

Abnormal cortisol levels in pediatric patients treated with glucocorticosteroids for acute lymphoblastic leukemia

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Abstract

Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy. Although in the past ALL was incurable, today's survival rate is as high as 80–90%. The most important drugs in its treatment are glucocorticosteroids (GCS). This study focuses on exogenous GCS – dexamethasone and prednisolone, which suppress the hypothalamic–pituitary–adrenal (HPA) axis.

The main objective of this study was to analyze articles about steroid side effects in ALL therapy, factors contributing to the frequency of HPA axis suppression, and possible methods for its assessment. According to research, abnormal cortisol values have been observed in almost every patient treated for ALL. This means it is important to perform HPA axis stimulation tests. In the reviewed studies, adrenal crisis, hyperglycemia, obesity, iatrogenic Cushing's disease, growth failure, increased risk of infection, and a high mortality rate have been reported to be the most important complications of this therapy. It is important to note that some authors classify patients in terms of cortisol level disorder predispositions. These include the age and sex of the patient, the type of glucocorticoid used in ALL therapy, and the duration of the therapy.

In conclusion, dexamethasone therapy may lead to prolonged adrenal insufficiency more often than prednisone. Moreover, dexamethasone use can cause a higher risk of infection, a higher risk of developing hyperglycemia, a greater incidence of osteonecrosis, and worse cognitive test results than the use of prednisone. Younger children tolerate adrenal insufficiency better and have a lower risk of developing osteonecrosis. Additionally, both high dose fluconazole administration and male sex can lead to prolonged HPA axis suppression.

Key words: acute lymphoblastic leukemia, glucocorticosteroids, hypothalamic–pituitary–adrenal axis suppression, adrenal insufficiency

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Introduction

The therapy of acute lymphoblastic leukemia (ALL) should be established as soon as possible. Research has revealed that delaying treatment until the 8th day can result in a 30% higher risk of death [1]. ALL treatment consists of a wide variety of drugs, ranging from glucocorticosteroids (GCS) to monoclonal antibodies [2]. Although GCS such as dexamethasone and predniso(lo)ne are crucial in ALL treatment, a variety of adverse effects can occur during this therapy. Exogenous steroids tend to suppress the hypothalamic–pituitary–adrenal (HPA) axis, causing a severe decrease in cortisol levels and therefore leading to adrenal crisis [3].

The aim of this study was to analyze various articles about steroid side effects in ALL therapy, factors contributing to the frequency of HPA axis suppression, and possible methods for its assessment. Impaired function of HPA axis usually occurs in the first few days after cessation of GCS therapy. Various studies have shown that dexamethasone and prednisolone are also associated with immunosuppression and numerous metabolic disorders such as iatrogenic Cushing's disease [4, 5]. The incidence of particularly disturbing cortisol values varies in terms of treatment duration and steroid dose. The age and sex of the patient should also be considered [6–8]. Multiple studies have suggested that regular monitoring of cortisol levels in daily medical practice is essential for their recovery.

HPA axis and GCS physiological role

As has been established by many sources, cortisol secretion in the human body is well controlled by the hypothalamic–pituitary–adrenal axis. Thanks to numerous studies this is much better understood than a decade ago [9]. Researchers have found that the HPA axis is one of the most important neuroendocrine axes regulating homeostasis and stress-related response [10]. It all begins in the paraventricular nucleus of the hypothalamus (PVN), where corticotropin-releasing hormone (CRH) is secreted into the hypophyseal portal vasculature connected to the anterior pituitary gland. As a consequence, CRH stimulates the release of adrenocorticotropic hormone (ACTH) into the systemic circulation causing adrenal glands to synthesize glucocorticoids. Similar to the other steroid hormones, glucocorticoids do not require much time to be released into the bloodstream [11]. Peripherally, glucocorticosteroids show a variety of functions. GCS are involved in immune response, metabolism, cell growth, development, and reproduction. In physiological amounts, cortisol regulates carbohydrate, lipid and protein metabolism, stimulates gluconeogenesis in hepatic cells, reduces glucose usage in peripheral tissues, and intensifies lipolysis and proteolysis causing muscular atrophy. However, in higher doses, GCS can cause immunosuppression due to lymphocyte T deactivation and leukocyte depletion [12].

