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The function of adrenal glands in children and adolescents during and after oncological treatment

Funkcjonowanie nadnerczy u pacjentów pediatrycznych podczas leczenia onkologicznego i po jego zakończeniu

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Abstract
The purpose of this work was to present the current state of knowledge on the effects of frequently used therapeutic forms, selected pharmacotherapy (including glucocorticosteroids, immune checkpoint inhibitors, mitotane, metyrapone, aminoglutetimide, etomidate, ketoconazole, fluconazole), but also radiation therapy on the functioning of the hypothalamic-pituitary-adrenal axis in children and adolescent during and after oncological treatment. The most common pediatric cancers, where complications of adrenal insufficiency occur, are presented. Moreover, current recommendations how to diagnose the function of the adrenal axis in oncological pediatric patients, as well during oncological treatment as after it, including patients treated with steroids and also patients in severe stages, are reported. The rules of the treatment of adrenal dysfunction in those patients are presented. This understanding is of key importance for oncologists and endocrinologists in the process of diagnosing, treating and developing patient health care, as well as during therapy as after it, offering safety and improving the quality of life.
Key words:
adrenal insufficiency, glucocorticosteroids, radiation therapy, children, acute lymphoblastic leukemia, brain tumors, diagnostics, treatment.

Introduction

Thanks to the development of effective cancer treatments, the survival rate of pediatric oncology patients is greater than ever before. According to the study of Saletta *et al*., the overall 5-year survival rate of all cancers in children aged 0-14 years has risen from 62%, for those diagnosed between 1975–1979, to 83%, for those diagnosed between 2002–2006. In the same period, the improvement in 5-year survival for acute lymphoblastic leukemia (ALL) increased from 63% to 90% [1]. In Central Europe, event free survival after 5 years in children 0-18 years old with ALL in 1982 was 38%, then improved to 79% in 2002–2011 and 90% in 2012 [2]. Chemotherapy and radiotherapy, widely used as the first- and second line treatments of various oncological diseases, kill uncontrolled growing cells, but also have negative effect on healthy cells which may lead to many side effects including endocrine dysfunction. Chemotherapy, as well as radiotherapy of the head, neck and abdomen area, may interfere temporarily or permanently with the proper functioning of the hypothalamic pituitary adrenal axis (HPAA). Although uncommon, the adrenal insufficiency can be a life-threatening complication of the cancer treatment.

We present possible adrenal complications in the most frequent pediatric cancers. Our goal was also to report the current knowledge of the impact on frequently used therapeutic forms, selected pharmacotherapeutic agents, as well as radiotherapy, on the functioning of the HPAA. Moreover, we present diagnostic guidelines for the evaluation of the function of the adrenal axis and we report available protocols for the management of its disturbances.

Pediatric cancers the most frequent associated with possible adrenal insufficiency

Brain tumors, are the most common tumors causing HPAA damage. Supra- and intrasellar tumors constitute 10% of all pediatric CNS tumors and their close proximity to the vital hypothalamic pituitary (HP) axis increases the risk of important endocrine dysfunction. Tumors located close to the HP area may result in HPAA dysfunction directly, through infiltration and mass effect, or as a consequence of treatment, such as radiotherapy or neurosurgery. The most common types of pediatric malignancy in the HP region are gliomas, craniopharyngiomas, suprasellar germinomas [3]. The most frequently deficiency of

