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Evaluation of selected endocrine disorders after anticancer treatment of solid tumors in childhood

Ocena wybranych zaburzeń endokrynologicznych po terapii przeciwnowotworowej u pacjentów leczonych z powodu guzów litych w wieku dziecięcym

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Abstract

Introduction. Continuously improving treatment of childhood cancers leads to the better survival rate, but at the same time causes long-term consequences. The aim of our study was to evaluate the incidence of selected endocrine disorders after anticancer treatment of solid tumors. **Materials and methods.** The study group consisted of 74 patients (48 boys), aged 3.25-27 years (mean 13.24± 6.21), at least one year after anticancer therapy of solid tumours. Thyroid function, concentration of: sex hormones, lipids (cholesterol/LDL/TG, HDL), IGF-1 (ng/ml), PTH (pg/ml) were assessed. BMD (Z-score) were evaluated. Following anthropometric parameters were examined: height SDS, body mass SDS and BMI SDS. **Results.** Endocrinological abnormalities were found in 66 (89.19%) of patients. Most of the patients (67.57%) had one or two disturbances. Most common abnormalities were dyslipidaemia found in 39 (58.21%) patients and overweight/obesity in 25 (33.78%). Other abnormalities were as follows: disturbance in sex hormones in 14 (27.45%) patients, abnormal PTH in 13 (19.4%), abnormal IGF-1 in 9 (14.75%), short stature in 9 (12.16%) underweight in 8 (11.11%), hypothyroidism in 7 (9.72%), low BMD 6 (8.69%) and hyperthyroidism in 2 (2.78%). **Conclusions.** Patients after anticancer treatment during childhood are significantly exposed to endocrine disorders. These patients require detailed follow-up examinations to detect abnormalities and to implement the appropriate treatment. It should be noted that there is frequent coexistence of multiple disorders to one patient.

Key words:
late effects, anticancer treatment, lipids, BDM, IGF1

Streszczenie

Wstęp. Coraz skuteczniejsze metody leczenia nowotworów wieku dziecięcego wpływają na lepszą przeżywalność, ale są przyczyną powstawania odległych następstw leczenia. Celem pracy jest ocena częstości występowania wybranych zaburzeń endokrynologicznych. **Materiały i metody.** Grupę badaną stanowiło 74 pacjentów (48 chłopców), w wieku 3,25-27 lat (średnia 13.24±6.21), co najmniej rok po zakończeniu leczenia przeciwnowotworowego z powodu guzów litych. Oceniono funkcję tarczycy, stężenie gonadotropin, lipidogram (cholesterol/LDL/TG, HDL) oraz BMD (z-score). Oceniono również parametry antropometryczne: wysokość SDS, masę ciała SDS oraz BMI SDS. **Wyniki.** Zaburzenia endokrynologiczne występowały u 66 (89,19%) pacjentów. U większości pacjentów (66,57%) obserwowano jedno lub dwa zaburzenia. Najczęstszymi nieprawidłowościami były dyslipidemia, występująca u 39 (58,21%) pacjentów, oraz nadwaga lub otyłość obserwowane u 25 (33,78%). Częstość występowania innych zaburzeń kształtowała się następująco: zaburzenia w stężeniu hormonów płciowych występowały u 14 (27,45%) pacjentów, nieprawidłowy poziom PTH u 13 (19,4%), nieprawidłowe stężenie IGF-1 u 9 (14,75%), niedobór wysokości u 9 (12,16%), niedobór masy ciała u 8 (11,11%), niedoczynność tarczycy u 7 (9,72%), obniżone BMD u 6 (8,69%), nadczynność tarczycy u 2 (2,78%). **Wnioski.** Pacjenci po leczeniu przeciwnowotworowym są w istotnym stopniu narażeni na zaburzenia endokrynologiczne. Wymagają oni szczegółowych badań kontrolnych w celu wykrycia nieprawidłowości oraz wdrożenia odpowiedniego leczenia. Warto zwrócić uwagę na częste występowanie więcej niż jednego zaburzenia u danego pacjenta.