GCS have rapidly become one of the most widely used drugs in all medicine. They are used for various inflammatory diseases, autoimmune disorders, adrenal insufficiency, chronic obstructive pulmonary disease, asthma and all kinds of dermatological, ophthalmological, rheumatological, pulmonary, hematological and gastrointestinal incidents [13]. The HPA axis operates in certain regular rhythms, with cortisol's highest peak coming in the morning between 4am and 8am, and its lowest trough in the evening between 8pm and midnight [12]. Additionally, the HPA axis is prone to suppression by exogenous GCS.

In terms of ALL treatment, predniso(lo)ne and dexamethasone are the two most common factors of HPA axis suppression and atrophy of the adrenal cortex. It has been observed that the cortisol level and the ACTH level decrease dramatically after GCS administration [14]. However, in short-term circumstances (i.e. within one week) no significant suppression has been seen [5]. On the other hand, during illness, cortisol secretion may be increased throughout the day. Stress is known to be the major factor contributing to HPA axis stimulation. Therefore, children diagnosed with a serious illness such as ALL due to stress may have escalating levels of cortisol in their bloodstream which can sometimes lead to adrenal crisis. Other equally important factors behind high cortisol levels include an inadequate diet, deprivation of sleep, and excessive physical activity.

Prevalence and factors affecting cortisol level disorders

Cortisol level disorders are inseparably linked to the HPA axis. The GCS used in ALL treatment impair its function. After sudden discontinuation of long-term GCS administration, the HPA axis may be suppressed and develop steroid withdrawal syndrome. This condition has no characteristic symptoms but can manifest itself as weight loss, hypotension, skin desquamation, malaise, lethargy and anorexia [15]. There are several factors impacting the duration of adrenal suppression that ought to be mentioned. A study by Salem et al. [7] revealed slight differences in the type of GCS used in the therapy, the age of patients and the antifungal prophylaxis with fluconazole. Loimijoki et al. in their study [6] indicated different tolerances of GCS therapy depending on the morning basal cortisol level. In addition to that, the intensification of adrenal suppression and recovery was shown to depend on the duration of treatment and the GCS dosage [8].

Doses of GCS can vary depending on the ALL treatment protocol. In the majority of the analyzed studies, the dosage of predniso(lo)ne was 60 mg/m²/day and of dexamethasone was 6 mg/m²/day usually divided into three oral administrations. More detailed information is provided in Tables I and II [3, 6–8, 14–23].

The duration of adrenal suppression after high-dose GCS treatment in ALL patients can vary: usually, it lasts

Table I. Percentage of patients with adrenal insufficiency after prednisone therapy (based on [3, 6–8, 15–21])

Percentage of adrenal insufficiency in first test after a GCS therapy [%]	Mean time needed for HPA axis regeneration [days]	Year of study	Type of GCS	Number of patients in study	Duration of induction remission therapy	Dose of predniso(lo)ne or dexamethasone [mg/m ² /day]	Authors
80	70 (10 weeks)	2008	Prednisone	40	4 weeks	60	Einaudi et al. [3]
78	9	1981	Prednisone	13	4 weeks	60	Lightner et al. [18]
72.5	30	2016	Prednisolone	40	5 weeks	60	Perdomo-Ramírez et al. [17]
70	40% of patients remained suppressed for >4 months	2003	Prednisolone	10	5 weeks	60	Petersen et al. [16]
67	8.5 months	2011	Prednisolone	96	5 weeks	60	Vestergaard et al. [19]
51.4	No information	2005	Prednisone	35	3 weeks	60	Saracco et al. [15]
50	21–34	2014	Prednisone	20	4 weeks	60	Salem et al. [7]
50	After 56 days, 73.3% of patients had normal adrenal function	2012	Prednisone	16	4 weeks	40	Kuperman et al. [20]
47	HPA axis suppression lasted more than a week	2005	Prednisolone	17	5 weeks	60	Rix et al. [21]
46	20 weeks	2004	Prednisolone	24	4 weeks	40	Mahachoklertwattana et al. [8]
38	12–31	2020	Prednisolone	270	5 weeks	60	Loimijoki et al. [6]

