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Evaluation of Carbohydrate and Lipid Metabolism and Risk of Obesity in Children after Brain Tumors Treatment

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Abstract

The aim of the study was to assess the carbohydrate and lipid metabolism disturbances as well as weight in children after brain tumors treatment.

The study included 33 boys (53.2%) and 29 girls (46.8%) aged 11.6 ± 3.9. 22 patients underwent treatment for tumors of hypothalamic-pituitary(h-p) area: IA–surgery(19/22); IB–surgery and radiotherapy(3/22). 40 patients were treated for tumors outside the h-p area: IIA– with surgery, chemo-and radiotherapy(22/40); IIB–only with surgery(15/40); IIC–patients treated for optic nerve glioma with chemotherapy(3/40).

BMI was assessed before and after the treatment. OGTT, HbA1c, lipid profile and WHtR after treatment were assessed. Indices of insulin resistance: HOMA-IR, Quickie, Matsuda and de Fronzo were calculated.

63% overweight/obese patients of IA-group and 27% of IIA-group were observed. Hyperinsulinemia was noted in 44% of IA-group, 20% of IIA-group, and insulin resistance in 38% of IA and 15% of IIA. DM2 was diagnosed in 1 patient of IA-group, IFG in 1 patient of IIB, IGT in 1 patient of IA and 1 patient of IIC. Dyslipidemia was noted in 47% of IA-group, elevated level of LDL-cholesterol in 30% of IIA-group.

The excessive weight gain, hyperinsulinemia and dyslipidemia were observed primarily in children treated for hypothalamic-pituitary tumors.

Keywords: Brain tumor; Hyperinsulinemia; Obesity; Dyslipidemia

Abbreviations

Acth: Adrenocorticotropic Hormone; All: Acute Lymphoblastic Leukemia; BMI: Body Mass Index; BMI-SDS: Body Mass Index Standard Deviation Score; CNS - Central Nervous System; DM: Diabetes Mellitus; DM2: Diabetes Mellitus Type 2; FT4: Free Thyroxine; GH: Growth Hormone; GHD: Growth Hormone Deficiency; H-P: Hypothalamic-Pituitary; HBA1C: Hemoglobin A1c; HDL: High-Density Lipoprotein; Homa-IR: Homeostasis Model Assessment: Insulin Resistance Index; IFG: Impaired Fasting Glucose; IGT: Impaired Glucose Tolerance; LDL: Low-Density Lipoprotein; MB: Medulloblastoma; OGTT: Oral Glucose Tolerance Test; PNET: Primitive Neuroectodermal Tumor; RGH: Recombinant Growth Hormone; TC: Total Cholesterol; TG: Triglycerides; TSH: Thyroid-Stimulating Hormone; WHTR - Waist-To-Height Ratio

Introduction

Central Nervous System (CNS) neoplasms are the most common type of solid tumors in children and the second type of all children neoplasms after leukemias. A significant improvement in the treatment of this condition was possible due to development of neurosurgery, radiotherapy and chemotherapy. Majority of brain tumor survivors present chronic complications due to neoplastic process and oncology management [1,2]. An assessment of abnormalities of carbohydrate metabolism and its etiology in patients after brain tumors treatment is still an unacknowledged area of interest.

The aim of the study was to assess the type and the frequency of carbohydrate and lipid metabolism disturbances as well as weight in children after brain tumors treatment.

Materials and Methods

Patients characteristics

The study included 62 children: 33 boys (53.2%) and 29 girls (46.8%), who have finished brain tumors treatment. At the time of laboratory investigations the age of patients ranged from 3 years and 10 months to 17 years and 11 months. Mean age at the diagnosis was 7 years and 10 months. The average time from the end of oncology treatment to laboratory investigations was 2.9 years.