Słowa kluczowe:
późne następstwa, leczenie przeciwnowotworowe,lipidy,BMD, IGF1

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Introduction

The progress in anti-cancer treatment caused that number of childhood cancer survivors (CCS) continues to increase. With the current treatment protocols the 5-year event free survival is over 80% and it is estimated, that in United States the number of CCS will exceed 500,000 by 2020 [1,2]. Enlarging population of cancer survivors has increased interest in the late complications of cancer and its treatment. Epidemiological data revealed, that about 62% of CCS demonstrate at least one late-effect [3]. By late-effect or late complication, we understand the side effect of cancer or its therapy, that manifests during or after treatment and does not disappear after the treatment is completed [4].

Endocrine disorders are the most common problems, affecting up to 50% of patients, and include problems with growth, weight, puberty, gonadal function, bone health, thyroid and adrenal function [2,5,6]. The endocrine system is sensitive to both chemotherapy and radiation [5]. Corticosteroids have strong impact on bone tissue and also increase the risk of obesity and metabolic syndrome [3]. The most widely known risk factors are accompanied by many other factors, e.g. genetic, which are only partly understood.

High prevalence of endocrine late-effects causes regular, long-term monitoring of growth rate, gonadal function, thyroid function, lipid profile and bone mineral density (densitometry), necessary among CCS [3].

The aim of our study is to evaluate the occurrence of endocrine disorders after anticancer treatment in the group of patients with solid tumours.

Material and methods

The study group comprised of 74 patients (48 boys), aged 3.25-27 (mean 13.24± 6.21 and median 12.54), treated for solid tumors in the Department of Bone Marrow Transplantation, Oncology and Hematology, Wroclaw. Patients underwent examinations evaluating the long-term effects of the anticancer treatment (at least one year after treatment). The patients were examined over the period 2009-2013. The description of the study group is presented in Table I. Body weight and height were measured. BMI was calculated using the formula: (kg / m^2). Because of the great diversity of groups in terms of age, body weight, height and BMI are expressed in SDS, based on centile charts, according to age and sex [7]. SDS was calculated using the formula. The values below normal, expressed in the SDS, were values <-1.6 (<10 percentile). The values above normal, expressed in the SDS, were values >1,6 (> 90 percentile). The following laboratory parameters were assessed: total cholesterol (mg/dl); LDL-C (mg/dl); triglycerides (mg/dl); HDL-C (mg/dl); TSH (uIU/ml); FT3 (pmol/l); FT4 (pmol/l); FSH (mIU/ml); LH (mIU/ml); progesterone PRG (ng/ml); estradiol (pg/ml); testosterone (ng/ml); PTH (pg/ml); IGF-1 (ng/ml); IGFBP-3 (ug/ml). The laboratory parameters mentioned above were evaluated according to reference values for sex and age. Sex hormones were measured and analyzed only in patients, who were in pubertal period or finished puberty (in girls over 8 years old, in boys over 10 years old). Patients with abnormal levels of sex hormones were examined by endocrinologist. According to values of sex hormones, physical examination and medical history, final diagnoses of sex hormones disturbances were established.Lumbar spine Bone Mineral Density (BMD) was measured by dual energy X-ray absorptiometry (DEXA) (Lunar DPX +). BMD was calculated as z-score value. Low BMD was defined as z-scores below -2.0.

Statistical analysis was performed using Statistica 12. Mann-Whitney U test was used to determine the differences between groups. The relationship between the two parameters was determined using the correlation and the Pearson's correlation coefficient. The p-values less than 0.05 were considered statistically significant.

Table I. Characteristic of the study group
Tabela I. *Opis grupy badanej*

Tumor type Typ nowotworu	No	Age at diagnosis (years) Wiek w momencie rozpoznania(lata)	Age at examination (years) Wiek w momencie badania
Mesenchymal Malignant Tumours Nowotwory tkanek miękkich	girls: 6 boys: 28	7.52 (±5.84) 8.38 (±5.41)	10.69 ±5.76) 13.87 (±6,34)
Bone Tumours Nowotwory kości	girls: 9 boys: 4	9.8 (±3.93) 12.97 (±5.21)	14.99 (±4.33) 16.64 (±6.63)
Neuroblastoma Neuroblastoma	girls: 0 boys: 5	 3.42 (±1.93)	 8.22 (±3.02)
CNS tumour Nowotwory OUN	girls: 7 boys: 7	10.17 (±4.62) 8.2 (±5,5)	15.28 (±5.84) 12.28 (±5.47)
Germ cell tumour Nowotwory germinalne	girls: 2 boys: 4	5.31 (±3.75) 4.85 (±8.52)	7.81 (±4.51) 9.95 (±6.43)

