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The Assessment of the Hypothalamic-Pituitary-Adrenal Axis After Oncological Treatment in Pediatric Patients with Acute Lymphoblastic Leukemia

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What is already known on this topic?

Acute lymphoblastic leukemia (ALL) is the most common malignancy in children. Treatment of ALL consists of high-dose corticosteroid therapy with the aim of suppressing the hypothalamic-pituitary-adrenal axis (HPAA). Despite successful transient HPAA suppression, survivors of childhood ALL can present with persistent dysregulation of the HPAA in adult life.

What this study adds?

Our data highlights the importance of post-chemo/radiotherapy follow-up assessment of adrenal gland function within five years of therapy cessation. Dehydroepiandrostendione-sulfate seems to be a good marker of adrenal gland function after oncological treatment. The disturbances of the adrenal axis may be associated with early metabolic complications in ALL survivors.

Abstract

Objective: Oncologic treatment can affect the adrenal glands, which in stressful situations may lead to life threatening adrenal crisis. The aim of the study was to assess adrenal function in pediatric acute lymphoblastic leukemia (ALL) survivors and to identify the best markers for this assessment.

Methods: Forty-three ALL survivors, mean age 8.5 ± 3.6 years and 45 age and sex-matched healthy controls were recruited to the study. ALL patients were assessed once within five years following oncological treatment completion. Fasting blood samples were collected from all participants to measure: fasting blood glucose (FBG); cortisol; aldosterone; plasma renin activity (PRA); dehydroepiandrostendione-sulfate (DHEA-S); and adrenocorticotropic hormone (ACTH). Moreover, diurnal profile of cortisol levels and 24-hour urinary free cortisol (UFC) were assessed. ALL survivors underwent a test with 1 ug of synthetic ACTH.

Results: The study revealed lower level of PRA (1.94 ± 0.98 ng/mL/h vs 3.61 ± 4.85 ng/mL/h, p = 0.029) and higher FBG (4.6 ± 0.38 mmol/L vs 4.41 ± 0.39 mmol/L, p = 0.018) in the ALL group compared to controls. UFC correlated with evening cortisol (p = 0.015, r = 0.26), midnight cortisol (p = 0.002, r = 0.33), and DHEA-S (p = 0.004, r = 0.32). UFC also correlated with systolic and diastolic blood pressure (p = 0.033, r = 0.23 and p = 0.005, r = 0.31, respectively). The ACTH test confirmed impaired adrenal function in 4/43 ALL survivors (9%). Two of the patients who needed permanent hydrocortisone replacement had low UFC, midnight cortisol and DHEA-S levels.

Conclusion: These results highlight the importance of reviewing adrenal gland functionality after chemo/radiotherapy in ALL survivors. DHEA-S proved to be a good marker to assess the adrenal glands after oncological therapy. Post-treatment disturbances of the adrenal axis could be associated with metabolic complications.

Keywords: Adrenal insufficiency, acute lymphoblastic leukemia, cortisol, dehydroepiandrostendione-sulfate, adrenocorticotropic hormone test

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Introduction

The incidence of childhood cases of acute lymphoblastic leukemia (ALL) between the ages of 0-14 years old is 3.7 to 4.9 per 100,000 (1). In Poland 250 to 350 young patients are diagnosed with ALL every year (2). Fortunately, the 5-year survival rate of ALL has greatly increased, due advances in medical treatment consisting of multi-agent chemotherapy, radiotherapy and hematopoietic stem-cell transplantation (HSCT). The 5-year survival rate has increased from 10% in the 1960s to 77% in 1985-1994 (3), up to 93.5% nowadays (4).

The first- and second-line treatment for ALL is chemotherapy in addition to radiotherapy in select patients to target the central nervous system (CNS). Destroying cancerous cells by chemotherapy and radiotherapy leads to the consequent damage of healthy cells resulting in endocrine dysfunction. Corticosteroids are the key component of ALL chemotherapy treatment plans and is the first drug to be used to induce remission. It is a cytotoxic agent that arrests growth and induces apoptosis of lymphocytes and thus, like chemotherapy and radiotherapy, can affect the proper functioning of the endocrine system. Research is lacking regarding the effects of treatment on the adrenal axis, which may become life threatening. Adrenal insufficiency (AI) is a chronic and subclinical condition that can occur insidiously in stressful situations and lead to a clinical emergency known as an adrenal crisis.

The aim of this study was to assess the frequency of AI in patients with ALL who had completed oncological treatment, to identify the most useful biochemical and hormonal parameters assessing the adrenal reserve, and to assess adrenal imaging, and antibodies against the adrenal cortex (AAA) in ALL survivors in comparison with healthy controls. Adrenal reserve tests enable early detection of AI and by doing so, minimize the risk of an adrenal crisis developing. Therefore, the secondary aim of the study was to prevent the consequences of adrenal dysfunction in patients after oncological treatment.