CNS neoplasms diagnosed by cytology included: gliomas in 23 patients (low grade gliomas - 22 patients, high grade gliomas - 1 patient); MB/PNET (11 patients), craniopharyngioma (18 patients), ependymoma in 3 patients and other types of tumor in 7 patients. 59 children had surgical treatment (a specimen for histopathological

diagnosis was obtained during surgery) and 3 were treated with chemotherapy exclusively (diagnosis based on imaging study). Radiotherapy was performed in 25 patients, including 6 patients treated with both: surgery and radiotherapy and 19 treated with surgery, chemotherapy and radiotherapy.

Group division

Patients were divided into 5 groups due to tumor localization and the type of treatment: IA: 19 patients surgically treated for tumors of hypothalamic-pituitary area (h-p); IB: 3 patients treated by surgery and radiotherapy for tumors of h-p area; IIA: 22 patients who received complex treatment (surgery, chemotherapy, radiotherapy) due to tumors of other localization than h-p area; IIB: 15 patients surgically treated for tumors of other localization than h-p area; IIC: 3 patients with optic nerve gliomas treated with chemotherapy. Three most numerous groups (IA, IIA, IIB) were included in statistical analysis.

Medical history data

History data of diabetes occurrence in patients' family members: parents, grandparents, their siblings and patients' siblings were taken.

Pubertal stage

Pubertal development of the patients was assessed according to Tanner scale.

Body mass index and waist-to-hight ratio (WHtR)

Body mass index (BMI) (weight / height [kg/m^2]) was established before the diagnosis based on available medical history data of patients aged 4.7 ± 2.6. To evaluate the influence of oncological treatment on body mass disturbances BMI was calculated at diagnosis, after 6 months of treatment, at the end of the treatment and one year after the treatment. These data were compared to BMI at the time of laboratory assessment and one year after the study, as previously planned in the research protocol.

Being overweight was defined with BMI between 90 and 97 percentile and obesity was diagnosed in patients with BMI above 97 percentile according to polish population BMI-for-age-and-sex percentile charts [3]. BMI was presented by standard deviation score (BMI-SDS).

A single waist circumference measurement was assessed by measure tape (accuracy of measurement 0.5 cm) at the time of laboratory investigation. Waist-to-height ratio (WHtR) was calculated (waist circumference/ height [cm/cm]). Values below 0.5 were accepted as regular regardless of age or sex [4].

Laboratory investigation

Laboratory tests were made 2.9 ± 2.5 years after oncology treatment.

Pituitary growth hormone (GH) reserve was assessed by two different stimulation tests: Clonidine (0.15 mg / m^2 per oral) and Insulin (0.1 j/kg intravenously) or Glucagon (0.03 mg/kg intramuscularly). GH night profile was also assessed (5 evaluations every 30 minute during sleep). Pituitary insufficiency was diagnosed when maximal GH serum concentration in all tests was below 10 ng/ml. Thyroid hormones (fasting TSH and fT4) and adrenal function (Cortisol and ACTH at 8 am and 11 pm) were assessed as well. Methods of immunochemiluminescency were used to perform all biochemical tests.

In all patients Oral Glucose Tolerance Test (OGTT) was performed. Serum glucose concentrations were assessed by spectrophotometry and insulin concentrations by immunochemiluminescency. Impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and diabetes mellitus (DM) were defined using World Health Organization criteria [5]. Patients were diagnosed with hyperinsulinemia when insulin level was higher than 15 μU/ml in a fasting state, more than 150 μU/ml in OGTT or more than 75 μU/ml in the 2nd hour of OGTT [6].

Serum HbA1c level was measured by high quality fluid chromatography.

Lipid profile was assessed by immunoenzymatic method (total cholesterol - TC, triglycerides - TG, high density lipids: HDL). Low density lipids (LDL) were calculated by Friedewald formula (TC-[TG/5+HDL]).

Insulin Resistance Indices

Based on the glucose and insulin levels established in OGTT insulin resistance indices were calculated: HOMA-IR (fasting insulin [mU/ml] × fasting glucose [mmol/l] / 22.5), normal level ≤ 3.16 [6,7]; Matsuda and de Fronzo (10000 / √(fasting insulin [mU/ml] × fasting glucose [mg/dl] × mean glucose concentration in OGTT [mg/dl] × mean insulin concentration in OGTT [mU/ml]), normal level ≥5 [6,8-10]; Quickie (1 / (log fasting insulin [uU/ml] + log fasting glucose [mmol/l]), normal level >0.34 [6,11].

