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Assessment of adrenal function in pediatric cancer survivors

Ocena funkcji nadnerczy u pacjentów pediatrycznych po leczeniu onkologicznym

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Abstract

Introduction: Oncological therapy can temporarily or permanently disrupt adrenal gland function. The aim of our study was to assess the function of adrenal glands in cancer survivors and to find the best diagnostic tools for it.

Material and methods: Sixty patients aged 1.2–14.9 years (mean 8.3 ±3.5) with diagnosed malignancies and 45 healthy children as controls were recruited to the study. Patients were assessed 0–8 years (mean 2.4 ±2.0 years) after the oncological therapy. In all patients fasting blood samples were collected to measure: glucose, sodium, potassium, cortisol, aldosterone, plasma renin activity (PRA), dehydroepiandrostenedione-sulphate (DHEA-S), adrenocorticotropic hormone (ACTH) and antibodies against the adrenal cortex (AAA). Moreover, 24-hour urinary free cortisol (UFC) was assessed. Test with synthetic ACTH was carried out with 250 μg in neuroblastoma and nephroblastoma patients and with 1 μg in other oncological patients.

Results: The levels of morning cortisol and sodium were significantly lower and blood glucose were higher in cancer survivors than in controls ($p = 0.006$, $p = 0.043$, $p = 0.008$). Basal laboratory tests confirmed adrenal insufficiency (AI) in 1 patient with neuroblastoma. Low-dose ACTH revealed AI in 3 patients with acute lymphoblastic leukemia. In the study group, UFC correlated with evening and midnight cortisol ($p = 0.001$, $p = 0.006$). In the control group UFC correlated with DHEA-S ($r = 0.623$, $p = 0.0001$). None of assessed parameters correlated with the time since the completion of oncological therapy.

Conclusions: The study confirmed possibility of developing asymptomatic AI in cancer survivors even several years after therapy. Instead of morning cortisol, classical diagnostic low-dose ACTH test seems to be an optimal tool for adrenal function's assessment.

Key words:
cortisol, acute lymphoblastic leukemia (ALL), adrenal insufficiency (AI), neuroblastoma (NBL), adrenocorticotropic hormone (ACTH) test.

Streszczenie

Wprowadzenie: Leczenie onkologiczne może przejściowo lub trwale zakłócić funkcjonowanie nadnerczy. Celem badania była ocena funkcji nadnerczy u dzieci po leczeniu onkologicznym.

Materiał i metody: Do badania zrekrutowano sześćdziesięciu pacjentów w wieku 1,2–14,9 roku, średnio 8,3 ±3,5 ze zdiagnozowanymi nowotworami i 45 zdrowych dzieci jako grupa kontrolna. Pacjentów oceniano 0–8 lat, średnio 2,4 ±2,0 lat po leczeniu onkologicznym. U wszystkich uczestników badania pobrano na czczo próbki krwi dla oceny: glukozy, sodu, potasu, kortyzolu, aldosteronu, aktywności reninowej osocza, siarczanu dehydroepiandrostendionu (DHEA-S), hormonu adrenokortykotropowego (ACTH) i przeciwciał przeciwko korze nadnerczy. Ponadto oceniono wydalanie kortyzolu w 24-godzinnej zbiórce moczu (UFC). U pacjentów z neuroblastomą i nefroblastomą przeprowadzono test z 250 μg syntetycznego ACTH, u pozostałych pacjentów onkologicznych zastosowano test z 1 μg ACTH.

Wyniki: Stężenia porannego kortyzolu i sodu były znacznie mniejsze, a stężenia glukozy we krwi większe u pacjentów onkologicznych niż w grupie kontrolnej ($p = 0{,}006$, $p = 0{,}043$, $p = 0{,}008$). Badania hormonalne potwierdziły niewydolność nadnerczy (AI) u 1 pacjenta z nerwiakiem zarodkowym. Test z 1 μg ACTH ujawnił AI u 3 pacjentów z ostrą białaczką limfoblastyczną. W grupie pacjentów onkologicznych UFC korelowało z wieczornym i nocnym kortyzolem ($p = 0{,}001$, $p = 0{,}006$). W grupie kontrolnej UFC

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korelowało z DHEA-S ($r = 0{,}623$, $p = 0{,}0001$). Żaden z ocenianych parametrów nie korelował z czasem od zakończenia terapii onkologicznej.
Wnioski: Badanie potwierdziło ryzyko rozwoju bezobjawowej AI u pacjentów pediatrycznych nawet kilka lat po terapii onkologicznej. Test z 1 μg ACTH wydaje się bardziej optymalnym narzędziem dla oceny czynności nadnerczy niż stężenie porannego kortyzolu.
Key words:
neuroblastoma, kortyzol, ostra białaczka limfoblastyczna, niewydolność nadnerczy, test z hormone adrenokortykotropowym (ACTH).