The hypothesis of our study was that oncological treatment protocols that include corticosteroids, chemotherapy, and radiotherapy all influence adrenal function and morphology.

Methods

Patients

Forty-three patients treated for ALL and in complete remission, aged 1.17-14.83 years (mean age 8.51 ± 3.55 years) were recruited by the department of pediatric oncology and hematology in Cracow. All consecutive ALL survivors admitted to the oncology clinic between 2019 and 2020 were examined with consent. Any patient with adrenal disease was excluded from the study. A control group of 45 healthy age- and sex-matched children and adolescents were selected among patients, who where diagnosed in the department of pediatric and adolescent endocrinology due to short stature, without other comorbidities including endocrinopathies (aged 3.6-14 years, with the mean age 8.78 ± 3.12 years).

All patients were referred for assessment of adrenal function at the department of pediatric and adolescent endocrinology. All patients in the study group had completed treatment for ALL at a mean age 7.35 ± 2.85 years (range, 1.62-13.8 years). The mean time since the cessation of oncological therapy was 2.4 ± 1.9 years (range, 0.25-7.17 years). In the study group, nine patients (21%) were stratified as high risk (HR) ALL, 27 patients (61%) as intermediate risk (IR) ALL, and seven patients (16%) as standard risk (SR) ALL, in accordance with the ALL stratification protocol. There were 40 patients with B line ALL and three patients with T line ALL. All patients in the research group underwent therapy according to the subsequent prospective randomized trials of the International Berlin-Frankfurt-Münster Study Group (I-BFM-SG) for the management of children and adolescents (up to 18 years of age) with *de novo* diagnosed ALL: ALL-IC BFM 2002 (n = 6 patients) and ALL-IC BFM 2009 (n = 37 patients).

There are five major steps/components of treatment of newly diagnosed ALL. The first step is (1) a remission induction, lasting about five weeks, which is the first block of chemotherapy including steroids, followed by step (2) an early intensification lasting for 4-8 weeks depending on individual stratification by risk group. The third phase of treatment (8-17 weeks) is (3) a consolidation, which aims to eradicate the submicroscopic residual disease that remains after a complete remission is obtained and to maximize synergy and minimize drug resistance, followed by (4) a reinduction therapy (seven weeks). The final part of chemotherapy is (5) a maintenance chemotherapy up to the 104th week of the whole treatment (about two years).

The important component of the treatment of ALL is prophylaxis for patients with subclinical CNS disease or treatment of patients with clinical CNS. It includes direct intrathecal administration of chemotherapy, systemic administration of chemotherapy able to penetrate the blood-brain barrier, and cranial radiation (5).

In these protocols steroids are given two or three times depending on risk group. During the induction treatment/phase, prednisone/prednisolone is administrated at 60 mg/m^2/d, PO/IV, in three single doses per day on days 1-28. This is the first four weeks of the whole therapy. From day 29 tapering to withdrawal of prednisone is used over nine days by halving the dosage every three days in three doses, with the highest dose given in the morning. During the reinduction treatment/phase, dexamethasone 10 mg/m^2/d, PO/IV is given in three single doses for 21 days, on days 1-21. From day 22 taper down stepwise is used to withdrawal over nine days by halving the whole dosage every three days in three doses, giving the highest dose in the morning. This usually occurs at between 18th-30th week of the whole therapy. Additionally, patients who were stratified to HR group received dexamethasone 20 mg/m^2/d, PO/IV, in three divided doses for five days, on days 1-5 in the consolidation phase, at about 10-14 weeks of the whole therapy. The duration of overall therapy in all patients is 104 weeks (24 months). Therefore, all the study patients were at least 74 weeks (about 16 months) after steroid use in the therapy.

In addition to chemotherapy, certain patients with ALL need radiation therapy to prevent or treat their disease. According to the ALL-IC BFM 2009 protocol, prophylactic cranial radiotherapy (CRT) is given to patients without an involvement of CNS or a suspicion/subclinical form of CNS involvement only in patients with T-ALL and white blood cells > 100,000/μL and in patients with ALL stratified as HR non-transplanted (except in B-cell precursor ALL only, due to prednisolone poor responders). It is used only for age ≥1 year (12 Gy), with age attained at the start of irradiation being determinative. In those groups of patients, prophylactic RT is administrated in the first 1.5 weeks after the completion of the reinduction therapy. In previous protocol ALL-IC BFM 2002, prophylactic CRT was used in all SR/IR T-ALL and all non-transplant HR patients without CNS involvement or with only suspicion of CNS involvement, age ≥1 year with the dose of 12 Gy.

All patients with ALL and involvement of CNS received therapeutic CRT at age-adjusted dosage, with age attained at the start of irradiation being determinative, for age ≥1 year. The doses are: for patients aged ≥1 < 2 years 12 Gy; and for patients aged ≥2 years 18 Gy. In those groups of patients therapeutic RT is administrated in the first 2.5 weeks after the completion of the reinduction therapy.