Statistical analysis

The statistical analysis included a describing analysis and a decision analysis. The describing analysis consisted of graphic presentations and numeric results. The statistical decision analysis comprised Mann-Whitney U test and Wilcoxon signed-rank test for dependent variables. An investigation of the dependence between attributes was based on Fisher test and χ^2 test. In a statistical testing, the accepted p-value was $p = 0.05$. If the statistical significance level was lower than 0.05, the decision about relevance or frequency was made. Calculations were performed by Statistica 8.0 and statistical calculations R 2.8.0.

Results and Discussion

Patient's hormonal status during laboratory investigation

A growth hormone deficiency was diagnosed in majority of patients from groups: IA (18/19), IB (3/3), IIA (17/22) and only in 2 patients from IIB-group. Nobody in IIC-group was GH-deficient. The therapy with the recombinant GH (rGH) was introduced in the majority of patients from IA-group (13/18) and in 3 of IIA-group. The rest of GH-deficient patients in IIA-group remained under observation because of greater risk of tumor recurrence.

Primary hypothyroidism was diagnosed in 4 IIA-patients and in 1 patient from group IIB. All patients from groups IA and IB and 3 patients from IIA-group revealed secondary hypothyroidism.

Pituitary-adrenal axis insufficiency was observed in all patients from group I. Diabetes insipidus was shown in 89.5% of patients of IA group and all patients of IB group. Every deficient patient received an appropriate substitute treatment.

Pubertal stage during laboratory investigation

The most of IA-group (15 patients), all patients from IB-group, 5 patients from IIA and 7 patients from IIB-group were pre-pubertal (Tanner I). 11 patients from IIA-group, all patients from IIC-group, 4 patients in IA-group and 4 patients in IIB-group were pubertal (Tanner II-III). Maturity stage (Tanner IV-V) was observed in 6 patients from IIA-group and 4 patients from group IIB.

Weight assessment

Most of patients with h-p tumors (IA: 12/19) revealed an excessive weight gain after treatment, more frequently than patients from other groups: IIA: 6/22, IIB: 3/15 (IA vs. IIA: $p < 0.023$; IA vs. IIB: $p < 0.041$). 26.3% (5/19) of IA-patients were overweight, whereas patients from other groups were twice less frequent overweight (IIA - 3/22 and IIB: 2/15). Obesity was diagnosed in 31.6% (6/19) of IA-patients and in 13.6% (3/22) of patients treated complex for tumors outside the h-p area (IIA). The location of a tumor in the hypothalamic-pituitary area and the age below 10 years at diagnosis significantly influenced the excessive weight gain ($p<0.012$; $p<0.029$ respectively) and the obesity ($p<0.041$). An excessive weight gain was more frequently observed in patients in a pre-pubertal stage at the moment of the laboratory investigation ($p<0.032$). It was established that neither intracranial hypertension with consciousness disorders nor steroid treatment had influence on weight gain and obesity after completed therapy.

Analysis of BMI variations

The most significant increase of BMI-SDS after the completed therapy was observed in patients with hypothalamic-pituitary tumors treated exclusively with surgery (IA). The highest BMI was noted 12 months after the end of the treatment. The rGH treatment had significant influence on BMI-SDS reduction for patients qualified for this therapy.

BMI-SDS values in patients with tumors outside the hypothalamic-pituitary location showed dependence on different types of treatment. Patients receiving complex treatment (IIA) had lower BMI-SDS after completed therapy than before it ($p<0.006$). Lesser BMI-SDS before treatment (-0.6 ± 1.09) was observed in patients treated exclusively with surgery (IIB) (Figure 1).

WHtR

IA-patients presented significantly higher WHtR values (0.5 ± 0.1), than other patients (IA vs. IIA: $p<0.027$; IA vs. IIB: $p<0.008$).