Results

Anthropometric parameters

Overweight or obesity was found in 25 (33.78%) patients, 10 girls and 15 boys. Underweight was present in 8 (11.11%) patients. 9 (12.16%) persons had height deficiency. Both short stature and height deficiency was observed in 4 (5.41%). There were no differences between girls and boys in body weight SDS (p=0.511), height SDS (p=0.583) and BMI SDS (p=0.550). We also did not find relationships between age at the time of the study and anthropometric parameters.

Thyroid function

Hypothyroidism was diagnosed in 7 (9.27%) patients, 6 boys and 1 girl. All of the patients with hypothyroidism had elevated concentration of TSH and normal value of FT4. One girl had hyperthyroidism with decreased TSH and normal level of FT4. One girl had increased FT4 and normal TSH. Patients with impaired thyroid function were consulted by an endocrinologist and proper treatments for hyperthyroidism or hypothyroidism were administered. Two patients with hypothyroidism had also dyslipidemia (elevated: cholesterol, LDL, TG and decreased HDL-C).

Lipids profile

Dyslipidemia occurred in 39 (58.21%) patients. Hypercholesterolemia was present in 26 (38.81%) patients. Elevated level of LDL-C was found in 24 (36.36%). Hypertriglyceridemia occurred in 16 (23.88%). Low HDL-C was observed in 8 (12.12%) patients. The description of lipids parameters is presented in Table II. We did not find any correlation between lipids parameters, anthropometric parameters (BMI SDS, body mass SDS) and thyroid function.

BMD

BMD z-score below or equal -1 was found in 20 (29.85%) cancer survivors, 6 of them had low BMD values (z-score below -2). Five of the patients with low BMD had short stature and decreased IGF-1, three of them had decreased PTH, of which two were underweight. Decreased IGF-1 was observed in 7 (11.48%), increased value was noted in 2 (3.28%) patients. Elevated PTH was found in 3 (4.48%) and decreased in 10 (14.95%) patients. There was positive correlation between BMD and IGF-1 (r=0.41 p=0.002), BMD and PTH (r=0.27 p=0.036), BMD and BMI SDS (r=0.25 p=0.042), BMD and height SDS (r=0.44 p<0.001).

Sex hormones

Concentration of sex hormones (LH,FSH, estradiol, progesterone-PRG) were analysed in girls over 8 years old, the group consisted of 20 females. Six (30%) of them presented abnormality in sex hormones. Decreased LH concentration was observed in 3 females, one of them also had decreased FSH value. Because LH and FSH were assessed according to age and sex, the results may be interpreted as abnormal pituitary function. One girl had increased concentrations of both FSH and LH, what may indicate incorrect gonadal function. One girl had FSH increased only. Low estradiol concentrations were present in 4 females. Decreased PRG was found in 4 girls. According to values of sex hormones and medical history, especially type of the treatment applied, final diagnoses of sex hormones disturbances were established. Delayed puberty was diagnosed in 3 females. Two girls had ovarian failure. One girl, who underwent cranial radiotherapy, had pituitary insufficiency.

Levels of sex hormones(LH, FSH, testosterone) were analysed in 31 males over 10 years of age. Abnormalities in sex hormones were observed in 8 (25.81%) patients. Increased level of FSH were found in 4 males, one of them had also increased LH. Four males had decreased values of LH, one boy also had decreased FSH. All of the males had testosterone in normal values. According to values of sex hormones and medical history, especially type of the treatment applied, final diagnoses of sex hormones disturbances was established. Delayed puberty was diagnosed in 4 males. Another four males had gonadal failure.

Coexistence of endocrinological disorders

Description of evaluated parameters is presented in Table II. Endocrinological abnormalities and their prevalence are presented in Table III.