Therefore, all our HR patients (9) were at least one year after prophylactic CRT (12 Gy in eight fractions). None of them needed therapeutic CRT.

According to both the ALL-IC BFM 2002 and ALL-IC BFM 2009 protocols, allogeneic HSCT is recommended for selected subgroups of HR patients on the basis of prognostically unfavorable constellations of disease biology and response quality. One patient in the HR group had to be referred for allogeneic HSCT.

All participants in this study and parents of those under the age of 16 were consented and relevant documentation was signed. The study was then approved by the Jagiellonian University Local Ethical Committee (no. 1072.6120.74.2019, date: 29.04.2019).

All participants had fasting blood samples collected between 7.00 and 8.00 am after waking in order to test for the following: cortisol, aldosterone, plasma renin activity (PRA), dehydroepiandrostendione-sulfate (DHEA-S), adrenocorticotropic hormone (ACTH), AAA, fasting blood glucose (FBG), sodium and potassium. The 24-hour urine was collected to assess free cortisol excretion. Additionally, the study group underwent a low dose (1 μg or 0.5 μg/m^2 BSA) synthetic ACTH test to assess the adrenal reserve. A basal cortisol level was analyzed and then the synthetic ACTH was administered intravenously. After administration, the cortisol levels were measured at 20, 30, and 60 minutes post ACTH injection. Standard biochemical methods were used to test FBG, sodium and potassium levels, while radioimmunological methods in-house that were employed to test for the hormones ACTH (BRAHMS, Germany), cortisol (Beckmann Coulter, Inc., Immunotech, Czech Republic), DHEA-S (Siemens, USA), PRA (Beckmann Coulter, Inc., Immunotech, Czech Republic), aldosterone (Beckmann Coulter, Inc., Immunotech, Czech Republic), and urine free cortisol (Siemens, USA). The AAA concentration was analyzed by enzyme-linked immunosorbent assay with isotope label sets from Brahms (Germany). The morphology of the adrenal gland was investigated using ultrasound and magnetic resonance imaging.

In order to analyze the influence of the duration of remission on the results obtained, the patients were divided into the following groups: 1) up to 2 years remission time [22 patients (51.2%)]; 2) 16 patients (37.2%) in the period 2-5 years in remission; and 3) 5 patients (11.6%) above > 5 years of remission.

Statistical Analysis

Statistical analysis was performed using the Statistica 13.1 64-bit package (StatSoft, Poland, Kraków) using Student's t-test and ANOVA with post-hoc Tukey test and linear and multivariate regression. A value of $p < 0.05$ was assumed to indicate statistical significance.

Results

The study revealed significantly lower level of morning PRA when standing upright (p = 0.029) and significantly higher levels of FBG (p = 0.018) in the ALL study group in comparison to the control group. The other hormonal and biochemical parameters did not differ between groups (Table 1).

In the ALL study group, there were significant positive correlations between urinary free cortisol (UFC) and evening (8.00 pm) cortisol levels (p = 0.016, r = 0.26), midnight cortisol levels (p = 0.002, r = 0.33), and DHEA-S (p = 0.004, r = 0.32). Moreover, UFC also correlated positively with systolic blood pressure (SBP) (p = 0.033, r = 0.23) and diastolic blood pressure (DBP) (p = 0.005, r = 0.31). With age taken into consideration, correlations between UFC and midnight cortisol levels (p = 0.003), and between UFC and DHEA-S (p = 0.008) were significant. The linear positive correlation between UFC and midnight cortisol levels as well as UFC and DHEA-S in ALL survivors are presented in Figure 1 and 2. Additionally, the correlation between UFC and DBP remained statistically significant after age adjustment (p = 0.008). The linear positive correlation between UFC and DBP in ALL survivors is presented in Figure 3. Furthermore, there was also a positive correlation between FBG and SBP (p = 0.035, r = 0.23) in the ALL group. The linear positive correlation between FBG and SBP in ALL survivors is presented in Figure 4. All analyzed parameters did not differ between groups of patients with ALL with regards to the remission time. Moreover, all analyzed parameters did not differ between groups of patients with ALL with regards to groups stratified by intensity of treatment.