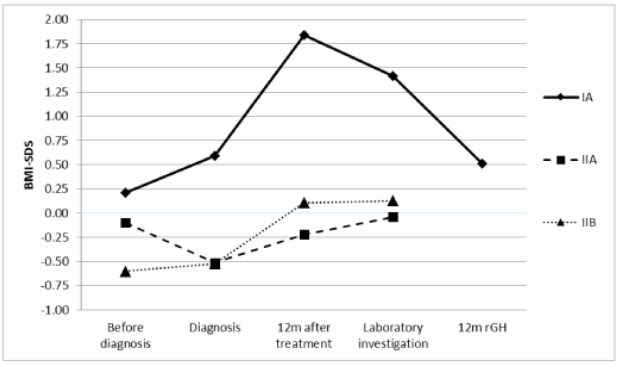

Figure 1: BMI-SDS changes in 3 main groups. IA – group of patients treated surgically for tumors of hypothalamic-pituitary area; IIA – group of patients treated for tumors outside the h-p area with surgery, chemo- and radiotherapy; IIB – group of patients treated surgically for tumors outside the h-p area. Before diagnosis- historical data; Diagnosis – at the moment of diagnosis; 12 m after treatment – 12 months after oncology treatment; Laboratory investigation – laboratory tests after oncology treatment; 12 m rGH- after 12 months of treatment with recombinant growth hormone.

Glucose [mg/dl]	Serum glucose concentrations					Statistical differences		
	IA	IB	IIA	IIB	IIC	p(IA/IIA)	p(IA/IIB)	p(IIA/IIB)
	n=16	n=2	n=20	n=15	n=3			
In a fasting state	79.05 ± 5.33	77.33 ± 7.23	81.90 ± 5.17	81.27 ± 7.27	90.67 ± 1.16	p>0.05	p>0.05	p>0.05
In 2nd hour of OGTT	113.69 ± 3.90	104.50 ± 16.26	93.35 ± 17.94	92.87 ± 15.27	124.00 ± 21.93	p<0.019*	p<0.010*	p>0.05
Mean concentration in OGTT	107.30 ± 24.22	93.40 ± 12.16	103.22 ± 17.98	100.40 ± 11.90	109.44 ± 6.15	p>0.05	p>0.05	p>0.05

Table 1: Serum glucose concentrations in OGTT (mean values and standard deviations) in particular groups. IA- group of patients treated surgically for tumors of hypothalamic-pituitary area; IB - group of patients treated with surgery and radiotherapy for tumors of hypothalamic-pituitary area; IIA –group of patients treated with surgery, chemo- and radiotherapy for tumors outside the h-p area; IIB – group of patients treated surgically for tumors outside the h-p area; IIC- patients with optic nerve glioma treated with chemotherapy. Analysis was made by Fisher test. Values marked by "*" were calculated by U Mann-Whitney test. Statistically important differences were marked as bold.

Carbohydrate metabolism assessment: family history

A diabetes occurrence in family members was more common in patients with tumors outside the h-p area receiving complex treatment (IIA) than in other groups, however the difference was not significant.

Glucose concentration in OGTT

Impaired fasting glucose (IFG) was noted only in one patient treated for an optic nerve glioma (IIC). A mean glucose level at 2nd hour of OGTT was significantly higher in patients surgically treated for h-p tumors (IA) in comparison to patients with other localization of tumor (IA vs. IIA: $p<0.019$; IA vs. IIB: $p<0.010$). Impaired glucose

tolerance (IGT) was diagnosed in one patient from IA-group and one from IIC-group. The type 2 diabetes was diagnosed in one patient from IA-group [Table 1].

The post-operative steroid treatment did not influence fasting glucose, glucose tolerance or diabetes occurrence in the patients.

Assessement of HbA1c

For all patients HbA1c values were within normal ranges. The highest HbA1c values were noted for patients with h-p tumors (IB: 5.53 ± 0.15%; IA: 5.38 ± 0.37%) and the lowest for patients receiving complex treatment for tumors outside the h-p area (IIA: 5.18 ± 0.33%). The difference between groups was not significant.