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adrenocorticotrophic hormone (ACTH) has been described in patients with craniopharyngioma, although its prevalence has reduced more recently as treatment preference moves towards less invasive surgery with the use of adjuvant therapies such as radiotherapy and chemotherapy. The substantial prevalence of ACTH deficiency of 64% was assessed at follow-up in those diagnosed between 2001 and 2010 compared with 95% from 1991 to 2000 [4]. About 13% of survivors of pediatric low-grade gliomas affect the optic pathway, hypothalamus, and suprasellar area present with ACTH deficiency in long-term follow up [5]. Patients with tumors located and/or had surgery performed near the HP region and those treated with an accumulative cranial radiotherapy dose of over 30 Gy are most at risk of ACTH deficiency. The effects of adjunct therapies also need to be considered, particularly, new immunotherapies. High-dose and/or prolonged courses of glucocorticoid treatment can result in secondary adrenal insufficiency, which may take months to resolve and hence reassessment is important to ensure patients are not left on long-term replacement steroids inappropriately. The prevalence and cumulative incidences of HPAA dysfunction are difficult to quantify because of its non-specific presentation and lack of consensus regarding its investigations [6]. A high incidence of ACTH deficiency (30–60% after 10 years) occur after more intensive irradiation (> 60 Gy) used for nasopharyngeal carcinomas and tumors of the skull base, and following conventional irradiation (30–50 Gy) for pituitary tumors [7]. In the study of Iersel the estimated prevalence for ACTH deficiency was 3.2% among childhood cancer survivors treated with HP radiotherapy (n = 1089), and < 1% without HP radiotherapy [8]. Non-irradiated infant and toddler brain tumor survivors seem to be more vulnerable to develop HP dysfunction than older children. They present ACTH deficiency despite the less frequent use of radiotherapy in infants. Clinical factors independently associated with ACTH deficiency besides HP radiotherapy > 30 Gy, included seizures and stroke [9].

ALL, followed by CNS tumors, is the most common type of childhood cancer. Treatment consists of chemotherapy, but also a long-term course of high-dose dexamethasone, which suppress the adrenal axis. Felner *et al*., assessed HPAA during the course of high-dose dexamethasone therapy. All patients experienced symptoms of adrenal insufficiency for at least 2 weeks after completing therapy and 30% of patients had normal adrenal function only after 8 weeks [10]. Therefore, it would be beneficial for patients to taper dexamethasone over the next 6 weeks, rather than sudden discontinuation, to avoid adrenal insufficiency. Moreover, it is important to monitor adrenal function in these patients and to administrate immediately the proper treatment if necessary in stressful situations. In the Salem et al. study, they assessed adrenal axis in 40 pediatric patients with ALL undergoing two different treatment protocols, 20 was treated with dexamethasone, 20 with prednisone [11]. They found that withdrawal syndrome occurred more frequently in patients with dexamethasone (75% patients) than in the prednisone group (50% patients). The recovery time of the adrenal axis was two times longer in dexamethasone than in prednisone [11]. The suppression of adrenal axis lasting 2.5–8 months in 41% of patients who received 5 weeks prednisolone in induction and 3 weeks dexamethasone in re-induction phases of treatment was observed in the study of Petersen *et al*. [12]. Despite transient HPAA suppression, 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 have caused a long-term dysregulation of the HPAA, as reflected in an increased cortisol production and an enhanced negative feedback mechanism [13]. This mechanism could be responsible for obesity and metabolic dysregulation often observed in childhood ALL survivors. In patients after hematopoietic stem cell transplantation (HSCT) central adrenal insufficiency occurs rare, because the cumulative dose of radiation is rarely higher than 30 Gy. Patients after HSCT which are treated for long time with steroids because of graft versus host disease may present the suppression of the adrenal axis, so secondary adrenal insufficiency, therefore sudden discontinuation of this treatment could be a cause of adrenal insufficiency. But in patients after HSCT, there are also descripted the cases of the primary adrenal insufficiency, even with adrenal crisis, the most probably due to dysregulation of immunological system. The cumulative incidence of secondary autoimmune disease after HSCT for primary autoimmune disease was 9.8% at 5 years [14]. Mainly it manifests as autoimmune cytopenias, autoimmune thyroiditis or myasthenia gravis, but Addison's disease can also occur [15].

Medicines that affect the function of adrenal glands

The HPAA is especially prone to interactions with many different drugs, the list of which is growing year by year. The most commonly used drugs affecting the HPAA are **glucocorticosteroids** (GCS), being an important element of the anti-cancer therapy. GCS have systemic roles in immune responses, metabolism, cell growth, development, and reproduction. The effect of their action is visible within a few hours to several days [16] (Table I). Therefore, sudden discontinuation of glucocorticoid therapy is the most common cause of a secondary adrenal insufficiency, which is a life-threatening medical emergency.