Only 8 (10.81%) of the patients had no endocrinological abnormalities. Most of the patients (67.57%) had 1 or 2 disturbances (Graph 1). Dyslipidemia was the most frequent and occurred in 39 (58.21%) patients. High occurrence of overweight or obesity, 25 (33.78%) patients had excess of body weight was also observed. In the group of patients with overweight or obesity, 10 (40%) had dyslipidemia. Patients with low BMD (8.96% of the study group) also had other abnormalities, most of them had short stature (5), underweight (4), dyslipidemia (5), decreased IGF-1 (5) or PTH (3). Five (6.76%) of the patients had at least 4 types of disturbances, the characteristics of those patients are presented in table IV. Other endocrinological diseases, not included into analysis, were also diagnosed in our group. One child had diabetes mellitus type one and one had abnormal profile of cortisol.

Discussion

Endocrinological disorders are common after anticancer treatment. The most frequent dysfunctions are: overweight/obesity, dyslipidemia, disturbances in sex hormones, hypothyroidism and osteoporosis. In our study only 10.81% of the patients did not have any endocrinological diseases. Most of the patients (67.57%) had one or two disturbances. Other authors had similar results. Miyoshi et al. observed endocrinological abnormalities in 87 (67%) of 122 Childhood Cancer Survivors (CCS), 96% of the patients with brain tumors and 62% patients with other solid tumors [5]. Brignardello et al. observed in study of 310 adult CCS, that 48.46% of females and 62.78% of males were effected by at least one of endocrine disease.

Table II. Parameters assessed in study group. Each of the following parameters were evaluated according to reference values for sex and age
Tabela II. *Oceniane parametry w grupie badanej. Każdy z badanych parametrów została oceniony zgodnie z normami dla wieku i płci*

Parameter Oceniany parametr	No	decreased (%) obniżony (%)	normal (%) norma (%)	increased (%) podwyższony (%)
Weight SDS Masa ciała SDS	72	6 (8.33%)	45 (62.5%)	21 (29.17%)
Height SDS Wysokość SDS	74	9 (12.16%)	65 (87.84%)	0
BMI SDS	72	6 (8.33%)	45 (62.5%)	21 (29.17%)
TSH (uIU/ml)	72	1 (1.39%)	64 (89.34%)	7 (9.27%)
FT4 (pmol/l)	73	1 (1.37%)	71 (97.26%)	1 (1.37%)
FT3(pmol/l)	73	1 (1.37%)	51 (69.86%)	21 (28.77%)
Cholesterol (mg/dl)	67	4 (5.97%)	37 (55.22%)	26 (38.81%)
LDL-C (mg/dl)	66	0	42 (63.64%)	24 (36.36%)
TG (mg/dl)	67	5 (7.46%)	46 (68.66%)	16 (23.88%)
HDL-C (mg/dl)	66	8 (12.12%)	53 (80.3%)	5 (7.58%)
BMD (z-score)	67	6 (8.96%)	61 (91.04%)	0
IGF-1 (ng/ml)	61	7 (11.48%)	52 (85.24%)	2 (3.28%)
IGFBP-3 (ug/ml)	68	2 (2.94%)	66 (97.06%)	0
PTH (pg/ml)	67	10 (14.95%)	54 (80.57%)	3 (4.48%)
FSH (mIU/ml)	48	2 (4.17%)	42 (83.33%)	6 (12.5%)
LH (mIU/ml)	48	7 (14.58%)	39 (81.25%)	2 (4.17%)
Testosteron (ng/ml)	31	0	31 (100%)	0
Progesterone (ng/ml)	17	4 (23.53%)	13 (76.47%)	0
Estradiol (pg/ml)	17	4 (23.53%)	13 (76.47%)	0

The authors observed that the prevalence of endocrine late effects increased over the time, from 26.26% in females and 24.03% in males at the age of 18 to 50.06% in females and 72.02% in males respectively after 12 years of follow up [8].

Overweight, obesity and underweight

Obesity, overweight and also underweight are common abnormalities in CCS. In our study group 33.78% patients were overweighed or obese and 11.11% were underweighted. Meacham et al. [9] in multicentre cohort study of survivors of paediatric cancer observed higher risk for underweight both in males and females with Wilms tumours, female survivors of bone tomour without amputation, male survivors of brain tumours, neuroblastoma and MMT (Mesenchymal Malignant Tumours). Survivors of solid tumours were not at higher risk of obesity. Authors observed that among males, young age at diagnosis (below 4 years old) and abdominal radiation were associated with increased risk of underweight, also females with Wilms tumours and male with MMT who received radiation were more often underweighted [9]. In contrary Warner et al. [10] in all cancer diagnosis observed no increased risk for overweight/obesity and underweight compared to controls. However, authors observed that males with CNS tumours were at increased risk for overweight. The study also confirmed that younger age