Insulin concentration in OGTT

Fasting insulin concentration above 15 μU/l was observed significantly more frequent in subjects who underwent surgical treatment for h-p tumors (IA) than in other groups (IA vs. IIA: p<0.016; IA vs. IIB: p<0.049). In those patients mean fasting insulin concentration was higher than in others (IA vs. IIA: p<0.03) [Table 2].

The highest average concentration of insulin in 1st hour of OGTT was observed in patients treated for tumors outside the h-p area (IIA: 60.07 ± 57.26 μU/ml), whereas in 2nd hour of OGTT it was supreme in IA-group. For those patients concentrations above 75μU/ml were more frequently seen in comparison to the others, but the difference was not significant.

The highest maximum concentration of insulin in OGTT was noted in patients of IA-group (130.09 ± 143.05 μU/ml). Five of them revealed insulin concentration above 150μU/ml [Table 2].

Elevated insulin concentrations were related to being overweight and obese (p<0.008).

	Serum insulin concentrations in OGTT and insulin resistance indices					**Statistical differences**		
	IA	IB	IIA	IIB	IIC	p(IA/IIA)	p(IA/IIB)	p(IIA/IIB)
	n=16	n=2	n=20	n=15	n=3			
Fasting insulin [μU/ml]	12.11 ± 8.51	7.80 ± 0.00	5.88 ± 3.41	12.11 ± 21.71	12.37 ± 4.37	p<0.03*	p>0.05	p>0.05
Fasting insulin > 15 μU/ml	6/16 (37.5%)	0/2 (0%)	1/20 (5%)	1/15 (6,7%)	1/3 (33.3%)	p<0.016	p<0.049	p>0.05
Insulin in 2nd hour of OGTT [μU/ml]	69.13 ± 112.74	25.30 ± 0.00	37.71 ± 38.87	31.26 ± 24.44	60.57 ± 29.70	p>0.05	p>0.05	p>0.05
Insulin in 2nd hour of OGTT >75 μU/ml	3/16 (18.8%)	0/2 (0%)	2/20 (9.5%)	1/15 (6.7%)	1/3 (33%)	p>0.05	p>0.05	p>0.05
Max insulin in OGTT > 150 μU/ml	5/16 (31.3%)	0/2 (0%)	2/20 (9.5%)	0/15 (0%)	0/3 (0%)	p<0.003	p<0.001	p>0.05
HOMA-IR (>3,16)	6/16 (37.5%)	0/2 (0%)	0/20 (0%)	1/15 (6.7%)	1/3 (33.3%)	p<0.012	p>0.05	p>0.05
Quickie (<0,34)	11/16 (68.8%)	2/2 (100%)	11/20 (55%)	8/15 (53.3%)	3/3 (100%)	p>0.05	p>0.05	p>0.05
Matsuda and de Fronzo (<5)	6/16 (37.5%)	0/2 (0%)	2/20 (10%)	2/15 (13.3%)	1/3 (33.3%)	p>0.05	p>0.05	p>0.05

Table 2: Serum insulin concentrations in OGTT and insulin resistance indices in particular groups. IA- group of patients treated surgically for tumors of hypothalamic-pituitary area; IB - group of patients treated with surgery and radiotherapy for tumors of hypothalamic-pituitary area; IIA –group of patients treated with surgery, chemo- and radiotherapy for tumors outside the h-p area; IIB – group of patients treated surgically for tumors outside the h-p area; IIC- patients with optic nerve glioma treated with chemotherapy. Analysis was made by Fisher test. Values marked by "*" were calculated by U Mann-Whitney test. Statistically important differences were marked as bold.

Insulin resistance indices

Patients treated for h-p tumors (IA) revealed HOMA-IR values above 3.16 more frequently than other subjects (IA vs. IIA p<0.012). Quickie index values below 0.34 were observed in most of the patients; however differences between groups were not significant. Matsuda and de Fronzo index lower than 5 revealed mostly patients treated for h-p tumors (IA) [Table 2].