Immune checkpoint inhibitors are potent therapeutic options for many types of advanced cancer, more and more often also in children, but their use could be associated with immune-related adverse events. One of them is the adrenal insufficiency due to the deficient of adrenocorticotropic hormone (ACTH). In the study of Manaka *et al*. 3.5% of adult patients treated with immune checkpoint inhibitors developed ACTH deficiency and secondary adrenal insufficiency. It regarded 29% of patients during the combination of nivolumab and ipilimumab therapy and 13% of patients during maintenance nivolumab monotherapy following the combination therapy [17].

Radiotherapy involves projecting ionizing radiation, in the form of high energy electromagnetic waves or electrically charged particles, into cancer tissues, depositing energy into the nuclei of cells where radiation ionizes molecules including DNA. It damages the genetic material of the cells, causing the cells to lose their ability to proliferate. Additionally, cells exposed

Table I. Comparison of the effects of individual glucocorticosteroids

Product	Anti-inflammatory effect	Pituitary inhibition	Dose equivalent [mg]	Half-life [h]
Hydrocortisone	1		20	8–12
Cortisone	0.8	+	25	8–12
Prednisone	3.5	++	5	~36
Prednisolone	4	++	5	~36
Betamethasone	30–40	+++	0.8	36–54
Triamcinolone	5	++	4	18–36
Methylprednisolone	5	++	4	18–36
Dexamethasone	30–100	++++	0.75	~56

to radiation may undergo necrosis or apoptosis [18]. During irradiation of neoplastic tissue in the head and neck region, the hypothalamic-pituitary (HP) region is exposed to radiation, which can cause damage to the HPAA. Consequently, adrenal insufficiency may develop from 6 months to even several years after the radiotherapy. Most often, adrenal insufficiency is encountered with tumors of the central nervous system, HP region, and adrenal gland tumors [19]. Proton radiotherapy seems not to reduce the risk of adrenal insufficiency in comparison with photon radiotherapy [20]. This risk is significantly reduced at maximum doses less than 30 Gy and fractionated doses less than 2 Gy [21].

There are some therapeutics that are dedicated to treat adrenal neoplasms, but they affect adrenal function. **Mitotane** is an anti-cancer drug used to treat adrenal cortex cancer. It directly influences the adrenal cortex by inhibiting the conversion of cholesterol to pregnenolone and 11-deoxycortisol to cortisol [22] and peripherally by inducing the activity of hepatic CYP3A4, causing accelerated inactivation of cortisol, and increasing the level of cortisol-binding globulin. Long-term treatment with mitotane almost always leads to adrenal insufficiency [23], often irreversibly. Since mitotane affects all steroid production in the adrenal cortex, it is necessary to substitute glucocorticoids and sometimes mineralocorticoids in treated patients. Moreover, the standard dose of substitution may be insufficient and patients may require higher doses of glucocorticoids [24]. **Metyrapone** is a pyridine derivative and an inhibitor of glucocorticoid synthesis. Metyrapone inhibits 11beta-hydroxylase, causing reduction of the synthesis and secretion of cortisol and aldosterone, and an increase in the concentration of adrenal androgens. As one of the therapeutic options, it is widely used in the pharmacological preparation of the patient for Cushing's disease (CD) surgery, alleviating CD symptoms such as arterial hypertension, and hyperglycemia throughout decreasing the cortisol level. **Aminoglutethimide** is an anti-cancer drug used in the treatment of breast cancer, prostate cancer, and adrenal cortex cancer. It inhibits the synthesis of steroid hormone precursors from cholesterol by CYP11A1, and thus all adrenal cortex hormones. GCS substitution should be performed during therapy [25].