Introduction

Each year, approximately 400 000 children and adolescents (aged 0–19 years) globally are diagnosed with cancer [1]. The most common types are leukemias, brain tumors, lymphomas and solid tumors. Depending on the type of cancer, the overall 5-year survival rate ranges from 64.3% (acute myeloid leukemia) [2], approximately 80% (brain tumors) in several European countries [3] to 97.3% (Hodgkin's lymphoma) [1]. The survival has significantly increased e.g. in acute lymphoblastic leukemia (ALL) 5-year survival rate has increased from 10% in the 1960s to 77% in the years 1985–1994 [4], and up to 93.5% nowadays [5]. Early diagnosed malignancies can be effectively treated. Pediatric cancer survivors have a lifetime ahead of them and it is important to provide them a safe and good quality life.

Acute lymphoblastic leukemia has the highest incidence in pediatric population 3.7–4.9 cases per 100,000 children 0–14 years of age [6]. In our country every year 250–350 young patients have been diagnosed with ALL [7]. Neuroblastoma (NBL) is one of the most common childhood solid tumors occurring in 1 : 7000 children [8]. In infants it is the most common cancer. It accounts for 7–10% of all tumors in children and as much as 30–50% of tumors in newborns. Annually, 6–11 cases are diagnosed in 1 million children aged 0–15 years, 50% of NBL cases occur at the age of < 2 years, and 90% before the age of 5. In our country, 60–70 new cases are diagnosed annually [9]. For children diagnosed with neuroblastoma 5-year survival is approximately 64% [10]. Brain tumors in children are second to leukemia cause of pediatric malignancies and are the most common type of solid childhood cancer. The incidence of pediatric brain tumors ranges from 1.15 to 5.14 cases per 100,000 children, depending on country. The incidence of congenital brain tumours ranges approximately from 0.3 to 2.9 cases per 100,000 live births in different parts of the world [11]. Five-year survival rate from brain tumors in children is higher than in adults, and the global range is very wide (from 45% in Thailand to 80% in Sweden and Denmark) [3].

Chemotherapy, glucocorticosteroids (GCS), as well as radiotherapy of the head, neck and abdomen area used in oncological protocols are risk factors of adrenal disease. They may interfere temporarily or permanently with the function of the adrenal glands. Studies show that GCS therapy for more than 7 days in a dosage of equivalent hydrocortisone above 10 mg/m^2 per day causes suppression of the adrenal axis [12]. Secondary adrenal insufficiency may develop after abrupt discontinuation of GCS and after radiation therapy of the head area, especially in the dose above 30 Gy.

Disorders of an adrenal axis resulting from cancer treatment have not been thoroughly studied, although it can play a crucial role in i.e. regulation of metabolism, immune system, blood pressure, and stress response.

Aim of our study was to assess the function of adrenal glands in cancer survivors. We focused on screening and early detection of this disease before symptoms of adrenal insufficiency (AI) occur, which minimise the risk of adrenal crisis and improves quality of life of those patients.

Material and methods

Patients

Sixty patients with diagnosed malignancies, aged 1.2–14.9 years (mean age 8.3 ±3.5 years), treated in the Department of Oncology and Hematology in University Children's Hospital were recruited to the study in years 2019–2020. The control group comprised 45 healthy persons (3.6–14 years, with the mean age 8.7 ±3.12 years). Fifty-eight patients were referred to the Department of Pediatric and Adolescent Endocrinology for adrenal function assessment in complete remission of the neoplastic disease. Two patients who was on the therapeutic protocol revealed adrenal insufficiency and were enrolled to the study. Mean age of patients who completed oncological treatment was 6.76 ±3.34 years (1.23–15.07 years). In that group, 44 patients were diagnosed with ALL (73.34%), 2 patients with AML (3.33%), 2 patients with β-cell lymphoma (3.33%), 1 patient with Hodgkin lymphoma (1.67%), 4 patients with neuroblastoma (6.67%), 4 patients with nephroblastoma (6.67%), 1 with retinoblastoma (1.67%), 1 with rhabdomyosarcoma (1.66%) and 1 with germline tumor (1.66%). The clinical characteristic of patients included to the study and details of their therapy are presented in Table I.