Table III. Endocrinological abnormalities and their prevalence in the studied group
Tabela III. *Częstość występowania wybranych zaburzeń endokrynologicznych w grupie badanej*

Type of disturbances[1] Rodzaj zaburzenia	No[2]	Patients with abnormalities Pacjenci z zaburzeniami	
		No(%)	Girls(%) n=26/Boys (%), n=48 dziewczynki/chłopcy
Underweight Niedobór masy ciała	72	8 (11.11%)	4 (15.38%)/4 (8.7%)
Short stature Niedobór wysokości ciała	74	9 (12.16%)	3 (11.54%)/6 (12.5%)
Overweight/Obesity Nadwaga/Otyłość	72	25 (33.78%)	10 (38.46%)/(32.61%)
Hypothyroidism Niedoczynność tarczycy	72	7 (9.72%)	1 (4%)/6 (12.77%)
Hyperthyroidism Nadczynność tarczycy	72	2 (2.78%)	2 (8%)/-
Dyslipidaemia Zaburzenia gospodarki lipidowej	67	39 (58.21%)	17 (73.91%)/22 (50%)
Disturbances in sex hormones[3] Zaburzenia gospodarki hormonów płciowych	51	14 (27.45%)	6 (30%)/8 (25.81%)
Low BMD Niskie BMD	67	6 (8.96%)	3 (12.5%)/3 (6.98%)
Abnormal IGF-1 Nieprawidłowe IGF-1	61	9 (14.75%)	6 (25%)/3 (8.11%)
Abnormal PTH Nieprawidłowe PTH	67	13 (19.4%)	6 (24%)/7 (16.67%)

1 Type of disturbances categorised according to results of available tests.
Rodzaje zaburzeń skategoryzowane w zależności od wyników badanych parametrów
2 Number of patients, who results of the tests were available to interpretation.
Liczba pacjentów, których wyniki ocenianych parametrów były dostępne
3 Sex hormones were measured and analysed in girls over 8 years old and boys over 10 years old.
Oceniono stężenie hormonów płciowych u dziewczynek powyżej 8 roku życia oraz u chłopców powyżej 10 roku życia.

at diagnosis is associated with weight disturbances, female survivors diagnosed at age 10 and under were more likely to be overweighed or obese.

In our study, underweight most frequently was observed in patients with brain tumours and sarcomas, overweight affects more patients with sarcomas and RMS. Obesity prevailed among older patients (over 14 years), although it also affects younger patients (2-5 years) and underweight dominated in the group of older patients (over 14 years). Underweight is most common in patients who are more than 5 years after treatment. In contrast, overweight occurred more frequently in patients who are less than 5 years after cessation of treatment. Unfortunately, because of small number of patients and diversity in types of tumours and types of treatment in our study group, our observations require further investigation in larger group of patients.

Thyroid function

In our study hypothyroidism was found in 9.27% of patients. All of these patients suffered from primary subclinical hypothyroidism (normal value of FT4 and elevated level of TSH). In Japanese study of 122 childhood cancer survivors in 21% of them hypothyroidism was found, 13% had primary and 7% had central hypothyroidism. One person suffered from both types