Some agents used in the supportive therapy of oncological patients could have significant side effects resulting in the disturbances of the adrenal function. **Ketoconazole,** a broad-spectrum antifungal drug, affects the cytochrome P-450 enzyme system in several organs (testicle, ovary, adrenal glands, kidney, liver) [26]. It inhibits the synthesis of an essential component of the fungal cell membrane and a steroid hormone precursor by dose-dependent transient inhibition of 14-alpha-demethylase. Currently, ketoconazole is unavailable in most UE countries, because of the risk of severe hepatotoxicity. **Fluconazole** is another antifungal azole therapy. The action of fluconazole leads to the inhibition of the synthesis of ergosterol, an essential component of the fungal cell membrane. The cell membrane is damaged, which results in the death of the fungal cell. It has a long half-life, approximately 30 hours. There are reports that fluconazole reversibly inhibits the function of the adrenal glands, leading to adrenal insufficiency requiring immediate treatment [27]. Fluconazole is widely used in oncological treatment regimens as a prophylactic antifungal agent. Therefore, oncologists should pay attention to the side-effect of fluconazole, blocking steroidogenesis, and consider it in the occurrence of symptoms suggesting adrenal insufficiency.

Moreover anesthetic agents used in the diagnostic of therapy procedures in children with malignancy could influence the adrenal action. **Etomidate** is an intravenous agent used for short-term diagnostic and therapeutic procedures under general anesthesia. Additionally, it influences steroidogenesis by reversibly blocking 11B-hydroxylase (CYP11B1 and CYP11B2) and cholesterol desmolase, which leads to inhibition of cortisol and aldosterone secretion [28]. This can cause temporary or permanent adrenal insufficiency, which is a life threatening side effect. It should not be used in patients with adrenal insufficiency without the aggravating of steroid replacement.

Diagnostic process for assessing disturbances of the adrenal axis

Cortisol production in children and adults is approximately 6–8 mg/m^2/day, with mean early morning plasma level of 7–22 μg/dl. During periods of stress, cortisol levels rise up to 15 times the normal level. Endogenous cortisol levels peak approximately half an hour after waking. The morning cortisol (8 am) is a common clinical assessment of the HPAA function, but since this is not standardized to waking time, it is not necessarily the highest concentration of the day. Serum cortisol levels greater than 13 μg/dl (365 nmol/l) were reported to predict normal adrenal function. However according to the Patterson et al. study [29], some patients with insufficiency may be missed by morning cortisol screening.

Prevalence of adrenal insufficiency increases significantly with the number of other concomitant endocrinopathies as complications after oncological treatment [29]. Therefore, it is important to pay attention to other medications when interpreting cortisol level. Oral estrogens affect total cortisol levels, as it can increase the production of cortisol-binding globulin, increasing total but not free cortisol levels. Glucocorticoid deficiency can mask symptoms of diabetes insipidus, such as polyuria, because of the impairment of free water clearance. Moreover, some antiepileptic drugs, used in children with brain tumors, reduce plasma levels of glucocorticoids (especially dexamethasone), e.g. carbamazepine, oxcarbazepine, phenytoin, topiramate, by enhancing hepatic CYP450 isoenzyme activity [16]. This effect may persist for several weeks after drug discontinuation. Inhibitors of cytochrome 3A4 P450 (CYP3A4): antibiotics such as macrolides (clarithromycin), antifungal drugs (ketoconazole, itraconazole, posaconazole), antiviral drugs (atazanavir, ritonavir) may increase glucocorticoid potency and exposure, especially methylprednisolone and dexamethasone.

The adrenal insufficiency observed in ALL, is rarely seen clinically, but it is more commonly present subclinically with normal basal cortisol level and manifests during periods of stress. It is associated with the transient or permanent suppression of the whole HPAA, presenting as central adrenal insufficiency. Therefore, it is very important to choose a proper diagnostic algorithm for adrenal axis evaluation. There are different rules to diagnose central and primary adrenal insufficiency. Moreover, some oncological patients can present with combined, central and peripheral, adrenal insufficiency. In primary adrenal insufficiency, we observe elevated ACTH level ($>$ 70 pg/ml), whereas in secondary adrenal insufficiency ACTH level may be decreased or normal. However one-time assessment of ACTH serum level is not a good diagnostic tool, because it's elevation could be only the result of the stress during blood sample drawing.

