular follow-up is essential in order to determine and correct endocrine and metabolic disorders aiming at better quality of life in these patients. We recommend to perform appropriate tests aiming to diagnose CNS tumor treatment consequences not longer than 6–12 months apart. Treatment should be started immediately if needed.

It would be useful to establish a Follow-up Clinics beside main pediatric cancer treatment centers in Lithuania. The Follow-up Clinics should provide medical care also psychosocial and educational support for patients and their families, coordinate the care. Also these clinics should participate in researches, accumulate the latest data, and provide family physicians and other specialists with recommendations for taking care of childhood cancer survivors.

Conflict of interest

The authors state no conflict of interest.

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