All of them had received chemotherapy, 15 additionally radiotherapy, one hematopoietic stem cell transplantation. Six patients with solid tumors underwent surgical treatment. Nine patients with ALL and one with AML had prophylactic head radiotherapy, one patient had radiotherapy of the rhabdomyosarcoma in the region of the head – tumor of the left pterygo-palatal fossa, three patients with neuroblastoma and one patient with nephroblastoma had radiotherapy of the abdomen.

Patients were assessed once after oncological treatment. Time between completion of oncologic therapy and the assessment were as follows: in 25 patients (41.7%) up to 1.5 year, in 12 patients (20 %) 1.5–3 years, and in 23 patients (38.3%) more than 3 years.

The Local Ethical Committee approved the study (No. 1072.6120.74.2019 of April 29, 2019). All parents of the participants of our study and participants, who were older than 16 years signed an informed consent.

Table I. The clinical characteristic of oncological patients included to the study and details of their therapy

Type of disease (number of patients)	Median age [years]	Median of time from the end of the treatment [years]	Type of treatment	Number of patients in specific treatment
Hematologic cancer				
ALL (44)	8.51 ±3.55	7.35 ±2.85	Chemotherapy	6 (ALL IC BFM – 2002)
				37 (ALL IC BFM – 2009)
				1 (AIEOP BFM – 2017)
			Radiotherapy	9 (12 Gy in 8 fractions)
			HSCT	1
AML (2)	14.66	5.67	Chemotherapy	2 (AML-BFM – 2012)
			Radiotherapy and HSCT	1 (18 Gy in 12 fractions)
B-cell lymphoma (2)	12.9	2.7	Chemotherapy	Inter-B-NHL-ritux 2010 protocol (rituximab + cyclophosphamide, vincristine, prednisolone, doxorubicin and etoposide)
Hodgkin lymphoma (1)	9.42	2.4	Chemotherapy	OEPA 2 cycles (vincristine, etoposide, prednisone, doxorubicin) 4 cycles COPDac (cyclophosphamide, vincristine, prednisone, dacarbazine)
Solid tumors				
Nephroblastoma (4)	6.35	3.49	Chemotherapy and surgery	4 (SIOP 2001)
			Radiotherapy	1 (15 Gy in 10 fractions)
Neuroblastoma (4)	5.74	1.88	Chemotherapy + surgery	LINES 2011
			Chemotherapy + radiotherapy + surgery	COJEC and LINES 2011 Radiotherapy of the abdomen
			Chemotherapy + radiotherapy	LINES 2011 Photon radiotherapy 21 Gy in 14 fractions
			Chemotherapy + autologous HSCT + radiotherapy + surgery	SIOPEN Radiotherapy 21 Gy
Retinoblastoma (1)	6.6	4	Chemotherapy	VEC (vincristine + etoposide + carboplatin) CADO (vincristine + cyclophosphamide + doxorubicin)
Rhabdomyosarcoma (1)	14.9	0	Chemotherapy + radiotherapy	I2VA (ifosfamide, vincristine, actinomycin), ACCTIVE protocol (adriamycin, cyclophosphamide, carboplatin, topotecan, trofosfamid, idarubicine, vincristine, etoposide), GeTaV protocol (vinorelbina, gemcitabine, docetaxel), ToTem protocol (temozolomide and topotecan)
Yolk sac tumor	5.58	2.75	Chemotherapy + surgery	radiotherapy of the tumor consisted of 55.8 Gy in 31 fractions