Central adrenal insufficiency is a lack of adrenal hormones caused by the deficiency of ACTH, because of disturbances of hypothalamus or/and pituitary functioning including their suppression due to long term administration of exogenous steroids, what is dose and term-dependent. Central adrenal insufficiency according to its source can be secondary (pituitary ACTH deficit) or tertiary (lack of ACTH as a consequence of hypothalamic corticotropin-releasing hormone deficit). European Society of Endocrinology and Pediatric Endocrine Society with endorsing association of the Pituitary Society recommend lifelong annual screening for ACTH deficiency in childhood cancer survivors treated for tumors in the hypothalamic–pituitary region and in those exposed to over 30 Gy hypothalamic–pituitary radiation. They suggest screening for ACTH hormone deficiency in childhood cancer survivors exposed to between 24 Gy and 30 Gy hypothalamic–pituitary radiation who are more than 10 years post-radiation or develop clinical symptoms suggestive of ACTH deficiency. They advise using the same screening and dynamic testing procedures to diagnose ACTH deficiency in these patients as are used in the healthy population [30].

Insulin tolerance test (ITT) is used as a gold standard to diagnose central adrenal insufficiency. Insulin induced hypoglycemia causes CRH secretion from the hypothalamus and ACTH release from pituitary, and in turn, stimulates cortisol production. ITT is particularly useful in the evaluation of HPAA after cranial irradiation. However, there are some limitations. To achieve hypoglycemia, complications during the test (like sweating, tremor, seizure, loss of consciousness) can occur. Hypoglycemia during diagnostic testing can be dangerous and requires close monitoring and supervision, especially in patients with pituitary disease, whose counter-regulatory response to hypoglycemia may be inadequate [31].

Low-dose corticotropin test (LDCT) test is an alternative to ITT, to investigate secondary adrenal insufficiency. It is a safer and easier option to ITT. It is also a more sensitive test than the standard dose ACTH test. LDCT test has lower specificity than ITT and up to 30 % patients can pass the test who fail ITT [26]. Stimulated cortisol level $>$ 18 μg/dl (500 nmol/l) or cortisol increase higher than 7 μg/dl (195 nmol/l) indicates normal adrenocortical function [32]. One ug (or 0.5 ug/m^2 BSA) ACTH stimulation test with the cut-off 18 μg/dl (500 nmol/l) has sensitivity 100% and specificity 67.3%. With the cut-off 14.5 μg/dl (400 nmol/l), the sensitivity is 100% and specificity is 93.9% [33]. It would be also beneficial for patients to assess carefully the adrenal axis after a course of glucocorticoids with the use of LDST, because the LDCT is more sensitive than the standard dose corticotropin test (SDCT) and enables detection of adrenal insufficiency at a lower threshold. The cortisol response to ACTH stimulation is usually determined by the LD-ACTH test (1 μg ACTH) is considered the most sensitive (94–100%) and specific (88–100%) tool that can even detect mild degrees of adrenal impairment [34].

Corticotropin relasing hormone (CRH) test is another therapeutic agent for the diagnosis of central adrenal insufficiency. CRH stimulates cortisol production by ACTH secretion. Patients with pituitary adrenal insufficiency have decreased ACTH and cortisol response to CRH. Patients with hypothalamic disorders have exaggerated and prolonged ACTH response and subnormal cortisol response. Normal response is described as a 4-fold increase in mean plasma ACTH or cortisol, or $>$ 34% increase in plasma ACTH and a $>$ 20% increase in plasma cortisol when compared to mean baseline values [31]. In primary

adrenal insufficiency, a two-fold or greater increase in ACTH concentration is observed at a cortisol concentration not exceeding 18–20 μg/dl (500–550 nmol/l), measured 15–30 minutes after CRH stimulation (1 μg/kg or bolus of 100 μg intravenously). While in secondary adrenal insufficiency, a less than 2-fold increase in ACTH concentration is observed after CRH stimulation [32].