GCS – glucocorticosteroids; HPA – hypothalamic–pituitary–adrenal

up to a few weeks, although some case reports have shown that the adrenal suppression may last longer, up to 19 weeks in prednisolone and 34 weeks in dexamethasone [16]. The detailed times needed for HPA axis recovery is set out in Tables I and II [3, 6–8, 14–23]. The mean time to restore normal adrenal function is dependent on morning basal cortisol level. The study by Loimijoki et al. [6] showed that a higher value of morning cortisol corresponds to a faster HPA axis recovery after GCS treatment. Patients were divided into three groups: group 1 with morning cortisol <107.00 nmol/L, group 2 with morning cortisol 107.01–183.00 nmol/L, and group 3 with morning cortisol >183.01 nmol/L. The mean time needed for the HPA axis to recover was 31 days in the first group, 24 days in the second and 12 days in the third. Patients in group 3 were 13 times more likely to recover than those in group 1. The type of glucocorticoid and the duration of HPA axis suppression were indicated in the study by Salem et al. [7]. This included a total of 40 standard risk ALL children divided into two groups: a 20-patient dexamethasone group and a 20-patient prednisone group. Children received a 28-day induction of remission therapy and a 3-week reinduction (induction 2) phase. In both groups, the dexamethasone and

prednisone doses were established at 6 mg/m² and 60 mg/m² respectively. The HPA axis was assessed with a low-dose ACTH (LD-ACTH) test. This revealed a notable difference in HPA axis suppression and recovery depending on the type of GCS which had been used. Prednisone patients recovered earlier than dexamethasone ones. A total of 65% and 75% of patients in induction phases 1 and 2 receiving prednisone, respectively, presented with recovery at week 2. Meanwhile, 45% and 50% of children treated with dexamethasone in induction phase 1 and 2 respectively reached recovery in four weeks. Yet patients with initial adrenal suppression presented with longer recovery. Similar conclusions were drawn in the Saracco et al. study [15], which revealed that signs of steroid withdrawal syndrome were more severe, and occurred in a greater number of patients, in the dexamethasone group. Moreover, they occurred earlier than in the prednisone group. This study consisted of 63 patients with ALL. The steroid treatment consisted of two phases: in the first one all of the children received 60 mg/m² of prednisone for seven consecutive days, and in the second one they were split into two groups receiving 10 mg/m² of dexamethasone and 60 mg/m² of prednisone for three consecutive weeks. A total of 28 patients received

Table II. Percentage of patients with adrenal insufficiency after dexamethasone therapy (based on [3, 7, 14–16, 20–23])

Percentage of adrenal insufficiency in first test after a GCS therapy [%]	Mean time needed for HPA axis regeneration [days]	Year of study	Type of GCS	Number of patients in study	Duration of induction remission therapy	Dose of predniso(lo)ne or dexamethasone [mg/m ² /day]	Authors
100	56 (8 weeks)	2000	Dexamethasone	10	4 weeks	6	Felner et al. [14]
83	70 (10 weeks)	2008	Dexamethasone	24	4 weeks	10	Einaudi et al. [3]
75	50	2014	Dexamethasone	20	4 weeks	6	Salem et al. [7]
75	No information	2005	Dexamethasone	28	3 weeks	10	Saracco et al. [15]
71	40% of patients remained suppressed for >4 months	2003	Dexamethasone	7	3 weeks	10	Petersen et al. [16]
40	After 56 days, 75% of patients had normal	2012	Dexamethasone	13	4 weeks	6	Kuperman et al. [20]
40	Mildly suppressed HPA axis up to two weeks	2001	Dexamethasone	15	6 weeks	6	Kuperman et al. [22]
20	HPA axis suppression lasted more than a week	2005	Dexamethasone	2	3 weeks	10	Rix et al. [21]
–	4 weeks	2004	Dexamethasone	35	4 weeks	6	De Freitas Cunha et al. [23]

GCS – glucocorticosteroids; HPA – hypothalamic–pituitary–adrenal

dexamethasone and 35 patients received prednisone. At least one steroid withdrawal syndrome was found in 75% of patients on dexamethasone and in 51.4% of patients on prednisone. In addition, there were more symptoms of HPA axis suppression in the dexamethasone patients than in the prednisone patients. Three or more symptoms were present in 39.3% of the dexamethasone patients compared to 8.6% in the prednisone group.