In the control group, morning cortisol levels correlated positively with UFC (p = 0.01, r = 0.38). There were also positive correlations between midnight cortisol levels and DHEA-S (p = 0.045, r = 0.33), midnight cortisol levels and SBP (p = 0.006, r = 0.40), and midnight cortisol levels and PRA (p = 0.0002, r = 0.52). Similarly in the ALL study group, there was a statistically significant correlation between UFC and evening cortisol levels (p = 0.0007, r = 0.57), between UFC and midnight cortisol levels (p = 0.046, r = 0.31), between UFC and DHEA-S (p = 0.038, r = 0.35), between UFC and SBP (p = 0.019, r = 0.36), and between DHEA-S and DBP (p = 0.028, r = 0.34). Furthermore, in the control group, a significant negative correlation between UFC

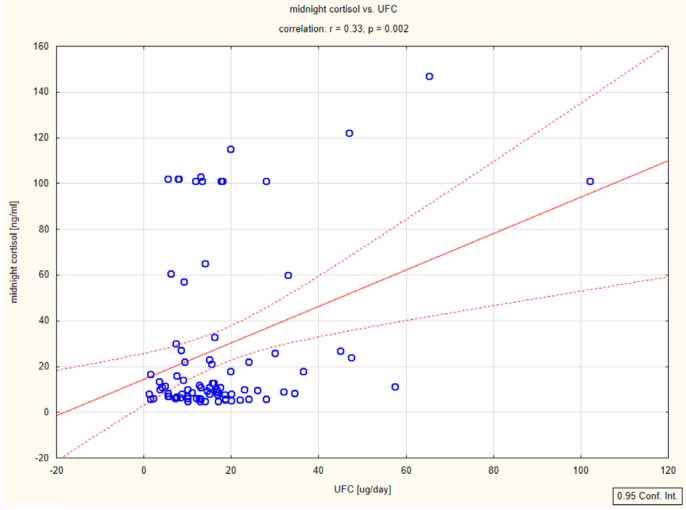

Figure 1. The linear positive correlation between 24-hour UFC and midnight cortisol in childhood acute lymphoblastic leukemia survivors

UFC: urinary free cortisol

Table 1. The results of biochemical and hormonal tests and blood pressure in ALL survivors and in controls

Parameter	ALL survivors (n = 43)	Controls (n = 43)	p
Na (mmol/L)	138.8 ± 1.4	138.9 ± 1.4	NS
K (mmol/L)	4.3 ± 0.2	4.4 ± 0.2	NS
Fasting blood glucose (mmol/L)	4.6 ± 0.4	4.4 ± 0.4	0.02
Systolic blood pressure (mmHg)	109.7 ± 11	105.2 ± 13	NS
Diastolic blood pressure (mmHg)	61.5 ± 8	60.3 ± 8	NS
ACTH (pg/mL)	32.9 ± 18.7	32.4 ± 17.7	NS
Cortisol 8.00 AM (ng/mL)	112.7 ± 41.4	127.5 ± 42	NS
Cortisol 8.00 PM (ng/mL)	19.1 ± 15.7	29.2 ± 37.5	NS
Midnight cortisol (ng/mL)	16.3 ± 25.4	19.5 ± 25.8	NS
UFC (µg/day)	17.9 ± 13.3	14.9 ± 10.6	NS
DHEA-S (µg/mL)	81.2 ± 63.1	65.1 ± 79.4	NS
Aldosterone (pg/mL)	143.3 ± 111	149.8 ± 101.8	NS
Plasma renin activity (ng/mL/h)	1.9 ± 1.0	3.6 ± 4.9	0.03
Maximal cortisol in ACTH test (ng/mL)	246.4 ± 44.3	Not assessed	

DHEA-S: dehydroepiandrostendione-sulfate, ALL: acute lymphoblastic leukemia, ACTH: adrenocorticotropic hormone, UFC: urinary free cortisol

and aldosterone (p = 0.043, r = -0.31) was seen. However, in spite of the correlations between midnight cortisol levels and SBP (p = 0.0098), as well as in midnight cortisol levels and PRA (p = 0.0002), all these correlations became statistically insignificant when patient age was taken into account. Interestingly, there was a positive correlation between DHEA-S and SBP (p = 0.002, r = 0.57), which remained significant (p = 0.0001) after adjusting for subject age. The linear positive correlation between DHEA-S and SBP in healthy patients is presented in Figure 5.

The ACTH test confirmed impaired adrenal function in four children. The first patient with AI was a girl aged 7 years with common ALL with AML/Tel+, stratified into the SR group and treated according to the ALL-IC BFM 2009 protocol. The time in remission prior to adrenal investigations was 2 years and 3 months. She was diagnosed with chronic AI due to our investigations as her maximal cortisol level with the ACTH test was 170.1 ng/mL and therefore treatment with hydrocortisone was initiated. The second patient was an 8-years and 7-months old boy, diagnosed with common ALL, stratified to the IR group, and treated with the ALL-IC BFM 2009 protocol. The time in remission prior to adrenal investigations was 3 years and 10 months. In spite of a lack of signs of AI before our investigations, he was also diagnosed with chronic AI with maximal cortisol level on ACTH test of 176 ng/mL and so hydrocortisone treatment was initiated. Simultaneously with the results of ACTH test confirming AI, both patients had low level of UFC (12.7 and 12.8 µg/day), midnight cortisol levels (6 and 5 ng/mL) and DHEA-S (8 and 28 µg/mL) in comparison to all the other ALL survivors and controls (respectively, mean UFC 17.9 and 14.9 µg/day, mean midnight cortisol levels 16.3 and 19.5 ng/mL, mean DHEA-S 79.4 and 65 µg/mL).