Glucagon test, widely used in the diagnostic process of growth hormone deficiency, is another alternative test to ITT. The dose of 0.1 mg/kg (maximum dose 1 mg) is given intramuscular. The test lasts 180 minutes. It requires endogenous ACTH to secrete cortisol. Peak plasma cortisol over 20 μg/dl (550 nmol/l) indicates the normal adrenal response.

Metyrapone decreases cortisol level by blocking the conversion of 11-deoxycorisol (11-DOC) to cortisol. It reduces negative feedback to CRH and ACTH and stimulates steroid biosynthesis. Metyrapone is given as a single dose at midnight (30 mg/kg, max dose 3.0 g). Cortisol, ACTH and 11-DOC are measured at 8 am next morning. In this test, cortisol decrease < 5 μg/dl (138 nmol/l), 11-DOC increase > 210 nmol/l, ACTH > 75 ng/ml means normal response. Measurement of ACTH will distinguish primary from secondary adrenal insufficiency. Metyrapone test has some disadvantages. It can precipitate adrenal crisis [31].

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. It is recommended that patients on chronic steroid therapy wear a medical alert bracelet or a medical information card to alert first responders in the event of an emergency.

Primary adrenal insufficiency is a consequence of the destruction of adrenal glands, due to tumors located in or involving one or both adrenals or their treatment (surgery, chemotherapy such as mitotane, rarely radiation) or due to immunological process or intraadrenal bleeding. The SDCT with 250 μg or 250 ug/1.73 m^2 BSA of synthetic ACTH is the first-line test for diagnosing primary adrenal insufficiency. The plasma glucose level, serum electrolytes, serum cortisol, plasma ACTH, plasma aldosterone, plasma renin, and aldosterone levels should be measured before administering of ACTH. At 30 and 60 minutes after intravenous ACTH administration, the serum cortisol level should be measured again. A normal response occurs with peak cortisol levels greater than 18 μg/dl (500 nmol/l). Lower response is diagnostic for adrenal insufficiency. A rise in ACTH levels is concomitant with the loss of adrenal hormones. Hypoglycemia, hyponatremia and hyperkaliemia are observed in primary adrenal insufficiency. One of the first indications that there is adrenal cortex dysfunction is an elevation in plasma renin level [35]. Therefore, plasma renin activity could be a sensitive marker of the primary adrenal insufficiency. Because the synthesis of adrenal hormones slows down gradually over years to decades, the levels vary between young and old patients.

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 ionogram.

Diagnostics of an adrenal axis in patients treated with steroid

Diagnostic process of adrenal function in patients during steroidotherapy is a different issue. Glucocorticoids is crucial part of different treatment protocols in ALL. Glucocorticoids therapy for more than 7 days in a dosage of equivalent hydrocortisone above 10 mg/m^2 BSA per day causes suppression of the adrenal axis. In the assessment of the function of adrenal axis during GCS treatment, the profile of plasma cortisol level is useful. Cortisol in patients with adrenal insufficiency prior to taking their medication is low. The peak plasma cortisol concentration is registered 2 hours after oral administering of hydrocortisone [36]. Therefore, measurement of a plasma cortisol before and 2 hours after every oral dose of hydrocortisone might be very beneficial in monitoring adrenal insufficiency treatment in patients.

Evaluating daily urinary excretion has the advantage of providing an integrated index of steroid production over 24 hours. Measurement of urinary free cortisol (UFC) is primary used to evaluate cortisol excess in the context of Cushing's syndrome or adrenal cancer. Reference ranges for urinary free cortisol vary by age. UFC may not be useful for evaluating adrenal insufficiency.

Very useful in the diagnostic process of adrenal axis recovery in patients treated previously with GCS seems to be the serum level of dehydroepiandrostenedione-sulphate (DHEA-S). After glucocorticosteroid treatment in ALL, serum levels of DHEA-S returned back to normal 2 weeks before complete adrenal recovery. In comparison with cortisol, half-life of DHEA-S is longer and it lasts 10–20 hours (half-life of cortisol is 2 hours). It has also less fluctuating concentrations than cortisol during the day. DHEA-S seem to be useful as an early indicator of adrenal recovery after the transient suppression of the adrenal axis. DHEAS might be assessed before starting steroid therapy, 2 and 4 weeks after the last dose of steroids. DHEA-S level is a reliable and sensitive substitute for evaluating adrenal function.