Age is another factor that can influence the time of HPA axis suppression. Many studies set the age of 5 years as the cut-off point. Salem et al. [7] concluded that children younger than five who were treated with prednisone recovered earlier than children older than five, although in the dexamethasone group age showed no impact on recovery. Similar results were observed by Perdomo-Ramírez et al. [17]. Their study highlighted that children aged over five were more likely to experience prolonged adrenal insufficiency. A total of 50 ALL patients treated with 60 mg/m² of prednisone for 35 days were enrolled in that study. Assessment of the HPA axis was performed using a LD-ACTH test. The results showed that in children older than 10 years, the probability of presenting HPA axis suppression was 2.3 times higher for each year beyond that age. Moreover, all patients who had adrenal suppression were aged over five [15]. Analogous conclusions were drawn

by Mahachoklertwattana et al. [8]. In their study, 24 ALL patients were treated with 40 mg/m² of prednisone for 28 days. The LD-ACTH test was performed two weeks after discontinuation of GCS administration. Adrenal insufficiency was observed in 67% of children older than five and in 25% of children younger than five. These results emphasize that children under five are more likely to regain their adrenal function earlier than children aged 5+. The study points out, however, that the age difference may be associated with the severity of the acute lymphoblastic leukemia in older patients [8].

Other drugs can influence the duration of HPA axis suppression as well. One of these medications is fluconazole, often used during the cessation of GCS to prevent febrile neutropenia. Its dosage also makes a difference. Among 40 children studied by Salem et al. [7], 80% of dexamethasone patients and 35–55% of prednisone patients received fluconazole. Half of them received more than 10 mg/kg/day (≥300 mg/day). The results revealed that those patients had a significant delay in adrenal recovery, unlike those who had lower doses of fluconazole. A similar conclusion was reached in the study carried out by Petersen et al. [16]. Ten ALL patients were treated with 60 mg/m² of prednisolone for five weeks and seven patients were treated with 10 mg/m² of dexamethasone for three weeks. Three

Table III. Tests used for hypothalamic–pituitary–adrenal (HPA) axis assessment and time of its execution (based on [3, 6–8, 14–23])

Type of test used for HPA axis assessment	Number of days between last dose of GCS and first HPA axis assessment [days]	Authors
Low-dose ACTH test and standard-dose ACTH test	10	Loimijoki et al. [6]
Low-dose ACTH test	3	Perdomo-Ramírez et al. [17]
Low-dose ACTH test	<1	Salem et al. [7]
Low-dose ACTH test	7	Kuperman et al. [20]
Standard-dose ACTH test	4 months (79% of patients) 4–6 months (remaining 21% of patients)	Vestergaard et al. [19]
Low-dose ACTH test	1	Einaudi et al. [3]
Low-dose ACTH test	5 days (prednisolone) 7 days (dexamethasone)	Rix et al. [21]
Morning plasma corticotropin (ACTH) and cortisol values	1	Saracco et al. [15]
oCRH stimulation test	2	De Freitas Cunha et al. [23]
Low-dose ACTH test	14	Mahachoklertwattana et al. [8]
Standard-dose ACTH test	1–14	Petersen et al. [16]
oCRH stimulation test	7	Kuperman et al. [22]
Standard-dose ACTH test	1	Felner et al. [14]
Morning plasma cortisol values	1.5	Lightner et al. [18]

GCS – glucocorticosteroids; ACTH – adrenocorticotrophic hormone; oCRH – ovine corticotropin-releasing hormone

dexamethasone patients received 30 mg of fluconazole daily. A standard dose ACTH test was performed within two weeks to assess the HPA axis. The results showed that two out of three patients receiving antifungal prophylaxis by fluconazole experienced longer adrenal suppression, lasting up to eight months. Nevertheless, the study carried out by Loimijoki et al. [6] found that patients receiving fluconazole had higher median baseline cortisol levels compared to patients without prophylaxis. It ought to be mentioned, however, that the doses of fluconazole were below 5 mg/kg/day.