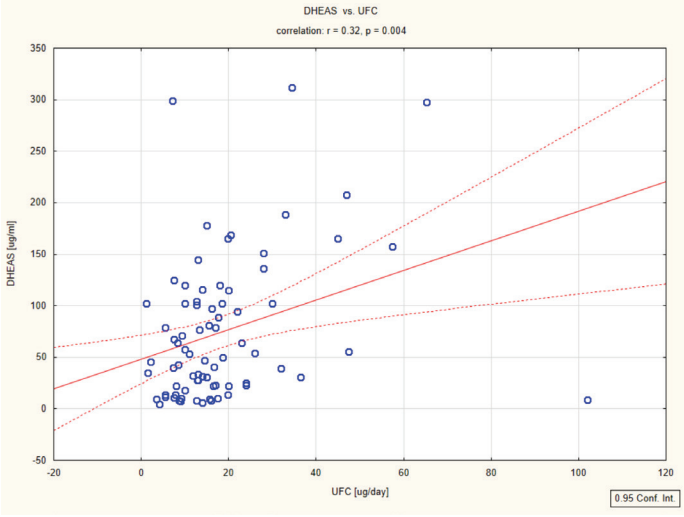

Figure 2. The linear positive correlation between 24-hour UFC and DHEA-S in childhood acute lymphoblastic leukemia survivors

UFC: urinary free cortisol, DHEA-S: dehydroepiandrostendione-sulfate

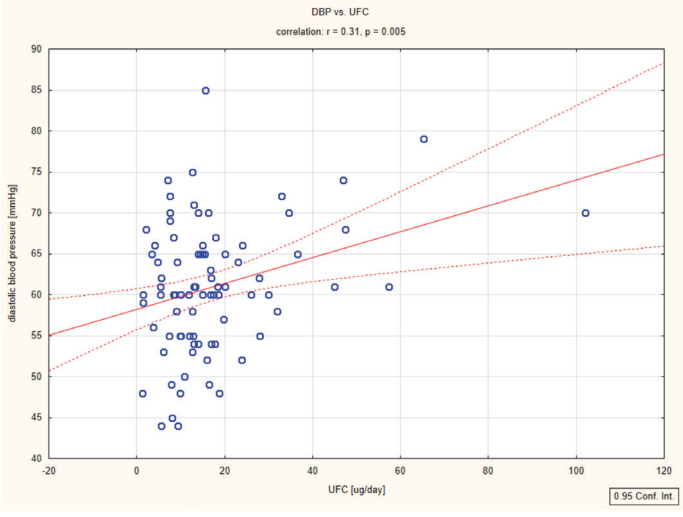

Figure 3. The linear positive correlation between 24-hour UFC and DBP in childhood acute lymphoblastic leukemia survivors

UFC: urinary free cortisol, DBP: diastolic blood pressure

Two additional patients had normal ACTH results but at the lower limit and displayed no AI symptoms. Maximal cortisol levels were respectively 185 ng/mL and 187.6 ng/mL. The first patient was a 10-years and 9-month old boy, with common ALL, in the IR group, treated with the ALL-IC BFM 2009 protocol. The time in remission prior to adrenal investigations was 3 years and 4 months. The second patient, was a 13-years and 7-months old girl with common ALL, in the HR group, treated with the ALL-IC BFM 2009 protocol. Her time in remission prior to adrenal investigations was 1.5 years. Both patients were advised to take hydrocortisone

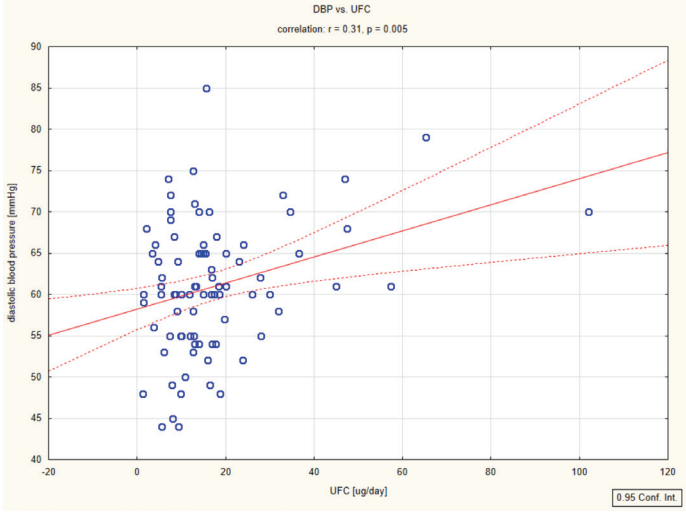

Figure 4. The linear positive correlation between fasting blood glucose and systolic blood pressure in childhood acute lymphoblastic leukemia survivors

UFC: urinary free cortisol, DBP: diastolic blood pressure

supplements in stressful situations. In summary, it appears that the time from completing treatment does not associate with the development of AI.