Methods

In all participants of the study, fasting blood samples after upright standing were collected between 7.00 and 8.00 am for the determination of the following hormones: cortisol, aldosterone, plasma renin activity (PRA), dehydroepiandrostenedione-sulphate (DHEA-S), adrenocorticotropic hormone (ACTH) and antibodies against the adrenal cortex (AAA), as well as thyroid stimulating hormone (TSH), free thyroxin (fT4), and moreover glucose, sodium, potassium. In study group, test with low-dose (1 μg or 0.5 μg/m^2 BSA) synthetic ACTH was performed to assess adrenal reserve. In the patients with neuroblastoma or nephroblastoma – ACTH test was carried out with high dose of 250 μg. A basal cortisol level was assessed and then the synthetic ACTH was administered intravenously and again cortisol levels were assessed 20, 30 and 60 minutes after ACTH injection. Fasting glucose, sodium, potassium in serum samples were measured by standard biochemical methods, hormonal tests were performed by radioimmunological methods (ACTH, cortisol, DHEA-S, PRA, aldosterone), AAA was determined by ELISA tests. The morphology of adrenal gland was imaged using an ultrasound device. In cases of inconclusive ultrasound image – magnetic resonance imaging of the adrenal glands was used.

Statistical analysis

Statistical analysis was performed using the Stat-Soft Statistica 12 package using ANOVA with post-hoc Turkey test and linear and multivariate regression. Data are presented as mean ± standard deviation (SD) and $p < 0.05$ was used as statistically significant.

Results

All participants of the study presented with biochemical and clinical euthyrosis, which allowed for appropriate interpretation of further biochemical parameters. The level of morning cortisol was significantly lower in cancer patients than in controls ($p = 0.006$). Likewise, the sodium level was significantly lower in the study group than in healthy group ($p = 0.043$). Moreover, the level of fasting blood glucose was significantly higher in cancer patients than in the control group ($p = 0.008$). The rest assessed parameters did not differ between both groups (Table II).

Because the study and the control groups differed regarding the age of participants ($p = 0.001$) we took the age into consideration in our statistical analyses. In linear correlations only DHEAS correlated with the age in the study ($r = 0.292$, $p = 0.026$) as well as in the control group ($r = 0.623$, $p = 0.0001$). After adjustment to the age, in the study group there was a correlation between UFC and evening and midnight cortisol (respectively, $p = 0.001$, $p = 0.006$). In the control group UFC correlated with DHEA-S ($r = 0.623$, $p = 0.0001$) and after adjusting age UFC correlated with evening cortisol ($p < 0.001$).

Table II. The results of biochemical and hormonal tests and blood pressure in cancer patients and healthy controls

Parameter	Cancer survivors ($n = 60$)	Controls ($n = 45$)	p-value
Na [mmol/l]	138.8 ±1.3	139.3 ±1.5	0.04
K [mmol/l]	4.3 ±0.3	4.3 ±0.3	NS
Fasting blood glucose [mmol/l]	4.6 ±0.4	4.5 ±0.4	0.04
Systolic blood pressure [mmHg]	108.6 ±11.4	109.5 ±14.3	NS
Diastolic blood pressure [mmHg]	61.7 ±8.1	61.9 ±8.4	NS
ACTH [pg/ml]	35.0 ±22.9	39.7 ±30.9	NS
Cortisol 8.00 AM [ng/ml]	110.9 ±46.1	133.3 ±42.6	0.007
Cortisol 8.00 PM [ng/ml]	22.1 ±21.1	33.0 ±37.1	NS
Midnight cortisol [ng/ml]	16.3 ±24.5	18.8 ±23.4	NS
UFC [μg/day]	18.6 ±25.7	18.3 ±12.8	NS
DHEAS [μg/ml]	74.5 ±62.9	94.1 ±90.1	NS
Aldosterone [pg/ml]	144.1 ±106.5	149.6 ±95.5	NS
Plasma renin activity [ng/ml/h]	2.3 ±2.0	3.3 ±4.4	NS
Maximal cortisol in ACTH test [ng/ml]	239.1 ±46.1	Not assessed	

Basal laboratory test results confirmed AI in one patient with neuroblastoma aged 1.6 years old, who had elevated ACTH level 144 pg/ml (normal range 10–40 pg/ml) and low cortisol levels in diurnal profile, 8.00 am: 84.4 ng/ml (normal range 55–230 ng/ml), 08.00 pm: 15.7 ng/ml (normal range for 8 pm cortisol is < 50% of the value of normal range for 8 am cortisol). Based on these results AI was diagnosed, he was excluded from ACTH test and started hydrocortisone treatment. Infection (fever, diarrhea and CRP 128.9 mg/l) occurred after 3 months of hydrocortisone treatment onset. He developed seizure episode, hyponatremia (128 mmol/l) and hypoglycemia (1.4 mmol/l). The course of infection confirmed AI and patient required higher doses of hydrocortisone. In other patients with NBL, including the patient after unilateral adrenalectomy, we excluded AI on the base of ACTH tests.