Hyperinsulinemia and abnormal insulin resistance indices: HOMA-IR (p<0.001), Matsuda (p<0.001) and Quickie (p<0.024) were related.

Obesity was diagnosed more frequently in patients with abnormal HOMA-IR and Matsuda indices values (p<0.049 and p<0.047 respectively). An excessive weight gain was dependent on abnormal values of these indices as well (p<0.009 and p<0.01 respectively).

Lipids profile

Elevated total cholesterol was noted in a half of IA-group and almost a half of IIA-group, but the second one revealed the highest average concentration of total cholesterol and LDL-cholesterol. The average concentration of HDL-cholesterol in patients treated surgically for h-p tumors was lower than in other groups (IA vs. IIA p < 0.029). Reduced HDL-cholesterol was noted more frequently in IA-group (IA vs.IIA p < 0.043).

The highest concentration of triglycerides was observed in patients with tumors of hypothalamic-pituitary area (IA), significantly higher than in other groups (IA vs. IIB: p<0.002; IA vs. IIA: p < 0.025). Elevated triglycerides were more frequently observed in IA-group (10/19) than in others (IA vs. IIA: p < 0.009; IA vs. IIB: p < 0.037) [Table 3].

	Serum concentrations of Total cholesterol, LDL, HDL, Triglycerides					Statistical differences		
	IA n=18	IB n=2	IIA n=20	IIB n=15	IIC n=3	p (IA/IIA)	p (IA/IIB)	p (IIA/IIB)
Total cholesterol [mg/dl]	192.84 ± 56.40	199.67 ± 52.00	204.43 ± 64.83	167.87 ± 31.16	148.67 ± 13.80	p>0.05	p>0.05	p<0.028*
Elevated total cholesterol	9/18(50.0%)	1/2 (50.0%)	8/20 (40%)	4/15(26.7%)	0/3 (0.0%)	p>0.05	p>0.05	p>0.05
LDL cholesterol [mg/dl]	117.50 ± 49.16	121.00 ± 25.46	137.10 ± 61.78	104.73 ± 22.89	78.33 ± 18.04	p>0.05	p>0.05	p<0.033*
Elevated LDL cholesterol	5/18 (27.8%)	1/2 (50.0%)	6/20 (30.0%)	2/15 (13.3%)	0/3 (0.0%)	p>0.05	p>0.05	p>0.05
HDL cholesterol [mg/dl]	41.11 ± 10.63	52.50 ± 10.61	48.30 ± 8.97	48.4 ± 14.29	53.67 ± 11.37	p<0.029	p>0.05	p>0.05
Reduced HDL cholesterol	7/18 (38.9%)	0/2 (0.0%)	2/20 (10.0%)	4/15 (26.7%)	0/3 (0.0%)	p<0.043	p>0.05	p>0.05
Triglicerides [mg/dl]	162.26 ± 100.77	151.33 ± 130.78	96.43 ± 41.32	78.33 ± 34.33	84.00 ± 9.54	p<0.025*	p<0.002*	p>0.05
Elevated triglicerides	10/18 (55.6%)	1/2 (50.0%)	1/20 (5.0%)	1/15 (6.7%)	0/3 (0.0%)	p<0.009	p<0.037	p>0.05

Table 3: Serum lipids concentrations in particular groups. IA- group of patients treated surgically for tumors of hypothalamic-pituitary area; IB - group of patients treated with surgery and radiotherapy for tumors of hypothalamic-pituitary area; IIA –group of patients treated with surgery, chemo- and radiotherapy for tumors outside the h-p area; IIB – group of patients treated surgically for tumors outside the h-p area; IIC- patients with optic nerve glioma treated with chemotherapy. Analysis was made by Fisher test. Values marked by "*" were calculated by U Mann-Whitney test. Statistically important differences were marked as bold.

Discussion

Patients with brain tumors who participated in the study were diverse. The subjects differed by histology of the tumor and its localization in the brain. The selection of patients was limited because the study included only those patients who already finished treatment in one clinical centre.