AAA were not found in any patients. Ultrasound of the abdomen in ALL survivors revealed normal adrenal morphology.

Discussion

The aim of treatment in patients with ALL is for complete disease eradication. First and second line treatment regimens for ALL consist of multi-agent chemotherapy, radiotherapy and, in select subgroups, HSCT. As mentioned previously, cancerous cells are killed and consequently healthy cells are also negatively impacted leading to side effects, such as endocrine dysfunction. Additionally, improper functioning of the adrenal axis can arise as a result of corticosteroid treatment and radiotherapy affecting the CNS.

Glucocorticoids are the key component of ALL chemotherapy protocol treatment regimens and is the first line treatment used to induce remission. The cytotoxic agents of choice are prednisolone/prednisone or dexamethasone which arrest cell growth and induce apoptosis in lymphocytes. Dexamethasone has proven efficacy in CNS penetration and is associated with reduced risk of relapse, but additionally it is associated with increased incidence of toxicities, including avascular necrosis, infection, and linear growth reduction (5,6). Glucocorticoid therapy is highly effective in suppressing the hypothalamic-pituitary-adrenal axis (HPAA) and can cause great effect in as little as five days of treatment (7,8). Therefore, abruptly stopping therapy can lead to secondary AI, which is a life-threatening condition. In a study conducted by Einaudi et al. (9) in 2008, 64 children with ALL underwent low dose ACTH (LD-ACTH) stimulation 24 hours after the last steroid administration. In the event of abnormally low cortisol levels during the LD-ACTH test, the test was repeated every 1-2 weeks until the cortisol values were normal. Adrenal suppression occurred in 52/64 (81.5%) patients and 7-14 days later, the ACTH test result revealed reduced morning cortisol levels in 8/52 (15.4%) patients in addition to an impaired test response in 12/52 (23%) patients. Normal adrenal reserve appeared in all patients within 10 weeks. There were no differences between the patients treated with prednisolone or dexamethasone. Clinical AI appeared in 35% of patients with impaired cortisol values in the first test which differed to results presented in a study by Salem et al. (10). These authors assessed HPAA function at different point in time: before starting therapy, after finishing therapy, and every two weeks after corticosteroid treatment until the adrenal axis recovered. They found that withdrawal syndrome occurred more frequently in patients treated with dexamethasone (75% of patients) than in those treated with prednisolone (50% of patients). The recovery time of the adrenal axis was twice as long with dexamethasone than with prednisolone. Similar results were presented by Mahachoklertwattana et al. (11). In a study by Felner et al. (12), 30% of children who received four weeks of dexamethasone had suppressed adrenal glands for 4-8 weeks. Comparatively, in a study by Petersen et al. (13), adrenal axis suppression was seen lasting 2.5-8 months in 41% of patients who received five weeks prednisolone in the induction phase and three weeks dexamethasone in the re-induction phase. The ALL survivors included in our study were in complete remission and were at least three months after the completion of oncological therapy, therefore at least 1.5 year after steroids use. All these patients were treated with prednisolone and dexamethasone according to the the ALL-IC BFM 2002 or ALL-IC BFM 2009 protocols. Conducted ACTH tests confirmed impaired adrenal function in four children (9%). Two of these children with chronic AI had completed two years of oncological therapy and the other two, who were 1.5 and 3 years post ALL therapy completion, had test results within the normal range but at the lower limit. These children were asymptomatic and were not previously diagnosed with AI prior to our study.

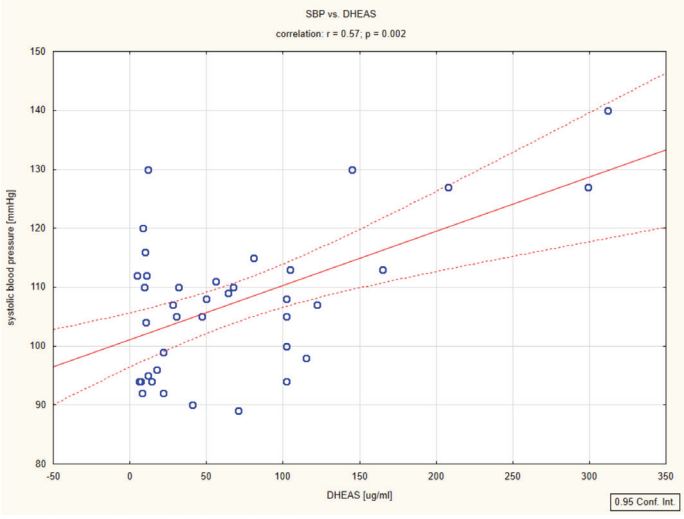

Figure 5. The linear positive correlation between DHEA-S and SBP in healthy ones

SBP: systolic blood pressure, DHEA-S: dehydroepiandrostendione-sulfate

The results of our study suggest that serum level of DHEA-S is a very useful marker in the diagnostic process of adrenal axis recovery in patients previously treated with corticosteroids. According to one pediatric report addressing corticosteroid treatment in ALL, serum levels of DHEA-S returned to normal two weeks before complete