Sex also plays an important role in terms of HPA axis recovery. The Salem et al. study [7] detected a sex difference mainly in the second induction treatment with dexamethasone. The results showed slight differences in adrenal suppression development in boys as opposed to girls. Male patients treated with dexamethasone had significantly later adrenal recovery than did female patients. Furthermore, boys presented with a higher risk of infection during this therapy. Moreover, male patients showed a longer duration of hospitalization and a higher average of days with neutrophil count $<500/\text{mm}^3$ than did girls. On the other hand, treatment with prednisone revealed no such differences.

Diagnostic methods

After long-term exposure to high non-physiological doses of GCS such as predniso(lo)ne or dexamethasone, the

recovery of each HPA axis component is not simultaneous. The pituitary gland regains its normal function faster than does the adrenal gland. The consequence of this is an increased basal level of corticotropin. This is why full recovery of the HPA axis can be determined by demonstrating the proper cortisol level after stimulation by exogenous corticotropin [14]. The time between the end of GCS administration and the performance of the first test varies in different studies. More detailed information can be found in Table III. There are various methods of detecting adrenal insufficiency, and there is no consensus regarding the optimal test for HPA axis assessment. The most commonly used test is the insulin tolerance test. This is considered the gold standard. Nevertheless, it has its limitations in child diagnostics, where its use is not recommended. In clinically uncertain cases, the insulin induced hypoglycemia test should be considered [24]. The metyrapone test is also very specific, but again it is not advised in child diagnostics [25]. The same is true for the glucagon test, which is considered safe. However, some studies have shown that it can cause adverse side effects [26].

The alternatives are ACTH stimulation tests. There are two types of ACTH stimulation test: the standard dose test and the LD-ACTH test which uses 1 µg of ACTH instead of the 250 µg in the standard one. The second test is more sensitive but less specific than the first one, which is distinguished by a higher specificity [27]. Additionally, the study by Thaler et al. [28] showed that the 1 µg ACTH test is more sensitive and specific than the metyrapone test and the

insulin tolerance test. However, in some studies the ovine CRH (oCRH) test has been used for HPA axis assessment as well [22, 23]. Another method for HPA axis evaluation is morning plasma cortisol values. Some studies have suggested that this is not an adequate parameter, because the cortisol response may not be sufficient under stress conditions despite normal morning plasma cortisol levels [29]. Nevertheless, significantly decreased morning cortisol values ($<3 \mu\text{g/dL}$) suggest a high possibility of adrenal insufficiency [30]. This was confirmed in Einaudi et al.'s [3] study where all patients with an impaired response to the LD-ACTH test had low morning cortisol levels. Loimijoki et al. [6] also suggested that morning cortisol levels could be treated as an adrenal insufficiency screening test. To assess HPA axis recovery after the course of GCS therapy, the level of dehydroepiandrosterone sulfate (DHEA-S) and dehydroepiandrosterone (DHEA) after ACTH stimulation can be measured. DHEA-S appears to be more sensitive to the ACTH stimulation than cortisol [7]. Of 14 studies analyzed, a LD-ACTH test was performed in seven, a standard dose ACTH test in four, morning plasma cortisol in two, and an ovine CRH test in two of them. Additional information is set out in Table III [3, 6–8, 14–23].

Complications of HPA axis disorders

Disorders of the HPA axis after GCS treatment have serious consequences, and therefore one ought to carry out absolute prophylaxis. Researchers have claimed that prolonged cancer-treated patients are particularly prone to abnormal cortisol level fluctuations, leading to numerous side effects. The most common complication is adrenal suppression, although other adverse effects are equally important.