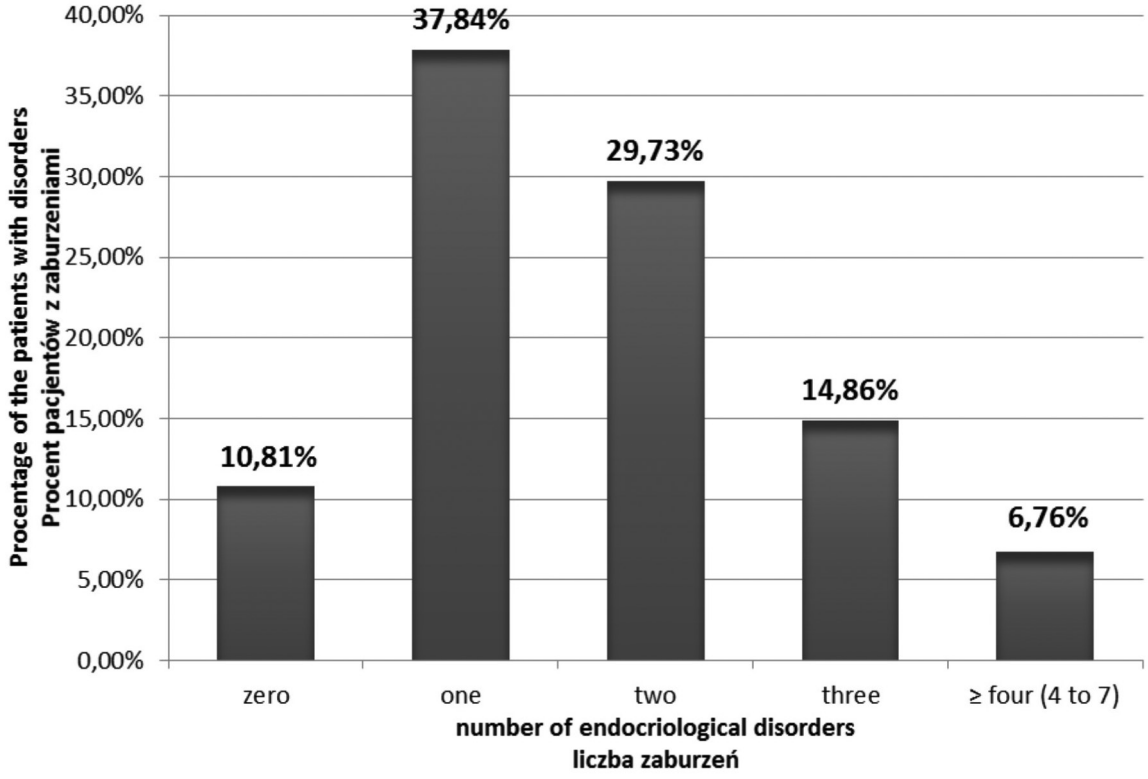

Fig. 1. Number of endocrinological disorders in the studied group
Ryc. 1. *Ilość zaburzeń endokrynologicznych w badanej grupie*

of hypothyroidism at the same time. Authors demonstrate that type of disorders depends on the diagnosis and therapy – all patients with central hypothyroidism were treated for brain tumours and the majority of patients with primary hypothyroidism (9 of 16) underwent neck irradiation before HSCT [5]. In our study group patients with subclinical primary hypothyroidism suffered from different types of cancers (brain tumours, RMS, neuroblastoma, PNET).

Among the risk factors for hypothyroidism most commonly noted are female sex, radiation therapy (especially cervical, neck and supraclavicular), radiation dose (> 20 Gy for primary and> 30 Gy for central hypothyroidism) and older age at tumour diagnosis [1]. In our study 6 of 7 patients with hypothyroidism were boys. All of these patients were treated with radiotherapy, none with neck irradiation. Also, age at diagnosis had no effect on the prevalence of disorders. Hypothyroidism was observed both in young children (2-5 years) and older (8-11 years).

Many authors describe the relationship between diagnosis, treatment and frequency of thyroid disorders. The most vulnerable are patients with a brain tumour, Hodgkin lymphoma, neuroblastoma who are undergoing cranial and neck irradiation [3,5,8]. On the other hand, other authors found no difference in incidence of hypothyroidism between different diagnoses [2]. In our study, 5 of 7 patients with hypothyroidism were treated for brain tumours and neuroblastoma.

Hyperthyroidism is a rare disorder occurring in the CCS [1]. Also in our study, only one patient with medulloblastoma (treated with radiotherapy) suffered from subclinical hyperthyroidism (normal value of FT4 and decreased level of TSH).

The incidence of thyroid disorders can be reduced by elimination of radiotherapy, which is not always possible, decrease of the radiation doses and thyroid protection against radiation [1]. Monitoring of patients and early treatment of detected disorders is very important.

Lipids profile

Lipid disorders are very important and common problems among CCS. In our study dyslipidaemia occurred in 39 (58.21%) patients. Hypercholesterolemia was diagnosed in 26 (38.81%), elevated level of LDL-C in 43.17%, low HDL-C in 12.12% and hypertriglyceridemia in 46.74% survivors. Overweight or obesity was found in 33.78% CCS. The results of our study emphasize that dyslipidaemia is one of the most frequent disturbances among CCS.