Assessments of hypothalamic-pituitary-adrenal axis in severe states

Severe general condition of the patient may cause a relative hormonal failure, including adrenal hormones. It appears after several days, in the second decompensation phase, which is the body's universal response to severe states, such as generalized infection, trauma, surgery, burns, bone marrow transplantation, poisoning or metabolic disease. There are different possible causes of corticosteroid insufficiency in critical illness. Reduced cortisol action can arise from effects of disease or therapeutic interventions on the hypothalamus, pituitary, or adrenal or at the tissue level. A decrease in cortisol breakdown, rather than an increase in cortisol production, has been suggested as the main contributor to elevated cortisol levels in critically ill patients. The pulsatile secretion of hypothalamic hormones and pituitary tropic hormones is inhibited, causing adrenal insufficiency. The concentration of ACTH decreases in

the adrenal axis, but ACTH persists, and cortisol levels are relatively increased because of decreased hepatic clearance. Relative adrenal insufficiency in phase II of the response to physical stress relates to the treatment used: infusion of catecholamines resulting in reduction of cortisol synthesis, glucocorticosteroids that inhibit the ACTH and cortisol secretion, β-blockers causing inhibition of glucocorticoid synthesis. In some studies, it has been suggested that as many as 75% patients in intensive care units have relative adrenal insufficiency. Experimental support for the concept is not possible, because measure of the action of steroids is not possible. The diagnosis is generally based on the interpretation of SDCT. To confirm relative adrenal insufficiency basal cortisol level or ACTH (1 μg/kg in newborn or 250 μg/m^2 BSA in others) test should be assessed [37]. Basal cortisol level under 15 μg/dl (415 nmol/l) indicates the diagnosis. In ACTH test, cortisol lower than 17 μg/dl (470 nmol/l), or the increase of cortisol less than 9 μg/dl (250 nmol/l) establishes a diagnosis of relative adrenal insufficiency. In severe states, random serum cortisol level below 10 μg/dl (280 nmol/l) 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% [38]. If the measurement is between 10 and 34 μg/dl, we propose to perform SDCT. Patients with septic shock who are pressor dependent or refractory to fluid resuscitation may receive a short course of hydrocortisone regardless of their serum cortisol levels or their response to SDCT. In patients with low or near-normal cortisol-binding proteins, a serum cortisol of $<$ 10 or 15 μg/dl (280 or 415 nmol/l), respectively, may trigger need for glucocorticoid treatment [39].

Treatment of relative adrenal insufficiency is hydrocortisone intravenously with the dosage 0.5–1.0 mg/kg/6 hours or 35 mg/m^2/24 hours.

The doses of steroids in patients with adrenal insufficiency being in severe states should be three up to 5 times higher than their normal daily requirement. In shock hydrocortisone with its mineralocorticoid activity should be 50–100 mg/m^2 given immediately i.v. or i.m. when i.v. access is currently impossible. It could be repeated, when there is a poor response to initial steroid and fluid treatment. The dose of HC should be followed every 6 hour and reduced when the state of the patient is stable. If the patient tolerates oral medications a triple dose oral HC replacement should be given, then gradually reduced to maintenance the proper level. Mineralocorticoid replacement should be started when the patient can tolerate oral fluids (fludrocortisone usually 0.05–0.1 mg daily). Previously it is achieved with fluids and the mineralocorticoid activity of stress dose hydrocortisone.

Conclusions

There is a growing list of medications using in the oncological therapy, which have a proven negative effect on the function of the HPAA. This effect can be transient or persistent. As well, radiotherapy can affect the HPAA. Adrenal insufficiency may be subclinical and underdiagnosed in this population. In stressful situation it can result in life-threatening adrenal crisis. This knowledge is crucial for the diagnosis, treatment and long-term care of pediatric patients with cancer.

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