Immunosuppression

GCS used in ALL treatment weaken the function of the immune system, leading to severe infections. In the Saracco et al. study [15], 33 of 63 (52%) treated patients were infected. Eight patients were more severe cases than the others. These results were comparable to those of Lightner et al. [18] and Einaudi et al. [3]. Their works also revealed a growing rate of infections among patients. Significant critical illness was observed in c.38% (5 of 13) and 8% (4 of 52) of patients respectively. Middle ear infections, pneumonia and sepsis have been observed within as little as nine days after GCS treatment discontinuation [3, 31].

Febrile neutropenia is another sign of immunosuppression commonly appearing among cancer-treated patients. This condition has been thoroughly observed and described by De Freitas Cunha et al. [23]. In that study, 11 of 28 patients showed signs of severe infection on the 8th day of GCS treatment, and on the 28th day two of the patients presented febrile neutropenia. Moreover, two studies have shown

an association between a high infection rate and the type of GCS used in the induction phase of treatment. In the study by Vrooman et al. [4], dexamethasone was associated with a higher risk of infection (19%) than prednisolone (11%). In the DFCl 91-01P protocol, 42% (16 of 38) of children had sepsis, with a mortality rate amounting to 11%. Moreover, such an occurrence emerged on account of substituting dexamethasone for prednisone [32]. According to Bostrom et al. [33], however, there was no specific correlation between the particular steroid and the risk of infection. Of all the children observed, c.13% showed signs of bacteremia regardless of the medication used. Fungal and viral infections were spotted in this group as well.

When it comes to mortality rate of infections, approximately 0.6% of Bostrom et al.'s [33] patients died during the induction phase and in the following month. The UKALL X study, carried out by Wheeler et al. [34], also proved that mortality is a major concern when it comes to GCS usage. In this study, 31 out of 1,612 infectious deaths were observed during the induction phase of treatment.

Cushing's disease

Cushing's disease (CD) is another of the most commonly occurring side effects of GCS. This is a two-way street, in the sense that the most frequent cause of iatrogenic CD seems to be prolonged exposure to exogenous steroids, especially when it comes to prednisolone used in lymphoproliferative disorders among children [35]. According to Mahachoklertwattana et al. [8], by the time of completion of the 28-day course of prednisolone therapy, all 24 patients exhibited physical signs of CD.

The clinical presentation of CD varies from person to person. It has been observed that among pediatric patients, the most characteristic features are weight gain and growth retardation [36]. Felner et al.'s [14] study, carried out among 10 children treated with dexamethasone for ALL, found the development of central obesity in 80% of them. The average weight gain amounted to 1.4–5.8 kg 28 days after beginning therapy. Other equally important symptoms include moon facies, muscle weakness, easy bruising, hypertension, virilization, delayed puberty, and psychological disturbances [37, 38]. Regarding Cushingoid moon face, according to De Freitas Cunha et al. [23], this condition has been observed in 9/28 patients (32%) on the 8th day of treatment and in 20/28 patients (71%) on the 28th day. Additionally, 19/27 patients (70%) developed similar features 48 hours after GCS discontinuation. Hyperglycemia is an important component of CD as well. Bozzola et al. [39] found the incidence of hyperglycemia to be 5% (dexamethasone) and 1.5% (prednisone). Moreover, in the study carried out by Salem et al. [7], hyperglycemia occurred in 15% and 12.5% of patients in the induction 1 and induction 2 phases of therapy respectively.

Bone toxicities

Bone toxicities, such as osteonecrosis and fractures, are common among patients treated for ALL, especially adolescents. Osteonecrosis, which is a condition mainly caused by the disruption of blood supply to one part of the bone, occurs among children, particularly white (in terms of ethnicity) females aged 10 years or older [40]. Commonly, there has been a correlation between the type of steroid used and the incidence of osteonecrosis. Many studies have shown a higher percentage with this condition among patients who received dexamethasone in the induction phase than among those treated with prednisolone [40–42]. Age seems to be an important factor in terms of osteonecrosis incidence. Bürger et al. [43] discovered exactly 31 patients with osteonecrosis during GCS treatment for ALL. The incidence for patients aged <10 years amounted to merely 0.2%, whereas for patients aged ≥10 years it was c.8.9%. According to Bürger et al. [43], more patients developed osteonecrosis in two or more joints. The most commonly affected parts included knees (14 patients) and hips (11 patients). Bone fractures have also been spotted more frequently among dexamethasone-treated patients compared to prednisolone ones [4].