In a study conducted by Pietilä et al., who analysed brain tumours survivors, aged 3.8-28.7 years, 25% patients had hypercholesterolemia, 27% had raised LDL-C, 17% had low HDL-

Table IV. Patients with the most number of endocrinological abnormalities
Tabela IV. *Pacjenci z największą ilością zaburzeń*

No	Tumor type Typ nowotworu	Sex Płeć	Age at the time of the study Wiek w momencie badania	No of disturbances Liczba zaburzeń	List of disturbances Zaburzenia
1	Medulloblastoma	girl kobieta	17.5	7	Short stature, underweight, hypothyroidism, dyslipidaemia, delayed sexual maturation (decreased progesterone, decreased estradiol), low BMD, decreased IGF-1 Niskorosłość, niedobór masy ciała, niedoczynność tarczycy, opóźnione dojrzewanie, niskie BMD, obniżone IGF-1
2	Medulloblastoma	boy mężczyzna	18	7	Short stature, underweight, dyslipidaemia, low BMD, decreased IGF-1 and PTH Niskorosłość, niedobór masy ciała, dyslipidemia, niskie BMD, obniżone IGF-1 i PTH
3	Medulloblastoma	girl kobieta	18	6	Short stature, pituitary insufficiency (decreased FSH,LH,TSH), decreased estadiol, dyslipidaemia, low BMD, decreased IGF-1 Niskorosłość, niedoczynność przysadki mózgowej (obniżone FSH, LH,TSH), obniżony estadiol, dyslipidemia, niskie BMD, obniżone IGF-1
4	Ewing Sarcoma	girl kobieta	14	6	Short stature, underweight, ovarian failure (increased FSH, LH), decreased IGF-1 and PTH, low BMD Niskorosłość, niedobór masy ciała, uszkodzenie jajników (podwyższone FSH, LH), obniżone IGF-1 i PTH, niskie BMD
5	Embryonal RMS	boy mężczyzna	4.5	4	Low BMD, dyslipidaemia, decreased IGF-1 and PTH Niskie BMD, dyslipidemia, obniżone IGF-1 i PTH

C and 10% had increased triglycerides [11]. According to Lipshultz et al., the most frequent disorders among both children and adult CCS are elevated triglycerides and low HDL-C, while elevated total cholesterol and LDL-C are less common in cancer survivors [12].

Factors contributing to increased occurrence of dyslipidaemia, overweight or obesity are primarily corticosteroids , chemotherapy, younger age during therapy, higher doses of radiation, and also according to some authors, being a female [3,13]. Location of the tumour also seems to be relevant. The prevalence of early occurring lipid disorders, similar to other endocrine disorders, is higher in patients treated for brain tumours, especially midbrain or optic nerve tumours [4,5]. In these cases radiotherapy to the brain, growth hormone deficiency and damage of the hypothalamus/pituitary area have been proposed as possible mechanisms leading to the abnormal lipid profile in cancer survivors [4,12]. Other factors, such as chemotherapy, especially with cyclophosphamide or L- asparaginase, have also been implicated in dyslipidaemia [12].

There are still only few data about prevalence of particular lipid abnormalities among children CCS. High frequency of disorders observed in our study suggests the necessity of further research. Regular control of lipid parameters, not only among adult CCS, is essential for early preventing cardiovascular implication of dyslipidaemia. It is recommended to evaluate lipid profile every 2 years in CCS, the education about healthy lifestyle is also significant [12]. It should be remembered that the assessment of lipid parameters should be based on age-appropriate values. Applying norms for adults to children may result in overlooking some abnormalities.

Bone Mineral Density and parameters related to bone mass turnover

Numerous studies confirm that low BMD is important problem of childhood cancer survivors [2,5,14,15]. In our study 6 patients showed a very low BMD less than -2 and almost 30% of patients achieved BMD z-scores below or equal -1.

Miyoshi et al. analysed results of survivors of solid tumours, brain tumours and haematological diseases. In 42% of patients low BMD was found, therein osteopenia was diagnosed in 31% and osteoporosis in 11% patients. It also presents a difference in BMD according to the diagnosis. 58.3% of patients after treatment of brain tumour had incorrect BMD, compared to 40% in solid tumour survivors [5]. Latoch et al. showed no significant difference in low BMD values between survivors of solid tumour, leukaemia and lymphoma. BMD less or equal -1 was observed in 25% patients and BMD ≤-2‰ were found in 9% [2]. On the other hand van Waas in the NHL survivors study found no difference in BMD values between patients and controls [16].