The low-dose ACTH test confirmed impaired adrenal function in 3 children with ALL. Maximum cortisol releases were as follows: 170.1 ng/ml, 83.6 ng/ml, and 176 ng/ml. The first patient, a 7-year-old girl, ALL type common with AML/Tel+ was classified into standard risk (SR) group and was treated according to ALLIC 2009 protocol. Treatment was completed 2 years and 3 months prior to the study. Second patient, a 8.5-year-old boy, with common ALL, in the high-risk (HR) group, treated according to AIEOP 2017 protocol with dexamethasone. He developed temporary adrenal insufficiency after dexamethasone withdrawal and was treated with hydrocortisone (5–2.5–2.5 mg a day). He remains on the treatment protocol. Third patient, a boy aged 8.5 years old diagnosed with common ALL, intermediate (IR) group, was treated with ALLIC 2009 protocol. Treatment protocol was completed 3 years and 10 months prior to the study. Apart from the second patient with transient AI, patients presented with no symptoms of AI, which was diagnosed only because they were enrolled in the study. The transient AI was diagnosed at the time of an infection. It is worth underlining that all three had low levels of UFC, midnight cortisol and DHEA-S (UFC 12.7, < 5.0 and 12.8 μg/day), midnight cortisol (6, < 3.1 and 5 ng/ml) and DHEA-S (8, 8.7 and 28 μg/ml) in comparison with controls (mean levels of UFC for controls 17.9 μg/day, midnight cortisol for controls 19.5 ng/ml, and DHEA-S for controls 65 μg/ml).

Two patients with ALL had results of 1 μg ACTH analogue (®Synacthen) within the normal range but at the lower limit: 185 ng/ml and 187.6 ng/ml. First was a boy aged 10.8 years old with common ALL, IR group, treated with ALLIC 2009 protocol. Therapy was completed 3.3 years prior to the study. Second was a girl aged 13.6 years old with common ALL, HR group, treated with ALLIC 2009 protocol. She completed the treatment 1.5 year prior to the study. Neither of the children presented with AI symptoms but first boy had lower levels of UFC (< 5.0 μg/day) and midnight cortisol (5.4 ng/ml) in comparison with healthy controls, although the level of DHEA-S (78.8 μg/ml) was comparable to them. A girl had only UFC level (1.4 μg/day) lower than that of healthy persons (UFC 16.0 μg/day, midnight cortisol 5.4 ng/ml, and DHEA-S 34.8 μg/ml).

The girl with AML was 12.4 years old and completed treatment 8 years prior to the study. Her test results were as follows: ACTH 75.6 pg/ml (normal range 10–60 pg/ml), morning cortisol 55 ng/ml (normal range 55–230 ng/ml). However, test with 1 ug ACTH excluded AI, with the maximum cortisol release 223.4 ng/ml.

None of assessed parameters correlated with the time since the completion of oncological therapy.

One patient out of 15 (6%) who had radiotherapy of the abdomen had AI in comparison with 3 of all 60 patients (5%). Moreover one patient with ALL after prophylactic head radiotherapy had normal range cortisol release in 1 μg ACTH test, but at the lower limit. Our data is too narrow because the group was too small to investigate the effect of radiotherapy on adrenal function.

In all participants of the study, antibodies against the adrenal cortex were negative.

Ultrasound of the abdomen in all cancer patients revealed normal adrenal morphology apart from 1 patient with neuroblastoma (4.8 years old) in whom one adrenal gland has been excised.