adrenal recovery (10). In comparison with cortisol, the half-life of DHEA-S is longer and lasts 10-20 hours whereas the half-life of cortisol is 2 hours. It also has less fluctuation in concentration ranges than cortisol during the day. DHEA-S seems to be useful as an early indicator of adrenal recovery after the transient suppression of the adrenal axis. DHEA-S could be assessed before initiating steroid therapy from 2 and 4 weeks after the last dose of steroids. DHEA-S level is a reliable and sensitive tool to evaluate adrenal function (14). It is worth highlighting that in our study DHEA S correlated with UFC, indicating DHEA-S to be a very good marker of adrenal gland function. A measurement of UFC is primarily used to evaluate cortisol excess in the context of Cushing syndrome or adrenal cancer, but UFC also represents 24 hour excreted cortisol. We found correlation between UFC and evening and midnight cortisol levels, in addition to UFC with SBP, and DBP with DHEA-S. This could be of great importance diagnostically and clinically in the assessment of adrenal gland function. UFC is used mainly in the diagnostic process of hypercortisolemia and reflects daily production of cortisol and correlates significantly with midnight cortisol. Therefore, midnight cortisol levels are proposed as a diagnostic tool in hypercortisolemia. Our data also confirmed the significance of low midnight cortisol levels being suggestive of AI. Therefore, besides the ACTH test, DHEA-S, UFC, and midnight cortisol levels can be used as screening tests in the assessment of adrenal function in oncological patients. However, the most useful among them was DHEA-S, because it required a single assessment, regardless of the time of day or food intake.

Hyperglycemia during chemotherapy occurs in approximately 10% to 30% of patients (15). It can happen frequently and transiently. The main chemotherapeutics causing hyperglycemia in the leukemia chemotherapy treatment protocol are glucocorticoids and L-asparaginase. It was used both in the induction and reinduction therapies in all our patients. Complications of glucocorticoid treatment are: increased insulin resistance, diminished insulin secretion and exaggerated hepatic glucose output. L-asparaginase is a cytotoxic chemotherapeutic agent and has a direct toxic effect on pancreatic β-cells, resulting in insulin production and release inhibition. Indirectly, it can also cause pancreatitis, which may lead to impaired β-cell function, even after cessation of chemotherapy (16). L-asparaginase may lead to long-term hyperglycemia more frequently than corticosteroids. Diabetes may occur in up to 15.6% of cancer survivors (15). Diabetes in ALL survivors is of compound etiology due to impaired β-cells function and increase insulin resistance as part of a metabolic syndrome, a well-known marker of cardiovascular morbidity and mortality, and importantly it is a modifiable risk. In the study of Oudin et al. (17), there were 1.025 leukemia survivors. Metabolic syndrome was defined according to the National Cholesterol Education Program's Adult Treatment Panel II criteria and was found in 10.3% of patients. They concluded that in every group (patients after chemotherapy, chemotherapy joined with cranial irradiation, patients transplanted without irradiation and patients transplanted with total body irradiation) there was an increased risk of metabolic syndrome. In a large cohort study (18) 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%). Hypertension was identified among 364 survivors (46.4%). In our study, in comparison with the control group, ALL survivors had higher blood pressure and FBG levels. Moreover, there was a correlation between FBG levels and SBP. Unique to this study, the abnormalities of SBP and FBG levels appeared as early as five years after the end of ALL treatment. There is data reporting that survivors of childhood ALL can present with persistent dysregulation of the HPAA in adult life. The experience of a stressful life event in the past may cause a long-term dysregulation of the HPAA, as reflected in increased cortisol production and an enhanced negative feedback mechanism (19). This mechanism could be responsible for obesity and metabolic dysregulation often observed in childhood ALL survivors. Glucocorticoid induction of hypertension is complex and tissue dependent. The main pathway is the interconversion of active cortisol to inactive cortisone by hydroxysteroid 11-beta dehydrogenase (11b-HSD). 11b-HSD type 2 (11b-HSD2) is expressed in nonselective mineralocorticoid receptor (MR)-rich tissues, especially the kidney, colon and salivary gland (20,21). MR has a similar affinity for cortisol and aldosterone. Aldosterone occupies the MR only when cortisol is inactivated to cortisone by 11b-HSD2 as this mechanism protects the MR from cortisol excess. 11b-HSD2 is saturated due to increased corticosteroid concentration, resulting in cortisol-induced mineralocorticoid excess. Dexamethasone is poorly metabolized by 11b-HSD2 (22). Corticosteroid-induced hypertension is mediated by excess sodium and water reabsorption by stimulation of the renal MRs (23,24,25).