Psychosis

Steroid treatment often results in psychosis [44]. It can cause mood swings, behavioral changes, violence, and a liability to develop severe depression. Due to increased dexamethasone penetration to the Central Nervous System, it is mainly linked to those psychotic adverse effects as compared to prednisolone. The MRC ALL 97/99 study reported behavioral toxicity in c.6% of patients treated with dexamethasone, but in only 1% of those treated with prednisolone. Additionally, three of the patients, all on dexamethasone, developed delusional psychoses. Those children, treated with dexamethasone, were switched to prednisolone with no significant recurrence of behavioral problems [45]. A historical comparison of the DFCI 87-01 and 91-01 protocols [46] showed that dexamethasone can aggravate cognitive functions. Children treated with dexamethasone in protocol 91-01 performed less well on their cognitive test consisting of working memory and on neuropsychological measures of learning disability than others. On the other hand, a study of children with ALL on protocol CCG-1922 [47] showed no significant neurological differences between two groups treated separately with either dexamethasone or prednisolone. However, c.16% of patients who received dexamethasone needed further special education after the treatment, whereas only 5% of the prednisolone group did.

Growth retardation

Exogenous glucocorticosteroids have been reported to inhibit growth hormone (GH) production, which may lead

to linear growth retardation and a delay in puberty among young patients. Moreover, Allen et al. [48] revealed that prepubertal children treated with GCS present with short stature, delayed skeletal maturation, and slowed growth rates for c.2.5–3.0 cm per year. Bozzola et al. [39] observed GH secretion among seven patients, showing that in fact, GH production decreases with prednisone usage. However, it seemed that absolute drug discontinuation improved the outcome of this research.

Conclusions

The increasing survival rate of children with ALL treated with GCS means that the adverse effects of this treatment ought to be even more carefully evaluated. GCS are very effective in terms of ALL-treated patients, although they tend to suppress the HPA axis leading to numerous side effects. In the analyzed studies, adrenal suppression occurred in most of the patients after discontinuation of GCS therapy. Nevertheless, in various studies the exact duration of HPA axis suppression has ranged from a few weeks up to a few months.

The reviewed studies were characterized by different doses of GCS, different lengths of study duration, and different methods of HPA axis assessment. However, some studies have indeed highlighted factors which can contribute to prolonged adrenal insufficiency. Attention ought to be paid to the type of GCS used. Dexamethasone therapy can lead to prolonged adrenal insufficiency compared to prednisone. Moreover, dexamethasone may lead to a higher risk of infection and the development of hyperglycemia, a greater incidence of osteonecrosis, and worse cognitive test results than prednisone.

The importance of age should also be underlined. Younger children present with better toleration and faster regeneration of adrenal insufficiency. Additionally, according to studies, younger children have a lower probability of developing GCS-induced osteonecrosis. The administration of fluconazole in high doses (i.e. exceeding ≥10 mg/kg/day) may be the reason for prolonged HPA axis suppression. Moreover, boys seem to have a worse toleration of dexamethasone and a greater chance of developing prolonged adrenal insufficiency than girls. Therefore, it is important to perform an HPA axis stimulation test to assess its response to stress. However, recent studies have shown that morning cortisol levels may be the screening test for adrenal insufficiency [6].

Larger randomized trials are needed to provide guidelines for GCS replacement therapy and to investigate differences between the types of GCS and the factors contributing to HPA axis suppression.

Authors' contributions

JZ, ML – conceptualization. JZ, AS, ZS – methodology. AS, ZS – writing, original draft preparation. JZ, ML – review

and editing. All authors read and agreed to published version of manuscript.

Conflict of interest

The authors declare no conflict of interest.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments and uniform requirements for manuscripts submitted to biomedical journals.

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