Discussion

The symptoms of chronic adrenal insufficiency, which may be a complication of oncological treatment, are unusual and very often difficult to detect by caregivers and even treating physicians. They include general fatigue, loss of energy, malaise, weight loss, nausea, anorexia, failure to thrive, muscle and joint pain. Late manifestations are symptoms of orthostatic hypotension and hypoglycemia. In chronic primary adrenal insufficiency, cardinal sign is skin and mucous membranes pigmentation. Patients may also crave salt. DHEA-S deficiency causes absence of pubarche in children, reduced libido and dry skin. Therefore, it would be advisable to define uniform protocols for the assessment of adrenal function in children after oncological therapy.

In our study, only one patient developed symptoms of adrenal insufficiency (AI). It happened after dexamethasone withdrawal during the therapy of ALL according to AIEOP2017 protocol. AI diagnosed at the base of ACTH test and treated with hydrocortisone was temporary and lasted for one month. This example stresses an importance of the assessment of adrenal glands in children with ALL after the completing of corticosteroids. We did not include such patients to our study, but according to other authors, for example Salem *et al*. [13], AI lasts for a different length of time depending on the type of steroid used rather not on its dose. The doses of steroids in this study were as follows: dexamethasone (DXM) 6 mg/m^2 and prednisone (PDN) 60 mg/m^2. When converting DXM to PDN, it was a smaller dose (40 mg/m^2). Despite the fact, DXM dose was lower, it caused AI more often than PDN (75% vs. 50%) [13]. Felner *et al.* [12] examined ALL children after steroids withdrawal. They found AI in every patient within 2 weeks. What is more, 8 weeks after treatment, up to 70% of them still had AI. Longer observation was carried out by Peterson *et al.* [14]. They described AI as much as 8 months after steroid use (prednisone and dexamethasone). These studies emphasize the necessity to evaluate the adrenal glands in

"post-steroid" patients and apply quickly the proper treatment in AI patients. Therefore, prolonged infection, orthostatic hypotonia, joint and muscle pain during steroid withdrawal may suggest AI. It would be beneficial, in every patient to assess immediately adrenal axis. However, ACTH analogue (®Synacthen) test should not be routinely performed during infection. In severe states, patients could present with relative AI, which is difficult to diagnose. In severe states, random serum cortisol level below 10 μg/dl (280 nmol/l) in patient priory healthy indicates relative adrenal insufficiency. Cortisol concentration over 34 μg/dl (940 nmol/l) correlates with high risk of death. Using baseline cortisol level of below 35 μg/dl (965 nmol/l) to diagnose adrenal insufficiency in septic shock patients, the sensitivity was 85%, the specificity was 62% and the accuracy was 72% [15]. The other patients in our study did not present with AI symptoms. Therefore, it is important to use a realistic tool to find patients with chronic AI. Referring to literature, morning cortisol (8 am) is a common clinical assessment of the function of hypothalamic-pituitary-adrenal axis (HPAA). Serum cortisol levels greater than 13 μg/dl (365 nmol/l) have been reported to predict normal adrenal function. However, because it is not standardized for wakefulness, it is not necessarily the highest concentration of the day. Moreover, it can be modulated by anxiety and sleep [16]. On the base of our results rather UFC, midnight cortisol and DHEAS seem to be good parameters in the monitoring of adrenal gland function. DHEA-S is an adrenal marker, which shows early adrenal recovery from post-steroid treatment inhibition. Salem study [13] demonstrated that DHEA-S was back to normal 2 weeks before normal adrenal function. Our study presents correlation between DHEA-S and UFC what makes the DHEAS a good marker of evaluation of adrenal function. Another parameter of adrenal assessment is midnight cortisol. It correlated with UFC. Therefore, it could be used in an initial diagnosis. However, the simplest and most convenient tool from mentioned above remains DHEA-S assessment, as a single blood draw, independently of the food intake, and the time of the day.

The question remains: why was morning cortisol significantly lower in cancer survivors compared to healthy controls? Also, even after exclusion of the patients with diagnosed AI this difference was still significant ($p = 0.039$). Interestingly, other parameters assessing HPAA did not differ between both groups. There are clinical data that exposure to childhood trauma may contribute to long-lasting alterations in HPA activity, therefore cancer survivors can present with persistent dysregulation of the HPAA in adult life. Gordijin et al. reported that ALL survivors have an enhanced of negative feedback mechanism [17]. That can explain why low levels of morning cortisol did not correspond with the rest parameters assessing adrenal glands function nor with the results of 1 μg ACTH analogue (®Synacthen) test.