Current studies in patients who completed oncological therapy describe various abnormalities of carbohydrate metabolism. An excessive weight gain is the most frequent observed complication [7,8,9-15]. Many authors emphasize that the main cause of obesity during or after oncology management is the neoplastic process itself (tumors of h-p area), steroid treatment in brain edema prophylaxis, pituitary insufficiency - particularly growth hormone deficiency, other endocrinopathies, lifestyle changes and accompanying neurological symptoms [18,19].

Childhood Cancer Survivor Study [9] evaluated adults treated for brain tumors in childhood. It reveal that the risk of obesity comparing to healthy adults is similar. On the other hand, Pietilä et al. [8] describe significant frequency of obesity and carbohydrate metabolism abnormalities in patients after brain tumors management. Patients in this study underwent treatment for brain tumors of various locations. In few patients tumors were situated in hypothalamus and sella turcica area. The majority of patients were treated exclusively with surgery. Obesity was diagnosed in 35% of patients (21% with the central one). Adiposity was observed more frequently in patients receiving radiotherapy for the whole brain, after damage of hypothalamic-pituitary area by neoplastic process, in patients with growth hormone deficiency and with decreased physical activity [8].

In our study the group with the highest risk of developing obesity were patients treated for tumors located in hypothalamic-pituitary area (60% of all patients with excessive weight gain).

No dependence between weight gain and chemotherapy or radiotherapy was noted.

Numerous authors inform that excessive weight gain frequently correlates with increased appetite. It relates mostly to patients treated for hypothalamic-pituitary tumors [8,14,20-22]. As far as some authors are concerned, hypothalamic obesity may develop even some years after hypothalamic tumors management [22], though there are observations that first symptoms may be present shortly after surgery [23].

Excessive weight gain related to an increased appetite is most common for patients after surgical treatment or radiotherapy of craniopharyngioma [10,12,13,15-17,21]. Meuric et al. [24] evaluated patients with craniopharyngioma after extensive treatment and primary damage of hypothalamus and observed correlation between weight gain and increased insulin secretion. Hyperinsulinemia can develop either before the surgical treatment or after completed therapy [21-25]. The cause of increased insulin concentration in the serum indirectly explained animal studies. The damage of ventromedial nucleus in hypothalamus of rats was the cause of hyperphagia and increased serum insulin concentration, which led to obesity [26]. In this study the correlation between hyperinsulinemia and increased activity of parasympathetic system was shown. Other studies also

confirm the hypothesis that increased insulin secretion may cause the hypothalamic obesity. It is considered that positive influence of Octreotide treatment in this type of obesity is by insulin secretion inhibition [14,27].

Pinto et al. [23] observed that carbohydrate metabolism abnormalities intensified during and after oncology treatment. There is a hypothesis, that the craniopharyngioma itself and the surgery in addition modified the insulin secretion. The correlation between hyperinsulinemia and the weight gain is described for healthy population as well [28].

In our study, in half of the patients who underwent surgical treatment for h-p tumors, elevated insulin concentrations after treatment were observed. The location of the tumor in this area had a significant influence on weight gain and hyperinsulinemia. There was dependence between hyperinsulinemia and an excessive weight gain. For the patients receiving complex treatment for tumors outside the h-p area increased fasting insulin concentrations were noted only in 5% of patients and elevated insulin concentrations in OGTT were seen in 15% of patients. In this group only 27% were overweight or obese. 20% of patients surgically treated for tumors outside the h-p area revealed weight gain. Elevated insulin concentrations in OGTT were noted for 13% of them. The imbalance between patients with tumors of different areas testifies that the tumor location in the h-p area has the greatest influence on weight gain and insulin resistance after treatment.

Carbohydrate metabolism disorders as diabetes mellitus and impaired glucose tolerance were described after treatment for brain tumors in hypothalamic-pituitary area [29,30]. Crowley et al. diagnosed diabetes mellitus in 11.5% of patients after surgical treatment of craniopharyngioma [29]. Furthermore, in Deepak et al. study diabetes mellitus was diagnosed in 9% of those patients [30]. In the other survey [31] diabetes mellitus incidence was 3.7%. In our present study type 2 diabetes mellitus was diagnosed only in one patient (1.6%) treated with surgery for craniopharyngioma. Impaired glucose tolerance was noted in one patient treated for h-p tumor and another treated exclusively with chemotherapy for optic nerve glioma. The highest average HbA1c value was observed in patients treated for h-p tumors [32].