There are numerous risk factors of decreased BMD, such as chemotherapy (steroids, methotrexate), radiation therapy (especially cranial, gonads, TBI), limited physical activity (which is a consequence of disease and therapy), poor nutrition, males, low lean mass and a young age at diagnosis [5,14,15]. There is no confirmation that the type of diagnosis has influence on the frequency of abnormality in BMD, but reduced BMD commonly affects patients after brain tumour and leukaemia [17]. Very important causes are endocrine disorders, as a consequence of disease and treatment. Several studies demonstrate correlations between GHD, hypogonadism and decreased BMD [5,18]. In our study we showed a positive correlation between BMD and IGF-1 ($r=0.41$, $p=0.002$), BMD and PTH ($r=0.27$, $p=0.036$), BMD and BMI SDS ($r=0.25$, $p=0.042$), BMD and height SDS ($r=0.44$, $p<0.001$).

Disorders of bone mineralization in young people at the age of puberty result in lower peak bone mass and osteoporosis in adulthood [5,15]. Therefore particularly important is monitoring of patients, replacement therapy of endocrinological deficiencies, proper diet enriched with calcium and vitamin D and regular physical activity [5,14,19].

Sex hormones

In our study group sex hormone disorders were found in 14 (27.45%) patients. The most common were primary hypogonadism and delayed puberty, defined as no evidence of puberty in girls above 15 years of age and in boys above 16 years of age. One of our female patients was diagnosed with pituitary insufficiency, which is not surprising considering tumour location and applied treatment (medulloblastoma treated with cranial irradiation).

In study conducted by Brignardello et al., gonadal dysfunction was one of the most common disorders. Primary hypogonadism was found in 13.33% males and 21.54% females. Authors suggest that in general men are more susceptible to gonadal dysfunction caused by chemotherapy and radiotherapy and that gonads of younger patients in both sexes (especially before puberty) seem to be less sensitive to the damage induced by cancer treatments [8]. Latoch et al. in their study also notice that younger females are more resistant to treatment-induced failure than older ones, because of increased numbers of follicles. The greatest damage therefore is related to prepubertal and postpubertal period [1].

In our study, out of 6 patients with gonadal failure, 4 were treated with radiotherapy to the pelvic or/and abdomen area and chemotherapy and other 2 only with chemotherapy (one person with bleomycin, viblastine and cisplatin; second one with vincristine, ifosfamide, adriamycin, actinomycin D). One of the most important risk factors of hypogonadism (understood as Leydig cell dysfunction in males or premature ovarian failure in females) is craniospinal irradiation, abdominopelvic irradiation and gonadal irradiation [1]. Chemotherapy is also significant, especially using alkylating agents, such as cyclophosphamide, ifosfamide, chlorambucil, melphalan, busulfan or cisplatin. Gonadal toxicity of these drugs is profound also in prepubertal period and depends on its cumulative doses [1,2].

In our study delayed puberty was diagnosed in 7 patients. Delayed puberty may be the clinical manifestation of hypogonadism in survivors treated before or during pubertal development. Patients with delayed puberty should have LH, FSH and estradiol/testosterone levels screened regularly. Additionally, annual assessment of pubertal development until sexual maturity using Tanner staging, is recommended [20,21]. Likewise it is important, that anti-cancer therapy can cause precocious puberty, which is due to the premature activation of the hypothalamus-pituitary-gonadal axis. Usually it is caused by cranial irradiation, which also in higher doses leads to combined hormonal pituitary deficiencies [22].

Conclusion

Almost all of the patients suffer from endocrinological abnormalities. In our study the most common are dyslipidaemia, overweight and disturbances in sex hormones. The results of our study indicates that the CCS require regular evaluation of lipids profile and sex hormones. The regular examination among CCS could improve their health status and quality of live. Particularly important is regular evaluation of endocrinological abnormalities in adult cancer survivors, who were treated in childhood. Most of those patients erase from their memory that they had cancer in childhood.

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