Next issue is, in which groups of cancer survivors does the risk of AI exist? Our data are in accordance with the literature and indicate ALL and NBL survivors as groups at risk of AI.

However, most authors reported that in ALL patients, a predominantly transient AI associated with steroid withdrawal was to be expected. Our data indicate that AI can also develop several years after completing oncological treatment. The detailed data regarding the late assessment of ALL survivors were presented in our previous study (in press).

In the van Waas study, adrenal function after adrenalectomy was investigated in 67 adult long-term survivors of nephroblastoma and 36 survivors of neuroblastoma. Patients underwent 1 μg ACTH analogue (®Synacthen) test. They concluded that there was no adrenal insufficiency in survivors of nephroblastoma and neuroblastoma. Patients after unilateral adrenalectomy had higher basal cortisol and ACTH levels, compared with survivors with both adrenals intact [10]. Our study presented one out of 4 patients with neuroblastoma, who developed AI early, on treatment protocol. This suggests necessity of further investigation of AI in patients with this type of cancer. In patients with nephroblastoma, there were no AI or subclinical AI.

Unfortunately, we did not have patients after the therapy of brain tumors, but in accordance with the literature the problem of dysfunction of HPAA after the completing the oncological therapy exists and is important for the further life in that group of patients. There were several studies of ACTH deficiency in brain tumors. Gal *et al.* found 13.3% of secondary AI in children with brain tumors localized in suprasellar region. Two patients out of 166 had transient HPAA dysfunction, probably after GCS withdrawal. Central adrenal insufficiency occurs frequently in craniopharyngiomas (64%). However, it has decreased after treatment preference changes to less invasive surgery with the use of radiotherapy and chemotherapy [18].

In other neoplasms (except for ALL, brain tumors, and neuroblastoma) there may be low risk of developing of AI, but we must always be vigilant with symptoms suggesting AI due to a risk of crisis, poor quality of life, etc.

What is important in clinic, the treatment of primary AI differs from secondary AI. Central adrenal insufficiency is treated with hydrocortisone 8–10 mg/m^2/24 hours in 2–3 divided doses (decreasing during the day), without fludrocortisone. The treatment of primary adrenal insufficiency includes hydrocortisone 8–17.5 mg/m^2/24 hours orally in 3 doses and fludrocortisone 0.05–0.2 mg/24 hours under blood pressure control and electrolytes. In chronic AI it is crucial to educate patients and their families how to prevent adrenal crisis. In case of infection or stressful situation, it is necessary to increase the dose of GCS.

The chronic dysregulation of HPPA as a consequence of childhood stress, which is as life-threatening disease can significantly affect metabolism. This mechanism could be responsible for obesity and metabolic dysregulation often observed in childhood ALL survivors. In large cohort study [19] of 784 ALL survivors, followed for more than 25 years from diagnosis, metabolic syndrome was identified in 259 survivors (33.6%). Fasting hyperglycemia or treatment for hyperglycemia was prevalent in 246 ALL survivors (31.4%). Although steroid-induced transient hyperglycemia in children with cancer often resolves after cessation of therapy, prolonged hyperglycemia with progression to permanent diabetes has been reported [20]. We found that fasting glucose level may increase as early as 5 years after the

end of ALL treatment, indicating an early onset of metabolic complications in survivors' life.

Study limitations

The study group was heterogeneous regarding the diagnosis of cancer and the time from cessation of therapy, however we used unified protocol for the assessment of adrenal glands function. The groups of patients with particular diagnosis were not numerous, what for sure cannot allow to assess the incidence of AI for each diagnosis. ACTH tests were not carried in healthy children according to the decision of The Local Ethical Committee, therefore we assumed that their adrenal function is normal.

Conclusions

The study confirmed the possibility of developing late AI and/or metabolic complications after oncological treatment. Chronic AI may be omitted and appear several years after remission. On the base of our data it seems to be important to check adrenal function in childhood ALL and neuroblastoma survivors, while in other neoplasms, the problem is less likely. Not morning cortisol, but the classical low-dose ACTH test should be a diagnostic tool for adrenal assessment. However, DHEA-S seems to be a good screening marker. Adrenal function screening as well as metabolic assessment should be a part of post-oncologic check-up.

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