For patients with abnormal glucose or insulin concentrations, the insulin resistance assessment is required. It can be evaluated by indirect calculation of insulin resistance indices. A more adequate method is the glucose clamp technique [33,34], but because of the complexity of the method, it is not routinely used in the clinical practice. Yeni-Komshian et al. [35] compared different insulin resistance indices with the glucose clamp technique and observed that fasting insulin concentration was the most sensitive insulin resistance index. A fasting glucose to insulin ratio and HOMA-IR index also showed high sensitivity, however they were less sensitive than fasting insulin.

In our study elevated fasting insulin concentrations, HOMA-IR and Matsuda abnormal values were noted more frequently in patients treated surgically for h-p tumors. Some patients treated with surgery followed by radio- and chemotherapy for tumors outside the h-p area also revealed insulin resistance. This was mostly accompanied by overweight and obesity. In the literature only few authors assessed insulin resistance indices for patients after complex treatment of brain tumors. Usually patients with h-p tumors and craniopharyngioma were described [15,36]. There are also studies concerning patients after treatment of acute lymphoblastic leukemia [37]. In those groups increased percentage of abnormal values of assessed indices has been observed comparing to control groups [15,36,37].

Steroid treatment in cancer therapy is an important factor influencing carbohydrate metabolism abnormalities [38,39]. The steroid use in therapeutic protocols of acute lymphoblastic leukemia (ALL) increases frequency of obesity and carbohydrate metabolism abnormalities [40-42]. On the other hand, in the studies assessing large population of ALL survivors, prophylactic radiotherapy was essential factor influencing obesity rate. Exclusive chemotherapy did not influence the obesity rate [43]. In our study correlation between chemotherapy and radiotherapy with the excessive weight gain was not observed. In brain tumor therapeutic schedules in children steroid treatment is used commonly in pre-operative period in order to decrease intracranial pressure, and less frequently in later treatment stages. Our results did not confirm correlation between carbohydrate metabolism disorders and the type of treatment.

An important constituent of the abdominal obesity assessment is a measurement of waist and hip circumferences and calculation of indices. In our study WHtR (waist-to-height ratio) index was used. It is widely accepted as a very good index assessing abdominal obesity and it is an excellent prognostic factor for abdominal obesity complications, especially in children [4,44,45]. In our study 26% of patients treated for h-p tumors revealed abnormal values of this index. Lower prevalence of abdominal obesity was noted in patients with tumors of other than h-p location.

While analyzing the causes of obesity, mainly abdominal type, hypopituitarism and decreased growth hormone secretion has to be taken into consideration. Many authors mentioned growth hormone deficiency (GHD) as one of the main factors increasing the risk of obesity and dyslipidemia in patients after treatment of brain tumors [46-48] and other neoplasms, mainly ALL [49,50]. In the present study patients with damaged hypothalamic-pituitary area by neoplastic process with accompanying GHD, more frequently revealed excessive weight gain and dyslipidemia. After the year of treatment with recombinant growth hormone significant reduction of SDS BMI was observed.

In our previous study influence of treatment with recombinant growth hormone (rGH) on metabolic functions in patients after craniopharyngioma with pituitary insufficiency was assessed [48]. Growth hormone therapy caused significant BMI, LDL-cholesterol and HbA1c reduction one year after treatment.

Conclusions

In summary our study showed that patients after treatment of brain tumors localized in hypothalamic-pituitary area have the highest risk of abnormalities in carbohydrate metabolism, hyperinsulinemia in particular.

Moreover, age below 10 years at diagnosis and tumor localization in hypothalamic-pituitary area is related with more frequent excessive weight gain.

This single study is not sufficient to assess a reversibility of found abnormalities and there is a need of further observation.

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