Besides corticosteroids, other drugs used in the therapy of leukemia increase the risk of metabolic syndrome in ALL survivors. Preclinical evidence has demonstrated endothelial injury and abnormalities in the renin-angiotensin system in animals treated with cyclophosphamide. Therefore, there is biological plausibility for cyclophosphamide-associated hypertension due to vascular injury. However,

cyclophosphamide has not been identified as an independent risk factor for hypertension in cancer survivors (23,26). Another chemotherapeutic, anthracycline, may lead to increased risk of cardiovascular disease in ALL survivors. The Childhood Cancer Survivor Study found that, while both cardiotoxic treatments and hypertension were independently associated with increased risk of coronary artery disease or heart failure, the combination of these factors resulted in a greater increase in risk that yielded an 86-fold increased risk of heart failure in survivors exposed to both anthracyclines and hypertension. This suggests that development of hypertension can exacerbate the damage caused by cardiotoxic cancer treatments (23). Moreover, radiation to the head and neck has been associated with baroreflex failure, which can manifest as labile hypertension or hypertensive crisis (23).

Changes in body salt content are buffered by reciprocal changes in PRA to maintain BP homeostasis (26). The PRA test is useful to define the relative involvement of body sodium-volume and to classify hypertension. Low renin hypertension is a common condition and accounts for 20 % to 30 % of all hypertensive patients (27) and might be associated with high aldosterone levels (Conn syndrome), normal aldosterone levels or low aldosterone levels, as in Liddle syndrome and syndrome of apparent mineralocorticoid excess and glucocorticoid remediable hypertension (28,29). High-dose corticosteroid therapy leads to inappropriate stimulation of the MR, mineralocorticoid excess and low level of PRA, resulting in elevated blood pressure. In our study the PRA was significantly lower than in the control group. ALL survivors also had higher blood pressure. This suggests a reduction in PRA levels compensating for sodium retention due to the stimulation of MR (cortisol-induced mineralocorticoid excess). Our suggestion is also based on our result of the positive significant correlations between UFC, DHEA-S and blood pressure.

Radiotherapy plays an important role in ALL treatment protocols. It stops cancer cells proliferating and often leads to cancer cell apoptosis (30). In parallel, it can lead to HPAA dysregulation, especially during CNS radiotherapy. The risk of AI is significantly reduced when the total radiation dose is less than 30 Gy and fractionated doses are less than 2 Gy (31,32). Prophylactic CRT used in some of our patients with a dose of 12 Gy in eight fractions minimized the risk of pituitary damage and dysfunction of HPAA.

Study Limitations

The ALL survivors included in the study were heterogeneous in regards to their duration of remission after oncological treatment but no precise time was provided how long after treatment the adrenals were assessed. The local ethical committee did not approve the testing of ACTH in the control group and so authors can only assume results of this test are normal in healthy controls.

Conclusion

Our study confirms the effect of ALL treatment protocols on the adrenal glands resulting in transient or occassionally persistent AI. These results highlight the importance of post-chemo/radiotherapy follow-up of adrenal function. The low-dose ACTH test is a reliable and quite sensitive method to exclude chronic, subclinical AI prior to symptoms developing. Our data indicates that DHEA-S, midnight cortisol levels and UFC may be good markers of adrenal function after oncological treatment. However, the most useful among them was DHEA-S, because it requires a single assessment independent of food intake and the time of the day. It is necessary to monitor ALL survivors with importance given to metabolic syndrome surveillance after the cessation of ALL treatment. Regular adrenal and metabolic assessment should be combined to prevent the adverse events caused by chronic, subclinical AI and asymptomatic metabolic disorders, thus promoting the efficacy of anti-cancer therapy and improving quality of life.

Ethics

Ethics Committee Approval: The study was then approved by the Jagiellonian University Local Ethical Committee (no. 1072.6120.74.2019, date: 29.04.2019).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Barbara Hull, Anna Wędrychowicz, Magdalena Ossowska, Aleksandra Furtak, Joanna Badacz, Szymon Skoczeń, Concept: Anna Wędrychowicz, Design: Barbara Hull, Anna Wędrychowicz, Szymon Skoczeń, Data Collection or Processing: Barbara Hull, Anna Wędrychowicz, Magdalena Ossowska, Aleksandra Furtak, Joanna Badacz, Szymon Skoczeń, Analysis or Interpretation: Barbara Hull, Anna Wędrychowicz, Szymon Skoczeń, Jerzy B. Starzyk, Literature Search: Barbara Hull, Anna Wędrychowicz, Writing: Barbara Hull, Anna Wędrychowicz.

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